Inflammatory signalling in atrial cardiomyocytes: a novel unifying principle in atrial fibrillation pathophysiology

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Abstract | Inflammation has been implicated in atrial fibrillation (AF), a very common and clinically significant cardiac rhythm disturbance, but its precise role remains poorly understood. Work performed over the past 5 years suggests that atrial cardiomyocytes have inflammatory signalling machinery — in particular, components of the NLRP3 (NACHT-, LRR- and pyrin domain-containing 3) inflammasome — that is activated in animal models and patients with AF. Furthermore, work in animal models suggests that NLRP3 inflammasome activation in atrial cardiomyocytes might be a sufficient and necessary condition for AF occurrence. In this Review, we evaluate the evidence for the role and pathophysiological significance of cardiomyocyte NLRP3 signalling in AF. We first summarize the evidence for a role of inflammation in AF and review the biochemical properties of the NLRP3 inflammasome, as defined primarily in studies of classic inflammation. We then briefly consider the broader evidence for a role of inflammatory signalling in heart disease, particularly conditions that predispose individuals to develop AF. We provide a detailed discussion of the available information about atrial cardiomyocyte NLRP3 inflammasome signalling in AF and related conditions and evaluate the possibility that similar signalling might be important in non-myocyte cardiac cells. We then review the evidence on the role of active resolution of inflammation and its potential importance in suppressing AF-related inflammatory signalling. Finally, we consider the therapeutic potential and broader implications of this new knowledge and highlight crucial questions to be addressed in future research.

Atrial fibrillation (AF) is a common and important clinical condition, associated with substantial morbidity and mortality related to a host of potentially serious complications, such as cardiomyopathy, heart failure (HF) and stroke[1]. A variety of treatment approaches for AF are available, including antiarrhythmic drugs to promote maintenance of normal sinus rhythm, bradycardic agents to prevent excessively rapid heart rates, anticoagulant drugs to prevent thromboembolism and ablation procedures to promote maintenance of sinus rhythm. Although each of these approaches is useful, they all have potential limitations and adverse effects, leaving a substantial unmet need for therapeutic innovation[2].

A role of inflammation in AF has been suspected for >20 years[3], and considerable evidence has subsequently accrued[4]. Nevertheless, the benefits of traditional anti-inflammatory agents for the treatment of AF have been small and unconvincing overall[4]. Although the classic view is that inflammation results from the production of cytokines by a variety of infiltrating white cells in response to tissue injury and/or immune cell responses, evidence has begun to emerge that other cell types, including cardiomyocytes, can have potentially important inflammatory signalling that results in tissue pathology and remodelling. In this article, we review the evidence suggesting the pathophysiological relevance of cardiomyocyte inflammatory signalling in AF and consider the potential therapeutic opportunities associated with these signalling pathways. We also provide the essential contextual background, in terms of the relevant biochemical components, the evidence for a role of inflammation in heart disease and more specifically in AF, the possible involvement of inflammatory signalling in non-inflammatory, non-myocyte cardiac cells (such as fibroblasts and adipocytes) and the potential utility of promoting the resolution of inflammation in protecting against AF.

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https://doi.org/10.1038/s41569-022-00759-w

Key points

- Atrial fibrillation is the most common cardiac arrhythmia, and new insights into the pathophysiological mechanisms are required to improve the available therapeutic options.
- Although inflammation has been thought to have a role in atrial fibrillation for ≥20 years, the precise nature of the association has proved elusive.
- Work over the past 5 years has revealed a key role for inflammatory signalling in cardiomyocytes in atrial fibrillation development, revealing the importance of non-leukocyte cardiac cells in mediating disease-promoting cardiac inflammation.
- The NLRP3 inflammasome in particular has been implicated in cardiomyocyte-mediated inflammatory signalling in atrial fibrillation.
- The active resolution of inflammation is thought to be mediated by endogenous bioactive agents, which can be administered as pharmaceutical products to attenuate the development of chronic conditions such as atrial fibrillation.

Inflammation, heart disease and AF

Inflammation is part of the response to infection and injury and is intimately involved in defence and healing processes. Distinct forms of inflammation result from sterile inflammatory signals (such as those generated by tissue injury and autoantigens, termed damage-associated molecular patterns (DAMPs))[5] and signals derived from exogenous pathogens (termed pathogen-associated molecular patterns (PAMPs))[6]. Bioactive signals promote the recruitment of innate immune cells to confine and neutralize the targeted threat and to begin the healing process. However, when the inflammatory response persists beyond the original threat, chronic inflammation can cause adverse tissue remodelling and disease. Growing evidence suggests a direct link between systemic or local inflammation and AF development (TABLE 1).

Inflammatory conditions associated with clinical AF. Available evidence indicates a relationship between AF and systemic inflammation in patients with autoimmune diseases, such as rheumatoid arthritis[7], psoriasis[8], inflammatory bowel disease[9] and sepsis[10–19] (TABLE 1). In patients with sepsis, the incidence of new-onset AF ranges between 1.9% and 40%[10–19], with patients with severe sepsis or septic shock having a higher incidence of new-onset AF than patients with milder forms of sepsis[11,13,15]. Risk factors associated with AF onset include advanced age[11–13,15,20], male sex[11,20], white ethnicity[11–13], obesity[11], HF[11,16,20], renal failure[11,20], chronic liver disease[20], organ failure[13], pulmonary catheter use[13], and chronic respiratory disease and failure[16,20], although new-onset AF also develops in patients with no cardiovascular co-morbidities[12]. In addition, in patients with sepsis, new-onset AF is associated with increased risks of stroke[11,13,16] and in-hospital death[11,13,15,17,20] and long-term (5-year) risks of hospitalization for HF, ischaemic stroke and death[14].

Local cardiac inflammatory conditions, including pericarditis and myocarditis, also increase the incidence of AF (TABLE 1). The incidence of new-onset AF in patients with pericarditis ranges between 4.3% and 46%[21–24], with spontaneous cardioversion to sinus rhythm occurring in 74.3% of patients within 24 h[24], but with a significant rate of recurrence during 30 months of follow-up (34.3% in patients with AF at the initial episode versus 0.9% in patients with pericarditis without initial AF; $P < 0.001$)[24].

During hospitalization, up to 26.9% of patients with acute myocarditis develop new-onset AF[25]. Among patients with myocarditis, mortality was higher in patients with AF than in those in sinus rhythm[25]. Although some studies found normal left ventricular (LV) function and left atrial size in patients with myocarditis and AF[26–28], other work showed that myocarditis-related AF was more often associated with chronic HF and an enlarged left atrium[29,30]. Finally, serious coronavirus disease 2019 (COVID-19) causes a major systemic inflammatory response and is associated with the development of a wide variety of arrhythmias, of which AF is one of the most common[31,32].

Insights from animal models on inflammation-associated AF. Animal models of systemic or local inflammation support the link between inflammation and AF (TABLE 2). Animals with sepsis, which have increased atrial infiltration of inflammatory macrophages and $CD68^+$ cells[33], have increased vulnerability to pacing-induced AF[33,34]. In animal models of lipopolysaccharide (LPS)-induced sepsis, the action potential duration and atrial effective refractory period decrease as a result of reduced L-type Ca^{2+} current ($I_{Ca,L}$) and increased I_{Kr} (rapid component of the delayed rectifier K^+ current) and I_{Ks} (slow component of the delayed rectifier K^+ current), together with slowed conduction velocity[33–35], pointing to re-entry as a potential mechanism. The atrial activity of the Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is higher during sepsis and causes hyperphosphorylation of cardiac ryanodine receptor 2 (RYR2) channels at Ser2814, which, together with increased Na^+–Ca^{2+}-exchanger levels, increases the likelihood of spontaneous sarcoplasmic reticulum Ca^{2+} release events[34], promoting delayed afterdepolarizations (DADs) and triggered activity[36,37].

AF induced in animals with sterile pericarditis is associated with heterogeneous conduction slowing[38–41], together with reduced connexin 40 and connexin 43 expression[39]. In these animals, the atrial effective refractory period and action potential duration are shorter[42–44] or unchanged[45–47]. Increased atrial ectopy[44–46] in experimental pericarditis is associated with DADs and cellular

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Table 1 | **Examples of inflammatory conditions associated with clinical AF**

Study	Study design	Number of patients	AF phenotype	Other clinical findings	Ref.
Sepsis					
Walkey et al. (2011)	Retrospective cohort from the California State Inpatient Database	3,144,787 (patients with pre-existing AF were excluded)	Increase in new-onset AF in patients with versus without severe sepsis (OR 6.82); sepsis present in 14% of patients with new-onset AF	Risk factors for AF: advanced age, male sex, white ethnicity, HF, obesity, renal failure; increased risk of stroke (OR 2.7) and in-hospital death (OR 1.07) in patients with severe sepsis and new-onset AF	11
Walkey et al. (2013)	Representative 5% sample from Medicare beneficiaries in the USA	–	25.5% of patients had an AF diagnosis during the hospitalization for sepsis; 7.2% had new-onset AF	Risk factors for AF: advanced age, white ethnicity; no association with cardiovascular risk factors	12
Kuipers et al. (2014)	Systematic review including 11 studies (studies primarily focused on postcardiotomy were excluded)	–	The incidence of new-onset AF was 8%, 10% and 23% in critically ill patients with sepsis, severe sepsis or septic shock, respectively	Risk factors for AF: advanced age, white ethnicity, organ failure, pulmonary artery catheter use; increased mortality (five studies) and risk of stroke (one study) in patients with new-onset AF and sepsis	13
Walkey et al. (2014)	Representative 5% sample from Medicare beneficiaries who survived hospitalization for sepsis in the USA	133,722	24% had previous AF and 7% had new-onset AF	Increased long-term (5-year) risk of HF hospitalization, ischaemic stroke and death in patients with new-onset AF during sepsis	14
Walkey et al. (2016)	Retrospective cohort study in patients with AF during sepsis in the USA	39,693	–	Reduced in-hospital mortality when AF during sepsis was treated with β-blockers compared with Ca^{2+} channel blockers, digoxin or amiodarone	241
Koyfman et al. (2015)	Retrospective cohort study in patients with sepsis in an intensive care unit in Israel	200	81 patients (40.5%) had new-onset AF, of whom 44 (54.3%) had a history of AF	In-hospital mortality was similar between patients with new-onset AF and those with previous AF	10
Klein Klouwenberg et al. (2017)	Retrospective cohort study in patients with sepsis in Netherlands	1,782	The cumulative risk of new-onset AF was 10%, 22% and 40% in patients with sepsis, severe sepsis and septic shock, respectively	Increased hospital stay and mortality in the intensive care unit in patients with new-onset AF during sepsis	15
Cheng et al. (2017)	Retrospective cohort study in survivors of septicaemia from the Taiwan National Health Insurance Database	68,324	1.6% had pre-existing AF and 1.9% had new-onset AF	Risk factors for AF: advanced age, HF, respiratory failure; increased risk of stroke with new-onset AF during sepsis	16
Bosch et al. (2019)	Retrospective cohort study in patients with suspected infection in an intensive care unit in the USA	9,528	2.5% had new-onset AF	Increased mortality with new-onset AF during sepsis	17
Fernando et al. (2020)	Retrospective cohort study in patients in an intensive care unit in Canada	15,014	10.3% had new-onset AF; significant interaction between new-onset AF and sepsis	–	18
Ko et al. (2021)	Retrospective cohort study in patients with new AF diagnosis from UMass Memorial Health	185	34.6% of patients with new-onset AF had sepsis as secondary precipitant	–	19
Long et al. (2021)	Retrospective cohort study in patients with sepsis from the MIMIC-II database	7,528	16.5% had a history of AF	Risk factors for AF: advanced age, male sex, HF, chronic respiratory disease, liver disease, renal failure; increased mortality with new-onset AF during sepsis	20
Pericarditis					
Spodick (1976)	Prospective study of consecutive patients with acute pericarditis	100	5% had new-onset AF (all among the 24 patients with definite heart disease)	–	21
Spodick (1984)	Study of consecutive patients in sinus rhythm with acute pericarditis and 24 h Holter monitoring; all patients received an anti-inflammatory agent (ibuprofen, aspirin or indomethacin)	50 (patients with previous arrhythmias were excluded)	–	40% had no cardiac disease and half of these patients had atrial ectopy; in patients with heart disease, 66% had atrial ectopy	242
Nagahama et al. (1998)	Study of consecutive patients with acute myocardial infarction	398	Of 105 patients with pericardial effusion, 36 (34%) developed new-onset AF	–	22

Table 1 (cont.) | **Examples of inflammatory conditions associated with clinical AF**

Study	Study design	Number of patients	AF phenotype	Other clinical findings	Ref.
Pericarditis (cont.)					
Ristić et al. (2000)	Study of patients with acute pericarditis	40	20% had new-onset AF without predisposing myocardial or valvular disease	–	23
Talreja et al. (2003)	Study of patients with constrictive pericarditis	143	31 patients (21%) had AF	–	243
Syed et al. (2012)	Study of patients with tuberculous pericarditis	80	20 patients (25%) had AF at presentation; incidence of AF decreased to zero by 6 months of follow-up	Patients with AF were more likely to have left ventricular systolic dysfunction and higher serum levels of N-terminal pro-B-type natriuretic peptide	244
Imazio et al. (2015)	Prospective, multicentre study of patients with acute pericarditis	822	4.3% developed new-onset AF within 24 h of pericarditis onset; 17% of patients with AF had structural heart disease; 74.3% of patients had spontaneous conversion to sinus rhythm within 24 h; in a 30-month follow-up, AF recurrence rate was higher in the AF (35%) than in the sinus rhythm (0.9%) group	–	24
Myocarditis					
Frustaci et al. (1991)	Study of patients with 'lone' AF resistant to conventional antiarrhythmic drugs	14	–	Three patients showed active myocarditis in left ventricular endomyocardial biopsy samples; LVEF ≥50%; LA ≤40 mm	26
Morgera et al. (1992)	Study of patients with myocarditis	45	Five patients had AF at presentation associated with HF and enlarged LA	–	29
Frustaci et al. (1997)	Study of 14 patients with 'lone' AF resistant to conventional antiarrhythmic drugs and 11 patients with Wolff–Parkinson–White syndrome (as controls)	25	–	Eight patients showed atrial myocarditis in biopsy samples from right atrial septum; LVEF ≥55%; LA ≤40 mm; no conduction abnormalities	27
Fuenmayor et al. (1997)	Study of eight patients with acute myocarditis caused by Chagas disease and 125 control patients	133	AF and atrial flutter could be induced by programmed electrical stimulation in four patients with Chagas disease	Normal LVEF and LA	28
Larsen et al. (2013)	Study of patients with atrial giant cell myocarditis	6	Four patients had AF with atrial dilatation, mitral or tricuspid regurgitation, or atrial mural thrombus	–	245
Deluigi et al. (2013)	Study of patients with biopsy-proven myocarditis	84	After hospital admission, four patients had AF associated with HF and atrial dilatation	–	30
Anderson et al. (2014)	Retrospective, multicentre study of children with myocarditis	2,041	44 (2.2%) had reported AF or atrial flutter	–	246
Blagova et al. (2016)	Retrospective study of patients with idiopathic arrhythmias	19	16 (84%) had AF (12 paroxysmal, 4 permanent)	15 (79%) had biopsy-proven myocarditis	247
Subahi et al. (2019)	Retrospective study of patients with acute myocarditis from the US inpatient sample registry	6,642	602 (9%) had reported AF	Patients with AF were older and more often were white and had HF, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, renal failure and coagulation disorder	248
Adegbala et al. (2019)	Retrospective study of patients with acute myocarditis from the US Nationwide Inpatient Survey Dataset	32,107	26.9% had AF during hospitalization	Patients with AF were older, had more co-morbidities and higher mortality	25
Rasal et al. (2021)	Prospective study of children with acute myocarditis	63	1.4% of children had AF during hospitalization	–	249

AF, atrial fibrillation; HF, heart failure; LA, left atrium; LVEF, left ventricular ejection fraction.

Table 2 | **Examples of clear inflammatory settings leading to AF in experimental studies**

Model	Species	Phenotype	Intervention	Refs.
Sepsis				
LPS-induced sepsis	Guinea pig	↓ Atrial cardiomyocyte APD ↓ Atrial $Ca_v1.2$ levels and ↓ $I_{Ca,L}$ ↑ Atrial $K_v11.1$ levels and ↑ I_{Kr} ↑ Atrial $K_v7.1$ levels and ↑ I_{Ks} ↑ NO production in atrial cells ↑ iNOS, but not eNOS, levels	Inhibition of NO production eliminated the changes in APD and ion currents	35
LPS-induced sepsis	Rat	↑ Vulnerability to pacing-induced AF ↓ LVEF ↓ AERP, APD_{20}, APD_{50} and APD_{90} ↑ Atrial conduction time ↑ CaMKII-mediated RYR2 phosphorylation at Ser2814 ↓ SERCA2A levels and ↓ CaMKII-mediated phospholamban phosphorylation at Thr17 ↑ NCX1 levels ↑ Total and autophosphorylated CaMKII at Thr287 ↑ ROS and MDA Abnormal iron metabolism (ferroptosis)	Suppression of ferroptosis prevented AF and reduced oxidative stress and Ca^{2+}-handling dysregulation	34
Pericarditis				
Sterile pericarditis	Dog	Rapid atrial pacing-induced AF on days 2–14 after surgery Unstable re-entrant circuits with fibrillatory conduction Underlying cellular and molecular mechanisms of AF not studied	AF duration and inducibility reduced or suppressed by administration of D,L-sotalol, JTV-519 (K201), AZD7009, ibuprofen, methylprednisolone, GAP-134, vanoxerine or ranolazine	250–272
Sterile pericarditis	Dog	Rapid atrial pacing-induced AF on day 2 after surgery Prolonged intra-atrial conduction time Increased plasma CRP level Perimyocarditis and atrial inflammatory infiltrates with lipid degeneration Interstitial fibrosis	AF and underlying tissue changes were suppressed by atorvastatin administration	38
Sterile pericarditis	Dog	Rapid atrial pacing-induced AF on day 4 after surgery ↓ Atrial conduction velocity ↓ Atrial connexin 40 and connexin 43 levels ↓ Atrial α-actinin level (myolysis) ↑ Atrial vimentin level (fibrosis)	–	39
Sterile pericarditis	Dog	Rapid atrial pacing-induced AF on days 2–4 after surgery ↑ Atrial myeloperoxidase level	–	273
Sterile pericarditis	Dog	Rapid atrial pacing-induced AF on day 2 after surgery Shorter AERP ↑ CRP, IL-6 and TNF levels in plasma Perimyocarditis and atrial inflammatory infiltrates with lipid degeneration	AF inducibility and duration and inflammatory indices were reduced by administration of polyunsaturated fatty acids	43
Sterile pericarditis	Goat	Inducibility of AF by rapid atrial pacing was highest 72 h after surgery ↓ AERP 24 h to 21 days after surgery with loss of AERP rate adaptation Normal atrial conduction velocity ↑ CRP, IL-6 and TNF levels in plasma ↑ Lymphocyte atrial infiltration, epicardial thickening, myocardial rupture and necrosis	↓ AF duration, but no increased AF inducibility; suppressed inflammatory indices with atorvastatin treatment	42
Sterile pericarditis	Rat	Rapid atrial pacing-induced AF on days 1–4 after surgery ↑ Atrial levels of IL-6, IL-1β, IL-17A and TGFβ1 Perimyocarditis and atrial inflammatory infiltrates with lipid degeneration Interstitial fibrosis (↑ atrial levels of collagen 1, collagen 3, αSMA, MMP2 and MMP9 and ↓ levels of TIMP2 and glycosylated TIMP3)	Neutralization of IL-17A reduced AF susceptibility and AF duration and suppressed inflammation and fibrosis	49

Table 2 (cont.) | **Examples of clear inflammatory settings leading to AF in experimental studies**

Model	Species	Phenotype	Intervention	Refs.
Pericarditis (cont.)				
Sterile pericarditis	Rat	Rapid atrial pacing-induced AF on day 3 after surgery Inhomogeneous conduction ↑ Atrial levels of IL-6, IL-1β, TGFβ1, TNF, STAT3 and miR-21 Interstitial fibrosis (↑ atrial levels of collagen 1, collagen 3 and αSMA)	Administration of antagomir-21 and STAT3 inhibition reduced AF susceptibility and suppressed inflammation and fibrosis	40
Sterile pericarditis	Pig	Rapid atrial pacing-induced AF 7 days after surgery ↓ Sinus cycle length Interstitial fibrosis Atrial myolysis Inflammation and leukocyte infiltration	Amiodarone treatment prevented AF	48
Sterile pericarditis	Rabbit	↑ Atrial premature contractions ↑ Spontaneous burst firing in pulmonary veins at baseline and with isoprenaline administration ↓ APD_{90} with reduced $Ca_v1.2$ and $K_v11.1$ levels Interstitial fibrosis	Histone deacetylase inhibition prevented fibrosis and reduced atrial premature contraction and spontaneous burst firing	44
Sterile pericarditis	Rat	Rapid atrial pacing-induced AF on day 3 after surgery Inhomogeneous conduction ↑ Atrial IL-6, TGFβ1, TNF and myeloperoxidase levels Interstitial fibrosis (↑ atrial collagen 1, collagen 3 and αSMA levels) ↑ Phosphorylation of STAT3, AKT and p38, but normal levels of phosphorylated ERK and phosphorylated JNK	Colchicine administration suppressed inflammation and fibrosis	41
Sterile pericarditis	Rabbit	↑ DADs and triggered activity in vitro in LA samples ↑ Pacing-induced burst firing in vitro in LA samples ↑ APD_{20} and APD_{50}, normal APD_{90} in LA samples ↑ Atrial IL-1α, IL-8 and CCL4 levels, but normal IL-17A and IL-21 levels IL-1β, TNF and MMP9 not detectable	Inhibition of TLR4 (with TAK-242), RYR2 (with ryanodine) or CaMKII (with KN-93) reduced pacing-induced burst firing	47
Sterile pericarditis	Rat	Rapid atrial pacing-induced AF on day 3 after surgery ↑ Atrial ectopy; AERP unchanged ↑ APD_{20}, APD_{50}, APD_{90} (↓ K^+ currents I_{peak}, I_{sus} and I_{to}) ↑ TRPV4 in atrial fibroblasts ↑ Atrial IL-6, TGFβ1 and TNF levels Interstitial fibrosis (↑ atrial levels of collagen 1, collagen 3, αSMA, and phosphorylated SMAD3, p38, AKT and STAT3)	TRPV4 inhibition reduced AF susceptibility and suppressed inflammation and fibrosis	45
Sterile pericarditis	Minipig	Rapid atrial pacing-induced AF 14 days after surgery Interstitial fibrosis	–	50
Sterile pericarditis	Rat	Rapid atrial pacing-induced AF on day 3 after surgery ↑ Atrial ectopy and re-entrant activity Normal AERP ↑ Atrial IL-6, IL-1β, MMP9 levels; plasma IL-6 level unchanged ↑ Myeloperoxidase level and $CD68^+$ cell numbers Interstitial fibrosis (↑ atrial αSMA level) Heterogeneous Ca^{2+} transient prolongation ↑ Incidence of discordant alternans ↑ Relative level of Ser2808-phosphorylated RYR2 and Ser2814-phosphorylated RYR2 caused by downregulation of total RYR2 level ↓ $Ca_v1.2$ levels and SERCA activity; normal NCX1 levels	Neutralization of IL-6 reduced atrial ectopy and susceptibility to AF and suppressed inflammation, fibrosis and Ca^{2+} handling abnormalities	46

Table 2 (cont.) | **Examples of clear inflammatory settings leading to AF in experimental studies**

Model	Species	Phenotype	Intervention	Refs.
Myocarditis				
Autoimmune or LPS-induced myocarditis	Rat	11 out of 15 rats with chronic autoimmune myocarditis had inducible AF with atrial cardiomyocyte hypertrophy, increased LA and interstitial fibrosis LPS-induced acute myocarditis led to a reduction in atrial connexin 43 levels and did not cause inducible AF	–	51

AERP, atrial effective refractory period; AF, atrial fibrillation; APD, action potential duration; CaMKII, calcium/calmodulin-dependent kinase II; $Ca_v1.2$, voltage-gated L-type Ca^{2+} channel subunit-α; CCL4, C-C motif chemokine 4; CRP, C-reactive protein; DAD, delayed afterdepolarization; eNOS, endothelial nitric oxide synthase; I_{Kr}, rapid component of the delayed rectifier K^+ current; I_{Ks}, slow component of the delayed rectifier K^+ current; I_{peak}, peak K^+ current; I_{sus}, sustained K^+ current; I_{to}, transient outward K^+ current; iNOS, inducible nitric oxide synthase; JNK, JUN amino-terminal kinase; K_v, voltage-gated K^+ channel; LA, left atrial; LPS, lipopolysaccharide; LVEF, left ventricular ejection fraction; MDA, malondialdehyde; MMP, matrix metalloproteinase; NCX1, sodium–calcium exchanger 1; NO, nitric oxide; ROS, reactive oxygen species; RYR2, ryanodine receptor 2; SERCA2A, sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2A; αSMA, α-smooth muscle actin; TGFβ1, transforming growth factor-β1; TIMP, tissue inhibitor of matrix metalloproteinases; TLR4, Toll-like receptor 4; TNF, tumour necrosis factor; TRPV4, transient receptor potential cation channel subfamily V member 4.

triggered activity[47]. Atrial structural remodelling in these animal models is characterized by myolysis[39,48] and interstitial fibrosis[38–41,44–46,48–50]. In a rat model of chronic autoimmune myocarditis, increased susceptibility to AF was associated with increased left atrial size, cardiomyocyte hypertrophy and interstitial fibrosis together with reduced connexin 43 expression[51]. However, AF inducibility was not significantly increased in the acute phase[51].

The NLRP3 inflammasome system. The production of pro-inflammatory cytokines central to inflammatory signalling is mainly controlled by the inflammasome, an intracellular multiprotein complex that functions as a molecular platform to activate the cysteine protease caspase 1 (FIG. 1), which subsequently cleaves pro-IL-1β and pro-IL-18 to generate pro-inflammatory IL-1β and IL-18. Although IL-1α triggers similar pro-inflammatory signalling to IL-1β and IL-18, IL-1α is produced in the active form and functions like an alarmin[52]. Inflammasome formation is initiated by PAMPs or DAMPs[53], which are recognized by specific pattern-recognition receptors expressed in innate immune cells, such as macrophages and neutrophils, and in cardiac cells, including cardiomyocytes[54] (FIG. 1). Pattern-recognition receptors can promote the formation of many inflammasomes, but NACHT-, LRR- and pyrin domain-containing 3 (NLRP3) is the main inflammasome linked to the pathology and progression of cardiovascular disease[53,55,56]. Extensive evidence shows that the adaptive immune response induced by NLRP3 inflammasome activation is involved in arrhythmogenesis, as discussed in detail below.

The NLRP3 inflammasome comprises the sensor NLRP3, the adaptor protein ASC and the effector pro-caspase 1 (FIG. 1). The leucine-rich repeats (LRR) domain in the carboxy terminus of NLRP3 controls ligand sensing and autoregulation. The pyrin domain (PYD) in the amino terminus mediates the protein–protein interaction with the PYD of ASC. ASC recruits pro-caspase 1 via a caspase recruitment domain (CARD)[57,58]. Under basal conditions, NLRP3 resides in the endoplasmic reticulum[59,60] and is in an inactive, ubiquitinated state until a priming signal induces deubiquitination[61]. ASC is predominantly located in the nucleus, but it can shuttle to the cytosol in close association with mitochondria[59,60,62]. ASC forms 1–2 μm structures called specks, which can leave the cell as large insoluble aggregates and propagate the inflammatory signal in phagocytic cells[63,64].

The activation of the NLRP3 inflammasome requires two steps. The first step is 'priming' (which upregulates the expression of key inflammasome components and associated cytokines, typically via transcriptional activation) and the second step is 'triggering' (assembly and activation of the NLRP3 inflammasome). NLRP3 inflammasome priming involves transcriptional activation via Toll-like receptors (TLRs), tumour necrosis factor receptors (TNFRs), IL-1 receptors (IL-1Rs), angiotensin II receptors and/or protease-activated receptor 4, which stimulate the nuclear factor-κB (NF-κB) transcription pathway[65–67] (FIG. 1). Non-transcriptional priming can occur through TLR and IL-1R type 1 (IL-1R1), which accelerate the deubiquitination of NLRP3, a process dependent on mitochondrial reactive oxygen species (ROS) production[68]. NF-κB also leads to deubiquitination of NLRP3 through the deubiquitinating enzyme BRCC3 (REF.[61]). Depending on the mechanisms of priming (transcriptional or non-transcriptional), increased expression of inflammasome components requires from 10–30 min to >3 h[69–71].

The triggering signal promotes the assembly of the sensor and effector proteins, facilitated by ASC, in a wheel-shaped hub that promotes the formation of the catalytically active caspase 1 in the centre of the NLRP3 inflammasome propeller[72]. Triggers of the NLRP3 inflammasome system that have been characterized in immunocompetent cells include ATP, urate crystals, cholesterol crystals, silica, ion flux (such as K^+ efflux, Ca^{2+} fluxes and Na^+ influx), mitochondrial dysfunction, excess ROS production, and lysosomal damage leading to cathepsin B release[68,73,74]. The spatial organization of NLRP3 inflammasome assembly is driven by the microtubule network[60,75]. The serine–threonine kinase NEK7 regulates NLRP3 inflammasome assembly, functioning downstream of K^+ efflux[76,77]. Ca^{2+} signalling is also required for NLRP3 inflammasome triggering[78]. In immune cells, the Ca^{2+}-sensing receptor can be sensitized by increasing extracellular Ca^{2+} levels to increase Ca^{2+} influx[79] (FIG. 1). Influx of Ca^{2+} via the transient receptor potential channels TRPM2 (REF.[80]), TRPM7 (REF.[81]) and TRPV2 (REF.[81]) also triggers NLRP3 inflammasome assembly.

In non-excitable cells, the inositol 1,4,5-trisphosphate receptor (IP_3R) is the main Ca^{2+} release channel from the endoplasmic reticulum[79]. Inhibition of IP_3R by 2-aminoethyl diphenylborinate reduces intracellular Ca^{2+} concentration and prevents IL-1β secretion in macrophages[74,79]. Ca^{2+} can also facilitate the interaction between NLRP3 and ASC[79], and increases in cytosolic Ca^{2+} levels can lead to mitochondrial Ca^{2+} overload and the generation of mitochondria-derived ROS, with subsequent NLRP3 inflammasome activation[78,82].

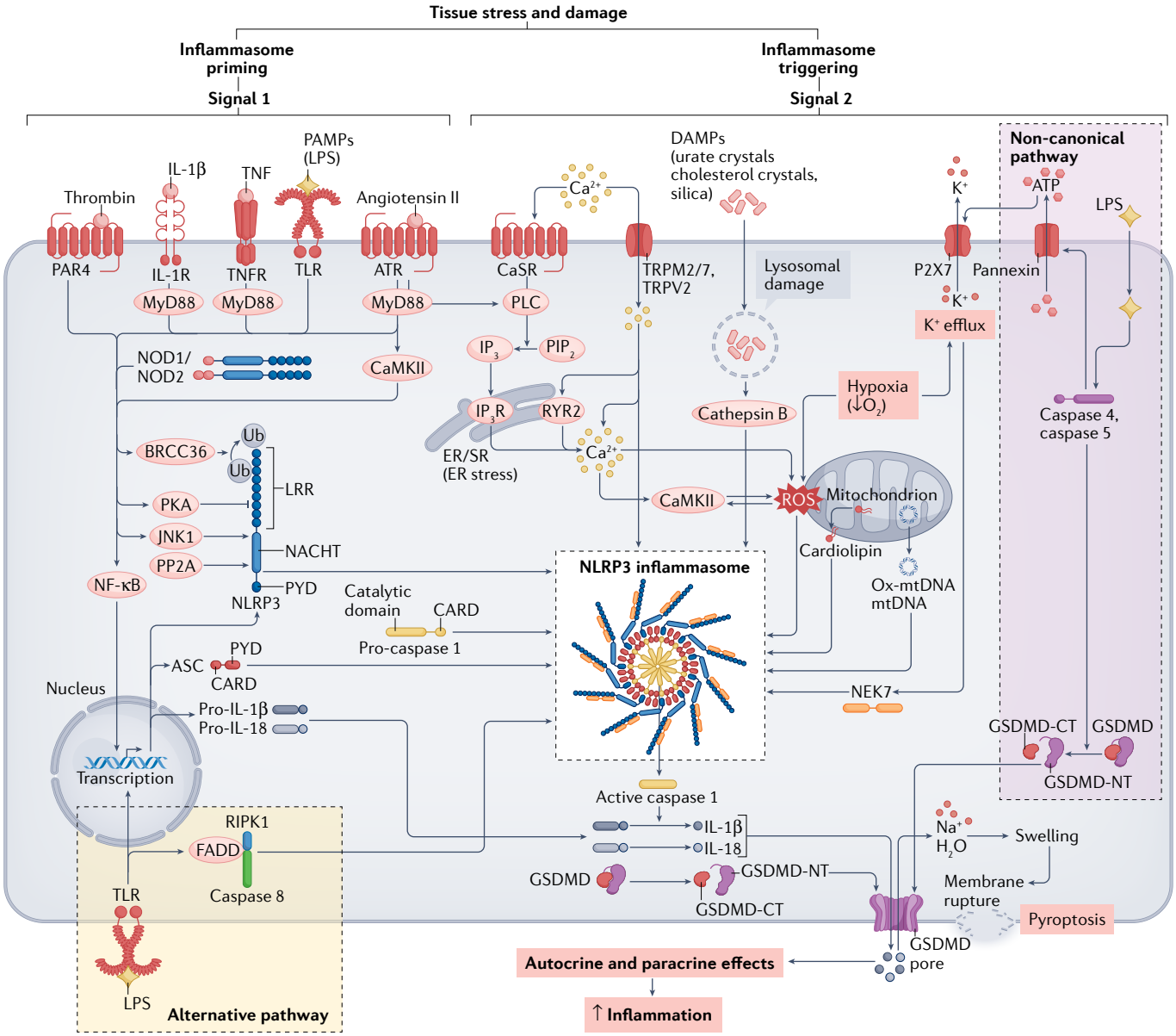

Fig. 1 | **Pathways involved in NLRP3 inflammasome activation.** Molecular pathways involved in NLRP3 inflammasome activation on the basis of information from classic models of inflammation. NLRP3 inflammasome activation in response to tissue stress and damage involves inflammasome priming (Signal 1), leading to increased expression of the major inflammasome components (NLRP3, ASC and caspase 1), and triggering (Signal 2), promoting assembly of the NLRP3 inflammasome. Subsequent activation of caspase 1 leads to activation of several proteins including IL-1β and IL-18, as well as gasdermin D (GSDMD) and IL-1β release through pores formed by the GSDMD amino terminus (NT) fragment. ATR, angiotensin receptor; BRCC36, Lys-63-specific deubiquitinase 36; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CARD, caspase recruitment domain; CaSR, calcium-sensing receptor; DAMP, damage-associated molecular pattern; ER, endoplasmic reticulum; FADD, FAS-associated death domain protein; GSDMD-CT, gasdermin D carboxy terminus; IL-1R, IL-1 receptor type 1; IP_3, inositol 1,4,5-trisphosphate; IP_3R, inositol 1,4,5-trisphosphate receptor; JNK, JUN N-terminal kinase 1; LPS, lipopolysaccharide; LRR, leucine-rich repeat; mtDNA, mitochondrial DNA; MyD88, myeloid differentiation primary response protein 88; NEK7, NIMA related kinase 7; NF-κB, nuclear factor-κB; NLRP3, NACHT-, LRR- and pyrin domain-containing 3; NOD, nucleotide-binding oligomerization domain-containing protein; Ox-mtDNA, oxidized mitochondrial DNA; P2X7, P2X purinoceptor 7; PAMP, pathogen-associated molecular pattern; PAR4, proteinase-activated receptor 4; PIP_2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PLC, phospholipase C; PP2A, protein phosphatase 2A; PYD, pyrin domain; ROS, reactive oxygen species; RIPK1, receptor-interacting serine/threonine-protein kinase 1; RYR2, ryanodine receptor 2; SR, sarcoplasmic reticulum; TLR, Toll-like receptor; TNF, tumour necrosis factor; TNFR, tumour necrosis factor receptor; TRP, transient receptor potential; Ub, ubiquitin.

Endoplasmic reticulum stress, partially caused by Ca^{2+} dysregulation, also triggers NLRP3 inflammasome assembly[83]. Mitochondrial recruitment of NLRP3 to the inner mitochondrial membrane, where it interacts with the mitochondrial protein cardiolipin, is followed by relocation from the inner to the outer mitochondrial membrane, promoting the interaction between NLRP3 and caspase 1 (REF.[84]) and NLRP3 inflammasome assembly. Multiple post-translational modifications (such as ubiquitination and phosphorylation) and endogenous modulators (such as CARD-only proteins and pyrin-only proteins) also regulate the activity of the NLRP3 inflammasome[85]. The regulation of NLRP3 activity is very complex and varies according to the type of cell and activating stimuli.

When the NLRP3 inflammasome is activated, caspase 1 triggers the cleavage of the inactive isoforms pro-IL-1β and pro-IL-18, releasing active IL-1β and IL-18. Caspase 1 also cleaves gasdermin D (GSDMD), removing its inhibiting C terminus (GSDMD-CT) and releasing the N terminus (GSDMD-NT), which forms pores in the plasma membrane (FIG. 1). These pores allow the products of the inflammasome cascade (such as IL-1β and IL-18) to leave the cell and propagate the activation of inflammatory signalling cascades to neighbouring cells[86]. The secretion of cytokines can be accompanied by inflammatory programmed cell death called pyroptosis. These effects can be mediated via caspase 1, known as the canonical NLRP3 pathway, or caspase 4 and caspase 5 (in humans; caspase 11 in mice), known as the non-canonical NLRP3 pathway.

Activation of the canonical NLRP3 inflammasome pathway in immune cells is mediated by cellular K^+ depletion[87]. Pore formation via P2X purinoceptor 7 (P2X7), pannexin 1 channels or other pore-forming subunits allows K^+ efflux (FIG. 1). Pannexin 1 channels release ATP, which rapidly opens P2X7, causing K^+ efflux[88] and NLRP3 inflammasome activation via the canonical pathway.

The non-canonical NLRP3 inflammasome pathway involves cleavage of caspase 4 and caspase 5 (REFS.[59,89,90]) (FIG. 1), which recognize strong LPS signals via their CARD domain and cleave GSDMD[59], leading to the formation of GSDMD-NT pores in the plasma membrane. Caspase 4 and caspase 5 are unique in terms of their very high selectivity for GSDMD, but cannot directly produce active cytokines from inactive precursors[91]. Caspase 4 and caspase 5 can also cleave pannexin 1 after LPS stimulation, causing ATP release with subsequent P2X7 activation and non-canonical NLRP3 inflammasome activation[92,93]. Triggering of NLRP3 inflammasome activation does not absolutely require K^+ depletion and seems to be independent of K^+ in human monocytes in vitro[94]. This alternative NLRP3 activation is mediated by the TRIF–RIPK1–FADD–caspase 8 pathway, and the release of IL-1β is much weaker than via canonical activation[92]. Caspase 8 suppresses RIPK3 activation, which participates in signalling processes leading to apoptosis[95]. Pathogens can facilitate the release of caspase 8-mediated suppression of RIPK3, increasing the generation of mitochondrial ROS that can activate the NLRP3 inflammasome[95].

GSDMD pore formation can lead to inflammatory cell death or pyroptosis. The cell swelling, cell membrane disruption and release of cytoplasmic contents (including cytokines) that occur during pyroptosis can cause tissue damage, organ failure and shock[96,97]. Pyroptosis is primarily executed by caspase 4/caspase 5-mediated GSDMD cleavage with subsequent GSDMD-NT pore formation and cell membrane permeabilization[98,99]. IL-1β release mediated by canonical NLRP3 inflammasome activation can occur in the absence of pyroptosis[100], which is likely to be the predominant mechanism in terminally differentiated cells such as cardiomyocytes.

Inflammatory signalling in heart disease

AF is promoted by numerous cardiovascular diseases and risk factors, several of which have been associated with activation of the NLRP3 inflammasome, as summarized below and illustrated in FIG. 2. A more detailed overview of the role of NLRP3 inflammasome activation in other cardiovascular diseases has been provided in previous reviews[101–104].

Acute myocardial infarction (MI) is a common trigger of AF[1]. The NLRP3 inflammasome is directly activated by intraplaque cholesterol crystals through leakage of the lysosomal protease cathepsin B[105]. NLRP3 is the predominant component of the inflammasome involved in the response to sterile injury, as occurs during acute MI[101]. Necrotic cell death releases cell contents, including several DAMPs, priming the NLRP3 inflammasome via activation of NF-κB[102]. In parallel, ischaemia-induced reductions in intracellular K^+ levels act as a trigger for NLRP3 inflammasome activation[102]. The important role of NLRP3 inflammasome activation and subsequent pyroptosis in MI is supported by numerous preclinical studies showing smaller infarct sizes after ischaemia–reperfusion in mice with genetic deletion of NLRP3, IL-1R1, ASC or caspase 1 compared with wild-type mice, as well as with small interfering RNA-mediated or pharmacological inhibition of NLRP3 (summarized previously[102]) or P2X7 (REF.[106]) after the ischaemic insult. Although the NLRP3 system activation induced by ischaemia–reperfusion injury was initially shown to occur preferentially in cardiac fibroblasts (versus cardiomyocytes) in mice[107], subsequent work clearly showed that the NLRP3 system is activated in both mouse ventricular and atrial cardiomyocytes[106,108]. Data on the clinical role of the NLRP3 inflammasome in MI are scarce and largely based on biomarkers or indirect evidence from clinical trials using non-selective NLRP3 inhibitors or IL-1 blockers[101]. For example, colchicine treatment significantly reduced infarct size (measured as the area under the curve for biomarkers of necrosis or by cardiac MRI) in patients with ST-segment elevation acute MI compared with placebo[109].

Inflammation is increasingly recognized as an important pathophysiological mediator of HF initiation and progression[104], which is a major driver of AF-promoting atrial remodelling. IL-1β directly inhibits cardiac contractility[102], in part as a result of alterations in cardiomyocyte Ca^{2+} handling, which can simultaneously promote cardiac arrhythmias[110]. Inhibition of NLRP3 inflammasome activation or downstream IL-1β

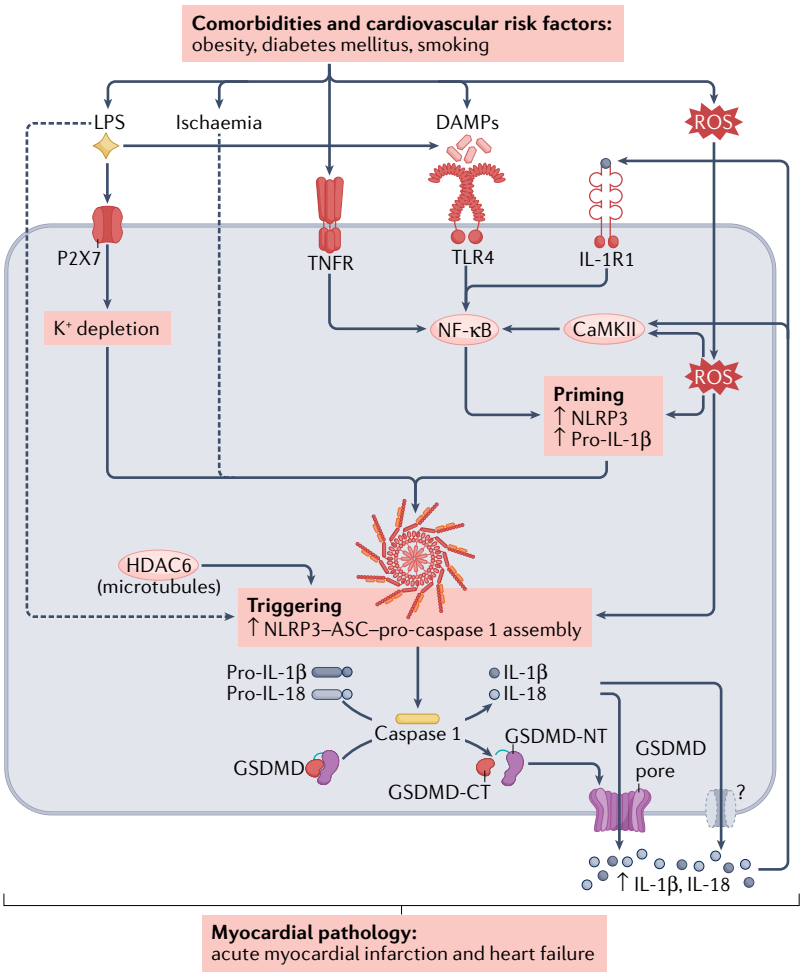

Fig. 2 | **Pathways leading to NLRP3 inflammasome activation induced by comorbidities and cardiovascular risk factors.** Main pathways through which risk factors, heart diseases and comorbidities can promote NLRP3 inflammasome activation, potentially leading to atrial fibrillation and contributing to myocardial pathology in conditions such as acute myocardial infarction and heart failure. Risk factors, including gut microbiota dysbiosis, obesity, diabetes mellitus, right heart disease and coronary artery disease, promote the production of several mediators that activate transmembrane receptors involved in NLRP3 inflammasome priming, including Toll-like receptor 4 (TLR4), tumour necrosis factor receptors (TNFRs) and IL-1 receptor type 1 (IL-1R1), as well as downstream activation of signalling pathways dependent on Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), reactive oxygen species (ROS) and nuclear factor-κB (NF-κB). Assembly of inflammasome components (triggering) is mediated, among other pathways, by P2X purinoceptor 7 (P2X7) signalling and K^+ depletion, as well as histone deacetylase 6 (HDAC6). Downstream activation of caspase 1 and formation of pores by the gasdermin D (GSDMD) amino terminus (NT) fragment subsequently allows the release of IL-1β and IL-18 from the cell. In parallel, these pathways promote pro-arrhythmic atrial remodelling, including spontaneous Ca^{2+} release events, delayed afterdepolarizations and triggered activity, as well as re-entry-promoting shortening of action potential duration and effective refractory period in combination with structural remodelling and associated conduction abnormalities. Dashed arrows indicate indirect effects. DAMP, damage-associated molecular pattern; GSDMD-CT, gasdermin D carboxy terminus; LPS, lipopolysaccharide; NLRP3, NACHT-, LRR- and pyrin domain-containing 3.

signalling reduces adverse cardiac remodelling and ameliorates the HF phenotype in preclinical models of HF induced by MI without reperfusion, transverse aortic constriction leading to pressure overload, anthracycline toxicity, radiation injury or septic cardiomyopathy[102]. Moreover, data from rodent models of HF with reduced or preserved ejection fraction suggest that the beneficial cardiac effects of empagliflozin are associated with reduced activation of the NLRP3 inflammasome through a Ca^{2+}-dependent mechanism[111].

In addition, AF risk factors such as smoking[1] are associated with increased NLRP3 activation[112]. Taken together, substantial evidence indicates a causative role of NLRP3 inflammasome activation, including in cardiomyocytes, in cardiovascular diseases associated with AF, ranging from stable coronary artery disease to acute MI and HF.

Atrial cardiomyocyte inflammatory signalling and AF

Inflammatory signalling component expression in atrial cardiomyocytes and AF. Although inflammatory signalling pathways are extensively studied in immune cells, emerging evidence supports the notion that atrial cardiomyocytes have the same inflammatory signalling pathways, the activation of which contributes to AF development[33,106,110,113]. Atrial cardiomyocytes not only produce potent pro-inflammatory cytokines such as IL-1β, IL-6, IL-18 and TNF, but also express the cytokine receptors (IL-1R1, IL-6R, IL-18R and TNFR) that mediate the effects of these inflammatory cytokines[106,110,114–116]. Activation of these cytokine receptors via autocrine or paracrine mechanisms stimulates several important AF-related signalling cascades, including those involving JAKs, STATs, MAPKs and NF-κB, which can in turn upregulate the transcription of genes encoding pro-inflammatory factors. Many stressors that increase the susceptibility to AF, such as ROS and endoplasmic reticulum stress[68,83], can independently activate these signalling pathways, further amplifying the inflammatory signal and its propagation.

Accumulating evidence also indicates the engagement of the NLRP3 inflammasome in atrial cardiomyocytes. In the mouse atria-derived cardiomyocyte cell line HL-1, in vitro priming with LPS and triggering with ATP or nigericin promoted the formation of ASC aggregates[106]. These changes were accompanied by increased caspase 1 activity and caspase 1-mediated pyroptosis, both of which are prevented by caspase 1 inhibition[106]. These results demonstrate that canonical NLRP3 inflammasome activation is operative in atrial cardiomyocytes. In addition, pharmacological inhibition of P2X7 mimics the results obtained with caspase 1 inhibition[106], suggesting that increased K^+ efflux via P2X7 contributes to cardiomyocyte NLRP3 inflammasome activation. Simulated ischaemia in cardiomyocytes in vitro caused by exposure to hypoxia and an 'ischaemic' buffer similarly promoted the formation of ASC aggregates and increased caspase 1 activity, pointing to activation of the NLRP3 inflammasome in atrial cardiomyocytes in ischaemic conditions[106]. In vitro tachypacing of HL-1 cells (to mimic the atrial tachycardia that occurs during AF) increased the polarization and migration of co-cultured macrophages, features that are typically associated with inflammatory settings[33]. Conversely, LPS-treated macrophages caused IL-1β-mediated reduction of $I_{Ca,L}$ in co-cultured HL-1 cells[33]. These data establish the potential for feedforward crosstalk between atrial cardiomyocytes and immune cells in the atria.

Evidence for a role of atrial cardiomyocyte inflammatory signalling in AF. Several studies have assessed the specific contributions to AF pathophysiology of the pro-inflammatory cytokine TNF, the IL-1β-maturation platform and the NLRP3 inflammasome[113,117–119]. Transgenic mice with cardiomyocyte-specific overexpression of TNF have enlarged atria, atrial fibrosis and abnormal atrial conduction together with downregulation of atrial connexin 40 levels, reduced atrial contractility and increased susceptibility to pacing-induced AF[120,121]. Conversely, genetic ablation of TNF or pharmacological inhibition of TNF with etanercept or a dominant-negative inhibitor of the soluble form of TNF (XPro1595) prevented exercise-induced adverse atrial remodelling and AF promotion in mice[117,118]. TNF-induced atrial arrhythmogenesis in mice is at least partly attributable to abnormalities in cardiomyocyte Ca^{2+} handling, including a higher frequency of triggered activity-promoting Ca^{2+} release events[117,118,120]. In vitro exposure of rabbit pulmonary vein cardiomyocytes to TNF for up to 10 h reduced $I_{Ca,L}$, led to larger amplitude DADs together with increased transient inward current and Na^+–Ca^{2+}-exchanger current, and increased diastolic Ca^{2+} levels, while reducing Ca^{2+} transient amplitude and sarcoplasmic reticulum Ca^{2+} content, and potentially causing AF-promoting triggered activity in the pulmonary vein cardiomyocyte sleeves[122].

Human atrial cardiomyocytes have all the key elements of the NLRP3 inflammasome system[110,113]. Most importantly, NLRP3 inflammasome activity is increased in atrial cardiomyocytes in patients with paroxysmal AF or long-lasting persistent AF[113]. Similarly, levels of ASC and pro-caspase 1, as well as the products of NLRP3 inflammasome activation, active caspase 1 and cleaved (pore-forming) GSDMD-NT, were significantly increased in atrial cardiomyocytes of patients undergoing cardiac surgery who subsequently developed postoperative AF compared with patients who remained in sinus rhythm[110]. These data suggest that NLRP3 inflammasome activation in atrial cardiomyocytes might be a common feature of many forms of AF.

The potential pathophysiological role of increased NLRP3 activity in atrial cardiomyocytes from patients with AF has been addressed by studies in animal models. Mice with cardiomyocyte-specific overexpression of a constitutively active form of NLRP3 (*Myh6:Nlrp3*$^{A350V/+}$; CM-KI mice) develop atrial ectopy and a re-entry-promoting shortening of atrial refractoriness, together with atrial hypertrophy and fibrosis, associated with increased AF susceptibility[113]. These mice have substantially increased prevalence of spontaneous atrial ectopic activity, associated with an increased incidence of Ca^{2+}-release events through RYR2 channels (Ca^{2+} sparks). The shortening of the atrial action potential duration and effective refractory period in CM-KI mice is likely to be due to upregulation of the expression of *Kcna5* (which encodes the voltage-gated K^+ channel $K_v1.5$) and the increase in the related repolarizing current I_{Kur} (ultra-rapid delayed rectifier K^+ current)[113]. Although overall conduction velocity is unchanged, CM-KI mice have atrial fibrosis[113], which is known to be associated with atrial arrhythmogenesis.

Atrial macrophage infiltration occurs in patients with AF[33,123], possibly as a result of NLRP3 inflammasome activation and IL-1β and IL-18 signalling in atrial cardiomyocytes, with subsequent macrophage recruitment to the atria. The released IL-1β (and perhaps IL-18) acts on adjacent cells causing NF-κB-mediated transcriptional priming of NLRP3-components in the same and other cell types, thereby potentially leading to further NLRP3 inflammasome activation in surrounding cells, irrespective of the initial source. Acute application of IL-1β to human atrial cardiomyocytes in vitro increases the incidence of Ca^{2+} release events, particularly in cells from patients prone to develop postoperative AF[110]. Similarly, acute application of IL-1β increases the incidence of Ca^{2+} release events in HL-1 cells[110], accompanied by increased CaMKII-mediated phosphorylation of RYR2 (which is an established molecular contributor to Ca^{2+} release events and AF[36,37]) together with activation of caspase 1 and the formation of pore-forming GSDMD-NT[110].

The effects of IL-1β on Ca^{2+} handling are likely to be amplified by IL-6 (REF.[46]). IL-6 also rapidly induces reversible atrial electrical remodelling by downregulation of atrial connexin levels in HL-1 cells[124]. However, the precise actions of IL-6 in the atria require further delineation. Similarly, although the activation of caspase 1 in AF is expected to increase the atrial levels of IL-18, the relative contribution of IL-18 to the actions of IL-1β in the atria is unknown. In addition, whether IL-18 acts on the atria via mechanisms different from those of IL-1β is unclear. Given that selective IL-18 inhibitors are clinically available, future work should define the atrial effects of IL-18 and the therapeutic potential of IL-18 inhibition for AF management.

Histone deacetylase 6 (HDAC6) has an indispensable role in the microtubule transport and assembly of inflammasomes in macrophages[60,75]. HDAC6 activity increases with AF-related atrial remodelling in patients as well as in HL-1 cells subjected to in vitro high-frequency pacing[125]. Therefore, HDAC6 activation could contribute to Ca^{2+}-dependent NLRP3 inflammasome activation. Ca^{2+}-dependent activation of CaMKII in cardiomyocytes seems to contribute to NLRP3 inflammasome activation because in mouse models of cardiac remodelling induced by chronic angiotensin II infusion or transverse aortic constriction, cardiomyocyte-specific deficiency of CaMKII suppresses NLRP3 inflammasome activation[66,126]. This observation is consistent with findings that CaMKIIδ can activate NF-κB by phosphorylating (inactivating) the inhibitor of NF-κB (IκB kinase)[127,128], thereby upregulating the transcription of multiple genes encoding NLRP3 inflammasome components. CaMKII can also increase mitochondrial Ca^{2+} entry via phosphorylation of the mitochondrial Ca^{2+} uniporter, which increases ROS production[129], a key trigger of NLRP3 inflammasome activation and AF promotion[130]. Therefore, NLRP3 inflammasome-mediated CaMKII activation in atrial cardiomyocytes might produce Ca^{2+} leak from the sarcoplasmic reticulum and drive mitochondrial ROS production, creating a vicious cycle of arrhythmogenic inflammatory signalling.

Several known risk factors for AF such as obesity, diabetes mellitus, gut microbiota dysbiosis and right-sided

heart disease can promote AF development via activation of inflammatory signalling in atrial cardiomyocytes[131,132]. Although the inflammatory signalling associated with risk factors is subtle compared with the more aggressive, well-recognized inflammation inducers such as acute tissue injury and pathogens, the chronic nature of risk factors could lead to substantial effects over the course of a lifetime. The activity of NLRP3 inflammasomes in atrial tissue of individuals with obesity correlates with increases in BMI[119]. In animal models of diet-induced obesity, increased atrial NLRP3 activity is required for obesity-induced atrial arrhythmogenesis[119]. Cardiomyocyte Ca^{2+} dysregulation, increased frequency of Ca^{2+} release events and atrial ectopy are key elements of the arrhythmogenic atrial substrate in obesity-driven AF in these animal models[119].

Gut microbiota dysbiosis is also associated with upregulation of the NLRP3 system in the atria in mouse models[131], with some gut microbiota-derived metabolites having direct effects on atrial arrhythmogenesis. For example, trimethylamine *N*-oxide (TMAO) upregulates NF-κB signalling, which leads to increased abundance of pro-inflammatory cytokines, including IL-1β, IL-6 and TNF, and synthesis of nerve growth factor in atrial ganglionated plexi, which activate the cardiac autonomic nervous system[131]. TMAO also causes oxidative stress and activates the NLRP3 inflammasome and the transforming growth factor-β1 (TGFβ1)–SMAD3 pathway in ganglion plexus tissues in animal models[133]. Gut microbiota dysbiosis-derived LPS strongly activates the NLRP3 inflammasome, increases the expression and lateralization of connexin 43 and downregulates L-type Ca^{2+} channel expression[131]. Similarly, NLRP3 activity is increased in the right atria of patients with diabetes mellitus[67]. NLRP3 protein levels and caspase 1 activity in atrial tissue and serum IL-1β and IL-18 levels are increased in rabbits with alloxan-induced diabetes mellitus[134]. In this rabbit model, administration of glibenclamide (a hypoglycaemic agent that inhibits the NLRP3 inflammasome) reduces the diabetes-induced atrial structural remodelling and the related increases in AF inducibility[134].

Right-sided heart disease is increasingly recognized as an important cause of AF[135,136]. In a rat model of right-sided heart disease induced by monocrotaline injection[135,137], AF promotion was associated with increased expression of NLRP3 inflammasome-related components in the right atria, as evidenced by increased levels of active caspase 1 and IL-1β[137].

Inflammatory signalling in non-myocyte heart cells

During sepsis, the NLRP3 inflammasome system is upregulated in mouse ventricular fibroblasts[138]. Cardiac dysfunction after MI in mice is also associated with upregulation of the NLRP3 inflammasome in ventricular fibroblasts[107,108], with the major trigger of NLRP3 inflammasome activation being increased K^+ efflux caused by ROS generation[107]. Similarly, in vitro treatment of mouse ventricular fibroblasts with LPS[138] or human ventricular fibroblasts with thrombin[67] activates the NLRP3 system, with increased secretion of IL-1β. These results support the notion that the NLRP3 inflammasome is activated in fibroblasts during cardiac injury.

Application of TNF to human cultured atrial fibroblasts from patients undergoing open heart surgery increased the expression and release of IL-6 and IL-1β via activation of TNFRs, with subsequent stimulation of p38–MAPK, PI3K–AKT and NF-κB signalling[139], pointing to the production and functional regulation of pro-inflammatory cytokines in atrial fibroblasts. Similar increases in pro-inflammatory signalling were also noted after stimulation of human atrial fibroblasts with IL-1α[52] and TGFβ1 (REF.[140]), together with downstream activation of pro-fibrotic signalling[140]. Abnormal inflammatory signalling in atrial fibroblasts has been implicated in AF development[141]. The AF-associated human variant p.Ile138Thr of *NPPA* (which encodes atrial natriuretic peptide) induced atrial inflammation and atrial fibrosis, causing both inducible and spontaneous AF, in a knock-in rat model[141]. RNA sequencing of *Nppa*-mutant rat atrial fibroblasts showed that the largest differences in expression were in genes related to TNF, NF-κB and NLRP3 signalling[141]. These data point to a role of atrial fibroblast inflammatory signalling in AF.

Obesity contributes to AF pathophysiology[142]. The highly secretory epicardial adipose tissue (EAT) surrounding the atria secrete a variety of pro-inflammatory and pro-fibrotic mediators that promote atrial remodelling, thereby increasing the susceptibility to AF[142]. EAT volume correlates with AF severity, postoperative AF incidence and AF recurrence rates after cardioversion or ablation[143]. In addition, EAT from patients with AF shows strong pro-inflammatory indices, as evidenced by a higher ^{18}F-fluorodeoxyglucose PET signal intensity than that of EAT from patients without AF[144]. Extracellular vesicles derived from EAT from patients with AF contain larger amounts of pro-inflammatory and pro-fibrotic cytokines than EAT from control patients[145]. Extracellular vesicles derived from EAT from patients with AF induced sustained re-entry in human induced pluripotent stem cell-derived cardiomyocytes in vitro, whereas extracellular vesicles from EAT from control patients had no effect[145]. Therefore, the NLRP3 system in atrial adipocytes might constitute an important source of pro-inflammatory cytokines, a hypothesis that requires direct evaluation.

Resolution of inflammation in AF

Concept of inflammation resolution. Under physiological conditions, reparative inflammation is a complex and active process characterized by an initiation phase and a resolution phase, promoting healing and restoration of homeostasis[146] (FIG. 3). The resolution of inflammation has traditionally been considered a passive process occurring when the stimulus to inflammation is no longer active. However, the discovery in the 1980s of the capacity of arachidonic acid derivatives, such as lipoxins and resolvins, to promote the resolution of inflammation led to a consensus that inflammation resolution is an active process following acute inflammation[147]. After infection or injury, the initiation of inflammation is followed by an augmentation of resolution-promoting signalling, arresting polymorphonuclear leukocyte (PMN)

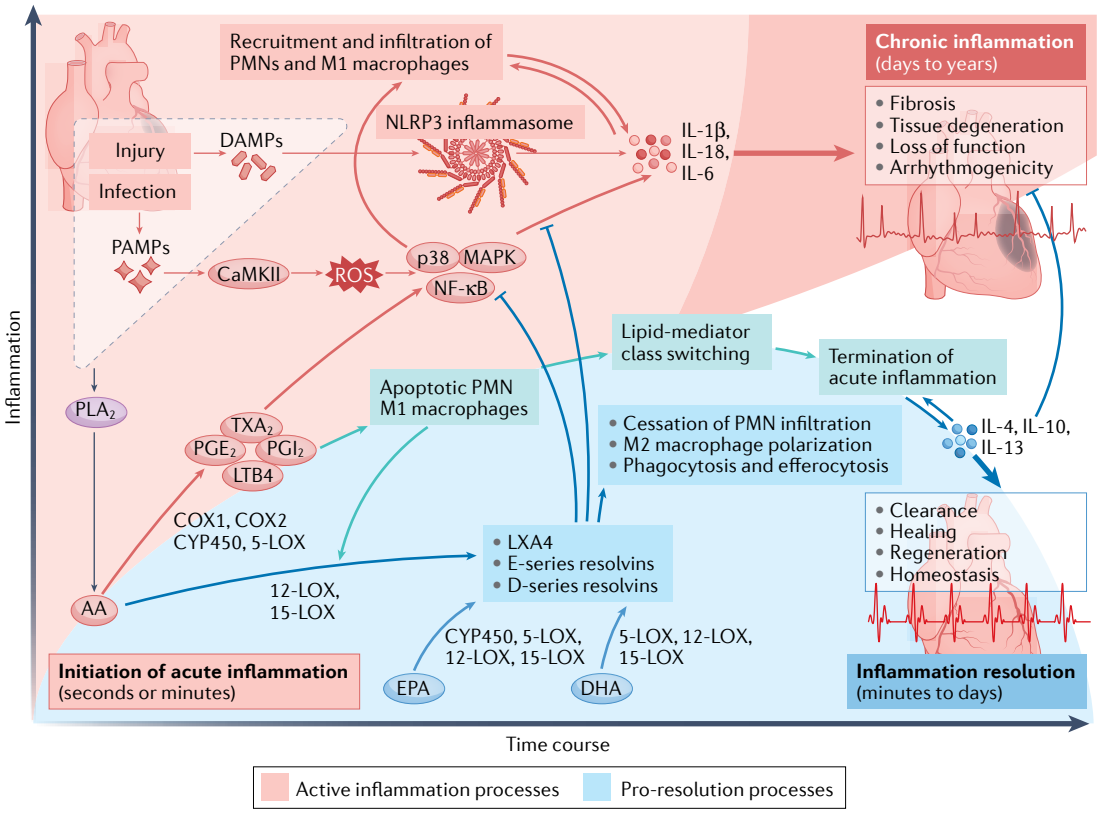

Fig. 3 | **Inflammation resolution concept.** In response to injury or infection, acute inflammation is activated to favour the return to homeostasis. During the initiation phase, damage signals (pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) promote phospholipase A_2 (PLA_2)-induced accumulation of arachidonic acid (AA), activation of the nuclear factor-κB (NF-κB) pathway and assembly of the NLRP3 inflammasome, leading to the release of pro-inflammatory substances, recruitment of polymorphonuclear leukocytes (PMNs) and monocyte polarization towards pro-inflammatory M1 macrophages. Apoptotic PMNs and M1 macrophages secrete 12-lipoxygenase (12-LOX) and 15-LOX, which triggers lipid-mediator class switching, signalled by increased production of resolution-promoting mediators from AA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Pro-resolution autacoids orchestrate the inhibition of PMN infiltration, the increased release of anti-inflammatory cytokines (IL-10 and IL-13) and increased macrophage polarization to anti-inflammatory M2 macrophages to phagocytize damaged cells. Inflammation resolution is characterized by efferocytosis, tissue repair, wound healing, preservation of functions and homeostasis. Failed resolution of inflammation is associated with dysfunctional triggering of lipid-mediator class switching, perpetuation of production and secretion of pro-inflammatory mediators (IL-1β, IL-6 and IL-18), aggravation and chronicity of the inflammatory status, development of fibrosis, myocardial damage, loss of myocardial function and arrhythmogenesis. CaMKII, calcium/calmodulin-dependent kinase II; COX, cyclooxygenase; CYP450, cytochrome P450; LTB4, leukotriene B4, LXA4, lipoxin A4; MAPK, mitogen-activated protein kinase; NLRP3, NACHT-, LRR- and pyrin domain-containing 3; PGE_2, prostaglandin E_2; PGI_2, prostaglandin I_2; ROS, reactive oxygen species; TXA_2, thromboxane A_2.

recruitment and suppressing pro-inflammatory signalling[148]. The active process of inflammation resolution involves specific enzymes (cytochrome P450, cyclooxygenase 1 (COX1), COX2, 5-lipoxygenase (5-LOX), 12-LOX and 15-LOX), endogenous lipid mediators (prostaglandins, leukotrienes, lipoxins and resolvins), cytokines (IL-10 and IL-13), immune cells (monocytes, anti-inflammatory M2 macrophages and dendritic cells) and biological processes designed to terminate acute inflammation, promote clearance of inflammatory cells and restore normal tissue and organ function[147–150]. Failure to undergo the complex shift from initial inflammatory signalling to pro-resolution signalling can contribute to abnormal accumulation of pro-inflammatory mediators and biomarkers (prostaglandins, leukotrienes, NF-κB, NLRP3 inflammasome, IL-1β, PMNs and pro-inflammatory M1 macrophages), which leads to chronic, unresolved inflammation, tissue fibrosis and impaired function[151] (FIG. 3 and TABLE 3).

Endogenous pro-resolution biochemistry. In response to pathological insults or infection by viral or bacterial pathogens, phospholipase A_2 accumulates in the affected tissue. This enzyme hydrolyses the *sn*-2 ester bond of cellular phospholipids to produce arachidonic acid, an essential n-6 polyunsaturated fatty acid (n-6 PUFA)[152]. Arachidonic acid is metabolized by cytochrome P450, COX1, COX2 and 5-LOX to produce numerous pro-inflammatory lipid mediators (thromboxane A_2, prostaglandin A_2 (PGA_2), PGB_2, PGE_2 and PGI_2) that activate pro-inflammatory signalling promoting PMN and M1 macrophage chemotaxis (NLRP3 inflammasome, IL-1β, IL-6, CXC chemokine ligand 1 (CXCL1)

Table 3 | **Anti-inflammatory therapeutics**

Agent	Specific targets	Beneficial effects	Limitations or adverse effects	Refs.
COX inhibitors	COX1 and COX2	Suppress the production of arachidonic acid metabolites (prostaglandins, leukotrienes, thromboxane A_2) Reduce NLRP3 activity, inhibit caspase 1 and prevent IL-1β secretion Reduce pain	Increase risk of clots, hypertension and cardiovascular events	173,177
Aspirin	COX1 and COX2	Irreversible acetylation of COXs Acetylated COX2 can metabolize docosahexaenoic acid and eicosapentaenoic acid Production of aspirin-triggered resolvins Restrains NLRP3 assembly and activity via blockade of reactive oxygen species release	No evidence of atrial fibrillation prevention with chronic aspirin use Not recommended for patients with low risk of cardiovascular disease	184,273
Glucocorticoids	Immune cells and pro-inflammatory biomarkers	Suppress pro-inflammatory biomarkers and activation of pro-inflammatory cells Promote clearance of apoptotic cells Reduce pain and swelling	Increase NLRP3 activation and IL-1β secretion Delay wound healing Increase the risk of hypertension Increase atrial fibrillation incidence	185
NLRP3 inhibitors	NLRP3 inflammasome components and signalling	Prevent maturation of NLRP3 components Prevent NLRP3 inflammasome assembly Reduce pro-inflammatory cytokine production Might promote lipid-mediator class switching	Further studies are required to assess the potential of NLRP3 inhibitors in inflammatory conditions and clarify their safety and potential adverse effects	195
IL-1 inhibitors	IL-1R1 and IL-1β	Prevent IL-1β interaction with its receptor IL-1R1 Inhibit IL-1β signalling Reduce IL-1β-induced production of pro-inflammatory interleukins (IL-6, IL-17, IL-18)	Increase the risk of infection Increase cholesterol plasma levels Decrease circulating leukocyte numbers Might increase the risk of cancer	102
Specialized pro-resolving mediators	Pro-inflammatory processes and immune cells	Prevent infiltration of polymorphonuclear leukocytes Activate M2 macrophage phagocytosis and clearance of cellular debris Resolvin D1 decreases atrial expression of NLRP3 components Non-toxic	Few clinical and preclinical data on cardiac tissue currently available Various clinical trials are ongoing or have been completed: NCT04575753, NCT04997057, NCT03609541, NCT04697719, NCT02322073	274–278

COX, cyclooxygenase; IL-1R1, IL-1 receptor type 1; NLRP3, NACHT-, LRR- and pyrin domain-containing 3.

and CXCL2) and the increase in adhesion molecules (intercellular adhesion molecule 1, vascular cell adhesion molecule 1 and E-selectin) at the site of injury[153–155]. During neutrophil-induced apoptotic and phagocytic activity, intracellular and secreted levels of 12-LOX and 15-LOX increase[153]. Arachidonic acid interaction with 12-LOX and 15-LOX leads to the production of lipoxins, including lipoxin A4 and LXB4, which activate the LXA4 receptor *N*-formyl peptide receptor 2 to stimulate intracellular signals that initiate pro-resolution processes such as cessation of neutrophil chemotaxis, inhibition of NF-κB signalling, alteration of NLRP3 assembly and activity, and stimulation of non-phlogistic (that is, non-inflammatory) monocyte invagination[156,157].

Shortly after the initiation of acute inflammation, the essential n-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are released at the site of injury[151]. EPA and DHA compete with arachidonic acid for cytochrome P450, COX2, 5-LOX, 12-LOX and 15-LOX[158]. EPA and DHA are metabolized to produce E-series resolvins (RvEs) and D-series resolvins (RvDs), respectively, including RvE1 and RvD1 (REFS.[158,159]). Production of anti-inflammatory PGD_2 from arachidonic acid via COX2 is also increased[159].

These bioactive lipid mediators interact with specific receptors (G protein-coupled receptor 32 (GPR32), GPR18, chemerin-like receptor 1 (ChemR23), PGD_2 receptor 1 and PGD_2 receptor 2) expressed on endothelial cells, PMNs, monocytes, macrophages, dendritic cells and T helper 2 (T_H2) cells, to stimulate the cessation of PMN chemotaxis, activation of M2 macrophage phagocytosis of apoptotic PMNs and cell debris, efferocytosis and clearance of inflammatory cells[160].

Chronic inflammation probably involves a failure of inflammation resolution[161]. If 12-LOX and 15-LOX production is insufficient, the generation of the n-3 PUFA-derived pro-resolving mediators RvEs and RvDs is inadequate[157]. Failure of resolution leads to accumulation of arachidonic acid metabolites, including thromboxanes, prostaglandins and leukotrienes, which promote pro-inflammatory signalling. In addition, continued generation of DAMPs and other inflammatory triggers contributes to inflammation persistence. The active phase of inflammation persists and chronic inflammation results, leading to thrombogenesis, formation of fibrous tissue, and loss of tissue and organ function[161,162]. Treatment with molecules that promote inflammation resolution properties ameliorates disease in animal models of chronic inflammation[137,163,164] (FIG. 3). Administration of RvD1 reduces NLRP3 inflammasome assembly by preventing the colocalization of NLRP3 with the inflammasome components ASC and pro-caspase 1 (REF.[165]).

Pathological and potential therapeutic relevance of inflammation resolution in heart disease. Evidence for a role of inflammation resolution in preventing chronic disease development is available for a range of cardiac conditions[166]. In a clinical study involving 27 patients with HF and 23 age-matched control individuals, patients with HF had significantly lower plasma levels of RvD1, together with decreased levels of the RvD1 receptor GPR32 in T cells and reduced 15-LOX activity in leukocytes[167]. In aortic valves from patients with aortic stenosis, the leukotriene B4 (LTB4) level was increased, whereas RvE1 and RvD3 levels were decreased in calcified regions compared with non-calcified regions[168]. In vitro treatment with RvE1 prevented human valvular interstitial cell calcification[168]. In addition, in *Apoe*-knockout mice that develop aortic valve disease, overexpression of the *Caenorhabditis elegans* gene *fat-1* (which encodes a protein that enables endogenous synthesis of n-3 PUFAs) increased the production of n-3 PUFA derivatives in aortic valves and reduced valvular calcification and improved echocardiographic indices of valve disease[168]. By contrast, knockout of *Cmklr1* (which encodes ChemR23) increased valve disease progression in these mice[168].

In a mouse model of experimental autoimmune myocarditis, daily injections of the LXA4 analogue BML-111 (1 mg/kg per day, starting 7 days after myocarditis induction) prevented the myocarditis-induced overexpression of inflammation-related and fibrosis-related genes, including those encoding IL-1β, TNF, TGFβ1 and collagen 1A1 (REF.[169]). In addition, BML-111 treatment prevented myocarditis-induced reductions in LV ejection fraction, LV hypertrophy and cardiomyocyte apoptosis[169]. In rats with MI induced by coronary artery ligation, treatment with RvE1 decreased infarct size, attenuated leukocyte infiltration and reduced caspase 3 levels in the infarct area[170]. In a mouse model of MI, RvD1 treatment for 5 days after MI decreased M1 macrophage recruitment to the infarct region, reduced the myocardial expression of IL-1β, IL-6 and TNF, prevented myocardial fibrosis and ameliorated LV function[171]. In a rat model of right-sided heart disease, RvD1 administration attenuated right atrial fibrosis, decreased the expression of NLRP3 inflammasome components, promoted ChemR23 expression and prevented AF inducibility[137]. All these studies support the relevance of inflammation resolution in heart disease, but this area of research requires further study.

Therapeutic implications

Therapeutic strategies targeting the NLRP3 inflammasome to reduce the consequences of inflammation can involve traditional or novel NLRP3 inhibitors, glucocorticoids or classic anti-inflammatory medications such as non-steroidal anti-inflammatory drugs, as well as novel interventions that promote inflammation resolution[172]. TABLE 3 summarizes the main categories of anti-inflammatory interventions and presents some of the potential benefits and risks associated with these strategies.

COX2 inhibitors. The discovery of the role of COX1 and COX2 pathways in producing most of the pro-inflammatory metabolites from arachidonic acid was followed by the development of a range of now widely used non-steroidal anti-inflammatory COX inhibitors[173]. Genetic or pharmacological inhibition of PGE_2 signalling reduces IL-1β secretion and caspase 1 activity in mice[174]. However, despite their anti-inflammatory properties, COX inhibitors can also disrupt inflammation resolution because, although they suppress COX-induced production of key pro-inflammatory lipid-mediators, such as PGE_2 and LTB4, COX inhibitors also prevent the production of arachidonic acid-derived pro-resolution mediators such as PGD_2 (which is involved in lipid-mediator class switching and efferocytosis)[175,176]. PGD_2 signalling, via its interaction with PGD_2 receptors 1 and 2 expressed on cells involved in inflammation termination (dendritic cells, mast cells and T_H2 cells), promotes clearance of inflammatory cells, efferocytosis and resolution of inflammation[175,176]. This observation might explain some of the adverse effects of COX inhibitors. Over the past 15–20 years, it has been noted that COX inhibitors can increase the long-term risk of cardiovascular disease, including coronary atherothrombosis and HF and decrease endogenous cardioprotection against arrhythmogenic substrates and oxidative injury[177]. Moreover, COX inhibition increases systolic blood pressure and exacerbates the hypertensive effects of angiotensin II in animal models[178,179]. Combined medication involving COX inhibitors and angiotensin II inhibition revealed that COX inhibitors attenuate the vasodilatory properties of angiotensin-converting enzyme inhibitors and type 1 angiotensin II receptor blockers[180]. Perhaps because of these mixed effects,

non-steroidal anti-inflammatory drugs do not seem to be effective for the treatment of AF[181,182].

Aspirin. Aspirin is a classic non-steroidal anti-inflammatory agent that is widely used in cardiovascular therapeutics as an antiplatelet agent. Although aspirin-induced acetylation of COX2 blocks the production of pro-inflammatory lipid mediators (prostaglandins and leukotrienes) from arachidonic acid, acetylated COX2 can also metabolize EPA and DHA to produce a class of resolvin homologues called aspirin-triggered resolvins[148]. A study in mice showed that aspirin inhibits the release of ROS, thereby restraining NLRP3 inflammasome assembly and activation in the endothelium of coronary arteries[183]. However, a prospective, 6-year study involving 23,480 male patients found no association between chronic use of aspirin and AF incidence[184].

Glucocorticoids. Glucocorticoids have well-known, broad-spectrum anti-inflammatory effects, promoting inflammation resolution via non-phlogistic monocyte polarization into M2 macrophages, stimulation of macrophage phagocytosis of apoptotic neutrophils and activation of pro-resolution processes[185–188]. Conversely, glucocorticoids increase NLRP3 mRNA and protein expression in human macrophages[189]. Glucocorticoids also sensitize cells to extracellular ATP and increase ATP-mediated release of pro-inflammatory molecules, including mature IL-1β, IL-6 and TNF[189]. Glucocorticoid use increases the risk of systemic hypertension, fluid retention, atherosclerotic vascular disease and atrial arrhythmias in a dose-dependent and duration-dependent manner[190–192].

Selective NLRP3 inflammasome inhibitors. Oridonin, which is extracted from the Chinese medicinal herb *Rabdosia rubescens*, inhibits NLRP3 inflammasome assembly and NLRP3 inflammasome-induced production of IL-1β and activation of the pro-inflammatory transcription factor NF-κB[193]. MCC950, a diarylsulfonylurea-containing compound, selectively inhibits NLRP3 inflammasome activity by blocking ASC oligomerization and IL-1β secretion[194,195]. However, the commercial development of MCC950 was discontinued because of hepatotoxicity. In a mouse model of acute MI, oridonin and MCC950 treatment reduce cardiac fibrosis as well as the protein levels of NLRP3, IL-1β and IL-18 (REF.[196]). In a mouse model of MI, knockdown of *Camk2n1*, which encodes an endogenous inhibitor of CaMKII, led to increased CaMKII function as well as increased cardiac fibrosis and ventricular fibrillation susceptibility, supporting the notion that the CaMKII–p38–JNK–NLRP3 inflammasome pathway might be a potential therapeutic target[197].

IL-1 inhibitors. IL-1β is among the most studied members of the IL-1 family. Evidence of the pro-inflammatory and cardiotoxic effects of IL-1β has led to the development of inhibitors of IL-1β signalling[102]. In the AIRTRIP trial[198], anakinra, an IL-1R blocker that efficiently antagonizes the effects of IL-1α and IL-1β, administered for 2 months reduced the recurrence of pericarditis in patients with recurrent corticosteroid-dependent pericarditis. In the VCU-ART study[199] in patients with ST-segment elevation MI, 14 days of treatment with anakinra improved ventricular function and decreased the risk of HF. Prevention of hospitalization for HF with anakinra treatment was also observed in the REDHART trial[200]. In the RHAPSODY trial[201], treatment with rilonacept, an IL-1α and IL-1β cytokine trap, decreased the risk of pericarditis in patients with pericarditis resistant to conventional therapy. In the CANTOS trial[202], therapy with canakinumab, a specific monoclonal antibody against IL-1β, reduced HF hospitalization in patients with previous MI and high-sensitivity C-reactive protein (hsCRP) levels of ≥2 mg/l compared with placebo.

Specialized pro-resolving mediators. In a study involving 27 patients with HF and 23 healthy individuals, plasma RvD1 levels, GPR32 levels in T cells and leukocyte 15-LOX activity were lower in patients with HF, suggesting that altered pro-resolution signalling might be involved in HF pathophysiology[167]. In a rat model of right-sided heart disease, RvD1 treatment decreased atrial expression of NLRP3 inflammasome-related genes (*Asc*, *Casp1*, *Il1b* and *Nlrp3*) and prevented the upregulation of genes encoding inflammatory cytokines (*Ccl2*, *Cxcl1*, *Cxcl2* and *Il6*), together with reduced atrial fibrosis and AF susceptibility[137]. RvD1 also upregulates the expression of ChemR23, the receptor of the specialized pro-resolving mediators RvE1 and RvE2 (REF.[137]). In patients with aortic valve stenosis, the most common valvulopathy, RvE1 and RvD3 levels were lower whereas the LTB4 level was increased in calcified tricuspid aortic valve tissue[168]. Promotion of RvE1–ChemR23 signalling was associated with increased M2 macrophage recruitment and prevention of valvular calcification in animal models[168]. In patients without overt atherosclerosis, salivary levels of RvD1 were lower in those patients with greater intima–media thickness (which indicates early atherosclerosis)[203]. Patients with acutely symptomatic carotid atherosclerotic plaque rupture had lower circulating levels of RvD1 than patients with asymptomatic high-grade carotid stenosis[204]. Administration of specialized pro-resolving mediators (including RvE1, RvD1, RvD2 or maresin 1) promoting the increase in the ratio of specialized pro-resolving mediators to LTB4 is associated with decreased progression of atherosclerosis and activation of efferocytosis in mouse models[205–207]. RvE1 and RvD1 have been evaluated in mouse models of MI, revealing that specialized pro-resolving mediators promote inhibition of MAPK and NF-κB signalling in the infarcted myocardium to limit inflammation, reduce myocardial apoptosis and increase M2 macrophage recruitment[208–210].

NLRP3 inhibitors currently in clinical trials. Several small molecules (<20 carbon–carbon bonds) have been developed that inhibit the NLRP3 inflammasome[211] (TABLE 3). Inzomelid (MCC7840) inhibits NLRP3 inflammasome with half maximal inhibitory concentrations of <100 nmol/l[211]. Inzomelid was being tested in a phase I clinical trial in patients with Parkinson disease[212] and in a phase II clinical trial in patients with

cryopyrin-associated periodic syndromes[213], but the studies have been withdrawn by the sponsor. In cardiovascular disease and arthritis, somalix has shown selective inhibition of the NLRP3 inflammasome, together with acceptable safety and tolerability in a phase I clinical trial in healthy individuals in Ireland[211]. In patients with HF with reduced LV ejection fraction, therapy with anakinra reduced circulating levels of CRP and IL-1 and improved cardiorespiratory function and quality of life compared with placebo[214]. Dapansutrile, also known as OLT1177, specifically targets NLRP3 inflammasome-induced release of IL-1β and IL-18 to prevent inflammation[215]. A phase Ib, randomized, double-blind, dose-escalation study of dapansutrile in patients with systolic HF found that treatment with dapansutrile for 14 days is safe, well tolerated and, at the highest dose of 2,000 mg, improves LV ejection fraction and exercise time compared with baseline[216]. Dapansutrile is currently being tested in phase II clinical trials in patients with Schnitzler syndrome[217] and in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced cytokine storm[218].

Tranilast (also known as rizaben), a well-known anti-allergic medication that has shown efficacy for the treatment of tissue fibrosis, is an antagonist of NLRP3 oligomerization via a specific interaction with the NACHT domain of NLRP3 (REF.[219]). The anti-inflammatory effects of tranilast are currently being tested in a phase I clinical trial in patients with mucinoses[220] and in a phase II clinical trial in patients with cryopyrin-associated periodic syndromes[221]. Pirfenidone, which has anti-pulmonary fibrosis properties, inhibits NLRP3 inflammasome activation and NLRP3 inflammasome-induced fibrosis in mice[222,223], and potential translational application in humans has been suggested[223]. Pirfenidone is currently being tested in several clinical trials in fibrosis-associated disorders, including pulmonary fibrosis[218]. Canakinumab blocks NLRP3 activity by inhibiting IL-1β. In the CANTOS trial[224], canakinumab therapy decreased cardiovascular events compared with placebo in patients with previous MI and hsCRP levels of ≥2 mg/l. Canakinumab is currently being tested in a phase II clinical trial evaluating the effect of IL-1β inhibition on inflammation and the risk of cardiovascular disease[217]. Belnacasan (also known as VX-765), a specific inhibitor of caspase 1, prevents NLRP3 inflammasome-induced inflammation after ischaemia–reperfusion in mice[225]. Belnacasan is currently being tested in a phase II clinical trial aiming to decrease the inflammatory response in patients with SARS-CoV-2 infection[226].

None of the clinically applicable specific NLRP3 inhibiting agents is currently under evaluation for AF, but several of them should be studied in both preclinical and clinical models in the future.

Colchicine, an anti-inflammatory medication that blocks NLRP3 oligomerization[227], is commonly used to treat gout and has been shown to reduce the incidence of MI, stroke and coronary revascularization compared with placebo when administered for secondary prevention in patients with coronary artery disease[228]. On the basis of the anti-inflammatory effects of colchicine and the evidence for the importance of NLRP3 inflammasome-related inflammatory signalling in AF, colchicine has been suggested as a potential AF-preventing agent, with particular interest for contexts involving inflammation, such as postoperative AF[229]. However, available data suggest no effects of colchicine therapy on AF occurrence[230,231]. Large, randomized, double-blind trials currently underway, such as the COP-AF study[232], will provide insights into this question.

Box 1 | **Main areas to be addressed in future research**

Basic and translational studies

- What are the factors leading to cardiomyocyte inflammatory signalling activation in atrial fibrillation and atrial fibrillation-promoting pathologies?
- Do cardiac cells other than cardiomyocytes (such as adipocytes, fibroblasts and neural cells) have intact inflammasome systems and are they altered in atrial fibrillation?
- Does activation of cardiomyocyte inflammatory signalling recruit and activate macrophages and other inflammation-associated leukocytes in the heart?
- What are the characteristics of inflammation resolution signalling in cardiomyocytes and other cardiac cells and how is this system altered in atrial fibrillation?
- Are there differences in pro-resolution mediators and signalling pathways between paroxysmal and persistent atrial fibrillation?
- How do the properties of inflammatory signalling activation differ at various stages of atrial fibrillation?
- How do resolution-promoting compounds affect NLRP3 inflammasome priming and triggering in animal models of atrial fibrillation?
- Are there specific properties of atrial cardiomyocyte inflammatory signalling that could be used to develop cardiac-specific or even atrial-specific anti-inflammatory interventions?

Clinical investigation

- What is the safety and toxicity profile of resolution-promoting compounds in humans?
- Can compounds be developed that target atrial cardiomyocyte inflammatory signalling with sufficient safety for long-term use in patients with atrial fibrillation and individuals with increased risk of atrial fibrillation?
- Are there biomarkers that can reliably identify and quantify cardiomyocyte NLRP3 inflammasome activation in humans?

Implications and future directions

Implications of the role of cardiomyocyte inflammatory signalling in AF. The observation that cells such as cardiomyocytes, fibroblasts and adipocytes, not previously considered to induce or maintain inflammation, have the biochemical machinery necessary to engage inflammatory signalling is interesting and potentially important. The observation that inflammatory signalling is increased in cardiomyocytes of patient populations with AF substrates and risk factors, and that cardiomyocyte-specific overexpression of active pro-inflammatory proteins creates the conditions for AF in animal models, points to the mechanistic relevance of this system in clinical AF.

These findings are of potential pathophysiological importance. Patients with so-called 'secondary' AF owing to acute illness, such as sepsis, acute infectious disease, recent surgery or MI, are likely to have recurrent AF in the future[233]. This observation has been largely unexplained. However, if atrial cardiomyocyte inflammatory signalling with consequent structural and/or

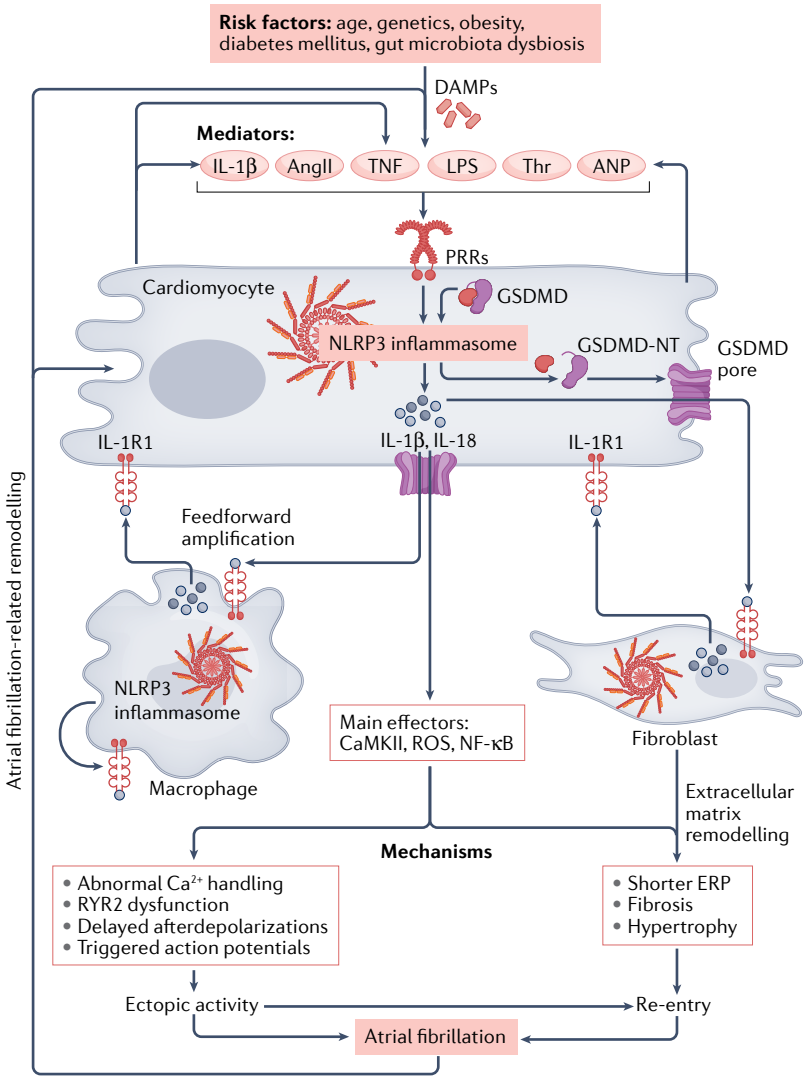

Fig. 4 | **Cardiomyocyte–immune cell interactions promote and maintain atrial fibrillation.** Dynamic interactions between cardiac cells and immune cells create a pro-inflammatory substrate for the promotion and maintenance of atrial fibrillation. Atrial fibrillation-promoting risk factors activate various mediators that signal through pattern-recognition receptors (PRRs) on cardiomyocytes to activate the cardiomyocyte NLRP3 inflammasome, leading to the release of IL-1β and IL-18 and activation of signalling pathways dependent on Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), reactive oxygen species (ROS) and nuclear factor-κB (NF-κB). Subsequent activation of IL-1 receptor type 1 (IL-1R1) on macrophages promotes feedforward amplification of inflammatory signalling, whereas IL-1R1-mediated stimulation of fibroblasts causes extracellular matrix remodelling. Together, these processes result in cardiomyocyte Ca^{2+} handling abnormalities, including ryanodine receptor 2 (RYR2) channel remodelling, delayed afterdepolarizations, and triggered action potentials and ectopic activity, as well as re-entry-promoting effective refractory period (ERP) shortening and fibrotic structural remodelling, thereby inducing the principal mechanisms responsible for atrial fibrillation. AngII, angiotensin II; ANP, atrial natriuretic peptide; DAMPs, damage-associated molecular patterns; LPS, lipopolysaccharide; GSDMD, gasdermin D; GSDMD-NT, gasdermin D amino terminus; NLRP3, NACHT-, LRR- and pyrin domain-containing 3; Thr, thrombin; TNF, tumour necrosis factor.

electrophysiological changes is a common underlying theme, this phenomenon can be explained by the notion that the atrial substrate must reach a critical threshold to manifest AF. This critical threshold can be achieved by gradual progression to the critical state of substrate progression, but if intercurrent, acute pro-inflammatory contexts provide a transient increase in the atrial substrate, AF might manifest in a transient way before the underlying substrate reaches the threshold for arrhythmogenesis on its own. Following the resolution of the acute stress, the substrate will generally return to the previous subthreshold level, only to reach the threshold for AF development by gradual subsequent progression. This interesting possibility requires verification in future studies.

Extensive, but in some ways circumstantial, evidence for a role of inflammation in AF was available before the observation of the contribution of cardiomyocyte inflammatory signalling to AF[4]. However, the manifestations of atrial inflammation have been mild, and conventional anti-inflammatory drugs have had little or no efficacy in clinical trials in AF. Part of the explanation for the lack of efficacy of traditional anti-inflammatory agents in AF despite a role of atrial inflammation in this condition might be the localized and atypical nature of cardiomyocyte-derived inflammatory signalling and the lack of direct clinical proof of the anti-AF efficacy of selective NLRP3 inhibitors. Much more work is needed to characterize this phenomenon, identify its causes and clarify its pathophysiological and therapeutic relevance. The therapeutic implications relate to better understanding of the natural history of AF and its mechanisms, as well as specific therapeutic targets, as discussed above and tabulated in TABLE 3.

Key areas for future research. The study of inflammatory signalling in atrial cardiomyocytes is a rapidly evolving area, and many important questions remain to be addressed (BOX 1). In the basic and translational arena, we need to understand the factors that prime and trigger (activate) the cardiomyocyte NLRP3 inflammasome. Do cardiac diseases and risk factors release DAMPs and/or other danger signals in atrial tissue? Does increased atrial pressure and/or volume affect cardiomyocyte inflammatory signalling? What is the precise role of atrial rate? What is the role of oxidative stress or other signals related to neurohormones (such as adrenergic neurotransmitters and angiotensin II)?

The role of NLRP3 inflammasome signalling in non-myocyte cardiac cells needs to be examined and, if validated, its effects on atrial electrophysiology, structure and function examined. We also need to know whether these systems are altered in different forms of AF in animal models and in patients. Cardiomyocyte NLRP3 inflammasome signalling has the capacity to release pro-inflammatory cytokines. It would be important to know whether such cytokine release can exert paracrine functions on neighbouring cells and whether it can result in more classic inflammatory cell recruitment and activation (FIG. 4). To identify which non-myocyte cell type is most relevant in different cohorts of patients or animal models with AF vulnerability, unbiased omics studies at the single-cell level could be performed. Single-cell and single-nucleus RNA sequencing or single-cell proteomics studies can help to identify discrete cell subtypes in atrial tissue from animal models and patients with AF[234,235]. Bioinformatic analysis can not only identify the differentially expressed genes or proteins within each

cluster of cells, but also reveal which cell types have the most prominent changes at the transcriptional or protein level. Furthermore, analysis of cell-to-cell interactions can uncover networks that drive the development and progression of cardiac diseases[236].

The systemic mechanisms leading to cardiac activation of inflammatory signalling and of the NLRP3 system in particular are unknown. Ageing-related increases in levels of circulating LPS derived from gut microbiota dysbiosis, together with increased glucose intolerance, are potential primers and triggers of the atrial NLRP3 inflammasome system[237]. Hepatocyte-derived angiotensinogen can be taken up by cardiac fibroblasts and can activate ventricular NLRP3 inflammasome via an angiotensin II-independent pathway, thereby causing IL-1β-mediated suppression of sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2A in cardiomyocytes[238]. Whether these mechanisms contribute to the activation of NLRP3 inflammasome in atrial cells of patients with AF is unknown and requires further study. The precise mechanisms of NLRP3 priming and triggering in heart cells need further assessment and potential atrial–ventricular differences in NLRP3 activation should be defined. For instance, at the ventricular level, IL-1β seems to be primarily released from cardiac fibroblasts rather than cardiomyocytes[102,105,106]. Conversely, GSDMD seems to be primarily synthesized and active in ventricular cardiomyocytes but not in fibroblasts, at least in mice[239]. GSDMD-mediated pyroptosis of ventricular cardiomyocytes is a key event during myocardial ischaemia–reperfusion injury[239]. Therefore, it seems that there is separation of labour between ventricular fibroblasts (IL-1β release) and cardiomyocytes (GSDMD-mediated pyroptosis) in the response to ischaemia–reperfusion injury[240]. Whether these principles apply to atrial cells is unknown and requires detailed investigation in future work.

The relative contributions of IL-1α, IL-1β and IL-18 to inflammatory signalling and cardiac dysfunction are unknown and should be studied in future work. Which atrial cells are the primary cell type for the synthesis and release of IL-1α, IL-1β and IL-18 remains to be determined.

The properties of inflammation resolution-promoting systems in cardiomyocytes and other cardiac cell types are very poorly understood. Further information is essential for a fuller appreciation of the role of inflammation resolution in the heart. We also need to understand whether the properties of these systems are affected by AF or AF-promoting conditions. The interactions between NLRP3 inflammasome signalling and resolution-promoting pathways need to be understood, and how activation of one system affects the other needs to be appreciated. Crucially, we need to understand whether atrial cardiomyocyte inflammatory signalling has specific properties that could be used to develop cardiac-specific or even atrial-specific anti-inflammatory interventions.

We need to understand how the properties of inflammatory signalling activation differ at various stages of AF. Does NLRP3 inflammasome activation differ in patients with paroxysmal, persistent or long-standing persistent AF? If there are differences, are parallel changes seen in relevant animal models? Similarly, does pro-resolution signalling differ at corresponding phases? Can blood biomarkers be identified that could be used to identify and quantitatively evaluate cardiomyocyte NLRP3 system activation in humans?

The ultimate key questions relate to therapeutic implications. Can we use this evolving basic science knowledge to develop compounds that target atrial cardiomyocyte inflammatory signalling with sufficient safety for long-term use in patients with AF and those at increased risk of AF, and thereby favourably alter the natural history of the condition? n-3 PUFAs are precursors of resolvins, but have not generally been found to be protective in AF, with some evidence for benefit, many studies suggesting no effect and other data suggesting adverse effects on AF occurrence[228]. Might the large number of bioactive products derived from n-3 PUFAs in humans be the explanation, with some being pro-inflammatory and others, such as resolvins, being anti-inflammatory? Could this explain the variable clinical results? What is the safety and toxicity profile of resolution-promoting compounds in humans? Can they be used in a practical way to prevent the promotion of the AF substrate and prevent recurrences after AF ablation, or even be used in primary prevention in patients at high risk of AF?

Conclusions

The existence of inflammatory signalling in cardiomyocytes and its pathophysiological importance in AF have been recognized only for the past 5 years. This knowledge has great potential importance, both for understanding AF pathophysiology and for improving the treatment of AF. A great deal of additional work is needed before the relevance of this new knowledge can be fully evaluated, but careful attention to this promising area of research is warranted.

Published online 15 September 2022

1. Andrade, J., Khairy, P., Dobrev, D. & Nattel, S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ. Res.* **114**, 1453–1468 (2014).
2. Heijman, J., Guichard, J. B., Dobrev, D. & Nattel, S. Translational challenges in atrial fibrillation. *Circ. Res.* **122**, 752–773 (2018).
3. Chung, M. K. et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* **104**, 2886–2891 (2001).
4. Harada, M., Van Wagoner, D. R. & Nattel, S. Role of inflammation in atrial fibrillation pathophysiology and management. *Circ. J.* **79**, 495–502 (2015).
5. Gong, T., Liu, L., Jiang, W. & Zhou, R. DAMP-sensing receptors in sterile inflammation and inflammatory diseases. *Nat. Rev. Immunol.* **20**, 95–112 (2020).
6. Zhao, C. & Zhao, W. NLRP3 inflammasome – a key player in antiviral responses. *Front. Immunol.* **11**, 211 (2020).
7. Lazzerini, P. E., Capecchi, P. L. & Laghi-Pasini, F. Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis. *Eur. Heart J.* **38**, 1717–1727 (2017).
8. Ahlehoff, O. et al. Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish nationwide cohort study. *Eur. Heart J.* **33**, 2054–2064 (2012).
9. Kristensen, S. L. et al. Increased risk of atrial fibrillation and stroke during active stages of inflammatory bowel disease: a nationwide study. *Europace* **16**, 477–484 (2014).
10. Koyfman, L. et al. Epidemiology of new-onset paroxysmal atrial fibrillation in the general intensive care unit population and after discharge from ICU. A retrospective epidemiological study. *Anaesthesiol. Intensive Ther.* **47**, 309–314 (2015).
11. Walkey, A. J., Wiener, R. S., Ghobrial, J. M., Curtis, L. H. & Benjamin, E. J. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA* **306**, 2248–2254 (2011).
12. Walkey, A. J. et al. Atrial fibrillation among Medicare beneficiaries hospitalized with sepsis: incidence and risk factors. *Am. Heart J.* **165**, 949–955.e3 (2013).

13. Kuipers, S., Klein Klouwenberg, P. M. & Cremer, O. L. Incidence, risk factors and outcomes of new-onset atrial fibrillation in patients with sepsis: a systematic review. *Crit. Care* **18**, 688 (2014).
14. Walkey, A. J., Hammill, B. G., Curtis, L. H. & Benjamin, E. J. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest* **146**, 1187–1195 (2014).
15. Klein Klouwenberg, P. M. et al. Incidence, predictors, and outcomes of new-onset atrial fibrillation in critically ill patients with sepsis. a cohort study. *Am. J. Respir. Crit. Care Med.* **195**, 205–211 (2017).
16. Cheng, C. A. et al. New-onset atrial fibrillation-related ischemic stroke occurring after hospital discharge in septicemia survivors. *QJM* **110**, 453–457 (2017).
17. Bosch, N. A. et al. New-onset atrial fibrillation as a sepsis-defining organ failure. *Ann. Am. Thorac. Soc.* **16**, 1332–1334 (2019).
18. Fernando, S. M. et al. New-onset atrial fibrillation and associated outcomes and resource use among critically ill adults – a multicenter retrospective cohort study. *Crit. Care* **24**, 15 (2020).
19. Ko, D. et al. Secondary precipitants of atrial fibrillation and anticoagulation therapy. *J. Am. Heart Assoc.* **10**, e021746 (2021).
20. Long, Y. et al. Early coagulation disorder is associated with an increased risk of atrial fibrillation in septic patients. *Front. Cardiovasc. Med.* **8**, 724942 (2021).
21. Spodick, D. H. Arrhythmias during acute pericarditis. A prospective study of 100 consecutive cases. *JAMA* **235**, 39–41 (1976).
22. Nagahama, Y. et al. The role of infarction-associated pericarditis on the occurrence of atrial fibrillation. *Eur. Heart J.* **19**, 287–292 (1998).
23. Ristić, A. D. et al. Arrhythmias in acute pericarditis. An endomyocardial biopsy study. *Herz* **25**, 729–733 (2000).
24. Imazio, M. et al. Incidence and prognostic significance of new onset atrial fibrillation/flutter in acute pericarditis. *Heart* **101**, 1463–1467 (2015).
25. Adegbala, O. et al. Predictors, burden, and the impact of arrhythmia on patients admitted for acute myocarditis. *Am. J. Cardiol.* **123**, 139–144 (2019).
26. Frustaci, A. et al. Cardiac biopsy in patients with "primary" atrial fibrillation. Histologic evidence of occult myocardial diseases. *Chest* **100**, 303–306 (1991).
27. Frustaci, A. et al. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation* **96**, 1180–1184 (1997).
28. Fuenmayor, A. J. et al. Results of electrophysiologic studies in patients with acute chagasic myocarditis. *Clin. Cardiol.* **20**, 1021–1024 (1997).
29. Morgera, T. et al. Electrocardiography of myocarditis revisited: clinical and prognostic significance of electrocardiographic changes. *Am. Heart J.* **124**, 455–467 (1992).
30. Deluigi, C. C. et al. ECG findings in comparison to cardiovascular MR imaging in viral myocarditis. *Int. J. Cardiol.* **165**, 100–106 (2013).
31. Coromilas, E. J. et al. Worldwide survey of COVID-19-associated arrhythmias. *Circ. Arrhythm. Electrophysiol.* **14**, e009458 (2021).
32. Gawalko, M., Kaplon-Cieslicka, A., Hohl, M., Dobrev, D. & Linz, D. COVID-19 associated atrial fibrillation: incidence, putative mechanisms and potential clinical implications. *Int. J. Cardiol. Heart Vasc.* **30**, 100631 (2020).
33. Sun, Z. et al. Cross-talk between macrophages and atrial myocytes in atrial fibrillation. *Basic. Res. Cardiol.* **111**, 63 (2016).
34. Fang, J. et al. Ferroportin-mediated ferroptosis involved in new-onset atrial fibrillation with LPS-induced endotoxemia. *Eur. J. Pharmacol.* **913**, 174622 (2021).
35. Aoki, Y. et al. Role of ion channels in sepsis-induced atrial tachyarrhythmias in guinea pigs. *Br. J. Pharmacol.* **166**, 390–400 (2012).
36. Landstrom, A. P., Dobrev, D. & Wehrens, X. H. T. Calcium signaling and cardiac arrhythmias. *Circ. Res.* **120**, 1969–1993 (2017).
37. Nattel, S., Heijman, J., Zhou, L. & Dobrev, D. Molecular basis of atrial fibrillation pathophysiology and therapy: a translational perspective. *Circ. Res.* **127**, 51–72 (2020).
38. Kumagai, K., Nakashima, H. & Saku, K. The HMG-CoA reductase inhibitor atorvastatin prevents atrial fibrillation by inhibiting inflammation in a canine sterile pericarditis model. *Cardiovasc. Res.* **62**, 105–111 (2004).
39. Ryu, K. et al. Effects of sterile pericarditis on connexins 40 and 43 in the atria: correlation with abnormal conduction and atrial arrhythmias. *Am. J. Physiol. Heart Circ. Physiol.* **293**, H1231–H1241 (2007).
40. Huang, Z. et al. Signal transducer and activator of transcription 3/microRNA-21 feedback loop contributes to atrial fibrillation by promoting atrial fibrosis in a rat sterile pericarditis model. *Circ. Arrhythm. Electrophysiol.* https://doi.org/10.1161/CIRCEP.115.003396 (2016).
41. Wu, Q. et al. Colchicine prevents atrial fibrillation promotion by inhibiting IL-1β-induced IL-6 release and atrial fibrosis in the rat sterile pericarditis model. *Biomed. Pharmacother.* **129**, 110384 (2020).
42. Zhang, Y. et al. Role of inflammation in the initiation and maintenance of atrial fibrillation and the protective effect of atorvastatin in a goat model of aseptic pericarditis. *Mol. Med. Rep.* **11**, 2615–2623 (2015).
43. Zhang, Z. et al. n-3 polyunsaturated fatty acids prevents atrial fibrillation by inhibiting inflammation in a canine sterile pericarditis model. *Int. J. Cardiol.* **153**, 14–20 (2011).
44. Chang, C. J. et al. Histone deacetylase inhibition attenuates atrial arrhythmogenesis in sterile pericarditis. *Transl. Res.* **200**, 54–64 (2018).
45. Liao, J. et al. TRPV4 blockade suppresses atrial fibrillation in sterile pericarditis rats. *JCI Insight* https://doi.org/10.1172/jci.insight.137528 (2020).
46. Liao, J. et al. Interleukin-6-mediated-Ca^{2+} handling abnormalities contributes to atrial fibrillation in sterile pericarditis rats. *Front. Immunol.* **12**, 758157 (2021).
47. Lin, F. J. et al. Toll-like receptor 4 activation modulates pericardium-myocardium interactions in lipopolysaccharide-induced atrial arrhythmogenesis. *Europace* **23**, 1837–1846 (2021).
48. Schwartzman, D. et al. A plasma-based, amiodarone-impregnated material decreases susceptibility to atrial fibrillation in a post-cardiac surgery model. *Innovations* **11**, 59–63 (2016). discussion 63.
49. Fu, X. X. et al. Interleukin-17A contributes to the development of post-operative atrial fibrillation by regulating inflammation and fibrosis in rats with sterile pericarditis. *Int. J. Mol. Med.* **36**, 83–92 (2015).
50. Tubeeckx, M. R. L. et al. Sterile pericarditis in Aachener minipigs as a model for atrial myopathy and atrial fibrillation. *J. Vis. Exp.* https://doi.org/10.3791/63094 (2021).
51. Hoyano, M. et al. Inducibility of atrial fibrillation depends not on inflammation but on atrial structural remodeling in rat experimental autoimmune myocarditis. *Cardiovasc. Pathol.* **19**, e149–e157 (2010).
52. Turner, N. A. et al. Interleukin-1α stimulates proinflammatory cytokine expression in human cardiac myofibroblasts. *Am. J. Physiol. Heart Circ. Physiol.* **297**, H1117–H1127 (2009).
53. Wang, Y. et al. NLRP3 inflammasome, an immune-inflammatory target in pathogenesis and treatment of cardiovascular diseases. *Clin. Transl. Med.* **10**, 91–106 (2020).
54. Liu, L. et al. Up-regulated TLR4 in cardiomyocytes exacerbates heart failure after long-term myocardial infarction. *J. Cell Mol. Med.* **19**, 2728–2740 (2015).
55. Takahashi, M. NLRP3 inflammasome as a key driver of vascular disease. *Cardiovasc. Res.* **118**, 372–385 (2022).
56. Scott, L. Jr., Li, N. & Dobrev, D. Role of inflammatory signaling in atrial fibrillation. *Int. J. Cardiol.* **287**, 195–200 (2019).
57. Latz, E. The inflammasomes: mechanisms of activation and function. *Curr. Opin. Immunol.* **22**, 28–33 (2010).
58. Schroder, K. & Tschopp, J. The inflammasomes. *Cell* **140**, 821–832 (2010).
59. Groslambert, M. & Py, B. F. Spotlight on the NLRP3 inflammasome pathway. *J. Inflamm. Res.* **11**, 359–374 (2018).
60. Misawa, T. et al. Microtubule-driven spatial arrangement of mitochondria promotes activation of the NLRP3 inflammasome. *Nat. Immunol.* **14**, 454–460 (2013).
61. Py, B. F., Kim, M. S., Vakifahmetoglu-Norberg, H. & Yuan, J. Deubiquitination of NLRP3 by BRCC3 critically regulates inflammasome activity. *Mol. Cell* **49**, 331–338 (2013).
62. Bryan, N. B., Dorfleutner, A., Rojanasakul, Y. & Stehlik, C. Activation of inflammasomes requires intracellular redistribution of the apoptotic speck-like protein containing a caspase recruitment domain. *J. Immunol.* **182**, 3173–3182 (2009).
63. Baroja-Mazo, A. et al. The NLRP3 inflammasome is released as a particulate danger signal that amplifies the inflammatory response. *Nat. Immunol.* **15**, 738–748 (2014).
64. Dick, M. S., Sborgi, L., Ruhl, S., Hiller, S. & Broz, P. ASC filament formation serves as a signal amplification mechanism for inflammasomes. *Nat. Commun.* **7**, 11929 (2016).
65. Bauernfeind, F. G. et al. Cutting edge: NF-κB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. *J. Immunol.* **183**, 787–791 (2009).
66. Suetomi, T. et al. Inflammation and NLRP3 inflammasome activation initiated in response to pressure overload by Ca^{2+}/calmodulin-dependent protein kinase II δ signaling in cardiomyocytes are essential for adverse cardiac remodeling. *Circulation* **138**, 2530–2544 (2018).
67. Fender, A. C. et al. Thrombin receptor PAR4 drives canonical NLRP3 inflammasome signaling in the heart. *Basic. Res. Cardiol.* **115**, 10 (2020).
68. Tschopp, J. & Schroder, K. NLRP3 inflammasome activation: the convergence of multiple signalling pathways on ROS production? *Nat. Rev. Immunol.* **10**, 210–215 (2010).
69. Juliana, C. et al. Non-transcriptional priming and deubiquitination regulate NLRP3 inflammasome activation. *J. Biol. Chem.* **287**, 36617–36622 (2012).
70. Lin, K. M. et al. IRAK-1 bypasses priming and directly links TLRs to rapid NLRP3 inflammasome activation. *Proc. Natl Acad. Sci. USA* **111**, 775–780 (2014).
71. Schroder, K. et al. Acute lipopolysaccharide priming boosts inflammasome activation independently of inflammasome sensor induction. *Immunobiology* **217**, 1325–1329 (2012).
72. Broz, P. & Dixit, V. M. Inflammasomes: mechanism of assembly, regulation and signalling. *Nat. Rev. Immunol.* **16**, 407–420 (2016).
73. Gong, T., Yang, Y., Jin, T., Jiang, W. & Zhou, R. Orchestration of NLRP3 inflammasome activation by ion fluxes. *Trends Immunol.* **39**, 393–406 (2018).
74. Weber, K. & Schilling, J. D. Lysosomes integrate metabolic-inflammatory cross-talk in primary macrophage inflammasome activation. *J. Biol. Chem.* **289**, 9158–9171 (2014).
75. Magupalli, V. G. et al. HDAC6 mediates an aggresome-like mechanism for NLRP3 and pyrin inflammasome activation. *Science* https://doi.org/10.1126/science.aas8995 (2020).
76. He, Y., Zeng, M. Y., Yang, D., Motro, B. & Nunez, G. NEK7 is an essential mediator of NLRP3 activation downstream of potassium efflux. *Nature* **530**, 354–357 (2016).
77. Sharif, H. et al. Structural mechanism for NEK7-licensed activation of NLRP3 inflammasome. *Nature* **570**, 338–343 (2019).
78. Murakami, T. et al. Critical role for calcium mobilization in activation of the NLRP3 inflammasome. *Proc. Natl Acad. Sci. USA* **109**, 11282–11287 (2012).
79. Lee, G. S. et al. The calcium-sensing receptor regulates the NLRP3 inflammasome through Ca2+ and cAMP. *Nature* **492**, 123–127 (2012).
80. Tseng, H. H., Vong, C. T., Kwan, Y. W., Lee, S. M. & Hoi, M. P. TRPM2 regulates TXNIP-mediated NLRP3 inflammasome activation via interaction with p47 phox under high glucose in human monocytic cells. *Sci. Rep.* **6**, 35016 (2016).
81. Compan, V. et al. Cell volume regulation modulates NLRP3 inflammasome activation. *Immunity* **37**, 487–500 (2012).
82. Horng, T. Calcium signaling and mitochondrial destabilization in the triggering of the NLRP3 inflammasome. *Trends Immunol.* **35**, 253–261 (2014).
83. Menu, P. et al. ER stress activates the NLRP3 inflammasome via an UPR-independent pathway. *Cell Death Dis.* **3**, e261 (2012).
84. Iyer, S. S. et al. Mitochondrial cardiolipin is required for Nlrp3 inflammasome activation. *Immunity* **39**, 311–323 (2013).
85. Swanson, K. V., Deng, M. & Ting, J. P. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. *Nat. Rev. Immunol.* **19**, 477–489 (2019).
86. Gaidt, M. M. & Hornung, V. Pore formation by GSDMD is the effector mechanism of pyroptosis. *EMBO J.* **35**, 2167–2169 (2016).
87. Munoz-Planillo, R. et al. K^+ efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. *Immunity* **38**, 1142–1153 (2013).

88. Burnstock, G. P2X ion channel receptors and inflammation. *Purinergic Signal.* **12**, 59–67 (2016).
89. Gaidt, M. M. et al. Human monocytes engage an alternative inflammasome pathway. *Immunity* **44**, 833–846 (2016).
90. Netea, M. G. et al. Differential requirement for the activation of the inflammasome for processing and release of IL-1β in monocytes and macrophages. *Blood* **113**, 2324–2335 (2009).
91. Man, S. M. & Kanneganti, T. D. Converging roles of caspases in inflammasome activation, cell death and innate immunity. *Nat. Rev. Immunol.* **16**, 7–21 (2016).
92. Kayagaki, N. et al. Noncanonical inflammasome activation by intracellular LPS independent of TLR4. *Science* **341**, 1246–1249 (2013).
93. Yang, D., He, Y., Munoz-Planillo, R., Liu, Q. & Nunez, G. Caspase-11 requires the pannexin-1 channel and the purinergic P2X7 pore to mediate pyroptosis and endotoxic shock. *Immunity* **43**, 923–932 (2015).
94. He, Y., Hara, H. & Nunez, G. Mechanism and regulation of NLRP3 inflammasome activation. *Trends Biochem. Sci.* **41**, 1012–1021 (2016).
95. Wallach, D., Kang, T. B., Dillon, C. P. & Green, D. R. Programmed necrosis in inflammation: toward identification of the effector molecules. *Science* **352**, aaf2154 (2016).
96. Aziz, M., Jacob, A., Yang, W. L., Matsuda, A. & Wang, P. Current trends in inflammatory and immunomodulatory mediators in sepsis. *J. Leukoc. Biol.* **93**, 329–342 (2013).
97. Miao, E. A. et al. Caspase-1-induced pyroptosis is an innate immune effector mechanism against intracellular bacteria. *Nat. Immunol.* **11**, 1136–1142 (2010).
98. Aglietti, R. A. et al. GsdmD p30 elicited by caspase-11 during pyroptosis forms pores in membranes. *Proc. Natl Acad. Sci. USA* **113**, 7858–7863 (2016).
99. Ding, J. et al. Pore-forming activity and structural autoinhibition of the gasdermin family. *Nature* **535**, 111–116 (2016).
100. Karmakar, M. et al. N-GSDMD trafficking to neutrophil organelles facilitates IL-1β release independently of plasma membrane pores and pyroptosis. *Nat. Commun.* **11**, 2212 (2020).
101. Toldo, S. & Abbate, A. The NLRP3 inflammasome in acute myocardial infarction. *Nat. Rev. Cardiol.* **15**, 203–214 (2018).
102. Abbate, A. et al. Interleukin-1 and the inflammasome as therapeutic targets in cardiovascular disease. *Circ. Res.* **126**, 1260–1280 (2020).
103. Silvis, M. J. M. et al. Immunomodulation of the NLRP3 inflammasome in atherosclerosis, coronary artery disease, and acute myocardial infarction. *J. Cardiovasc. Transl. Res.* **14**, 23–34 (2021).
104. Mezzaroma, E., Abbate, A. & Toldo, S. The inflammasome in heart failure. *Curr. Opin. Physiol.* **19**, 105–112 (2021).
105. Rajamaki, K. et al. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation. *PLoS ONE* **5**, e11765 (2010).
106. Mezzaroma, E. et al. The inflammasome promotes adverse cardiac remodeling following acute myocardial infarction in the mouse. *Proc. Natl Acad. Sci. USA* **108**, 19725–19730 (2011).
107. Kawaguchi, M. et al. Inflammasome activation of cardiac fibroblasts is essential for myocardial ischemia/reperfusion injury. *Circulation* **123**, 594–604 (2011).
108. Sandanger, O. et al. The NLRP3 inflammasome is up-regulated in cardiac fibroblasts and mediates myocardial ischaemia-reperfusion injury. *Cardiovasc. Res.* **99**, 164–174 (2013).
109. Deftereos, S. et al. Anti-inflammatory treatment with colchicine in acute myocardial infarction: a pilot study. *Circulation* **132**, 1395–1403 (2015).
110. Heijman, J. et al. Atrial myocyte NLRP3/CaMKII nexus forms a substrate for postoperative atrial fibrillation. *Circ. Res.* **127**, 1036–1055 (2020).
111. Byrne, N. J. et al. Empagliflozin blunts worsening cardiac dysfunction associated with reduced NLRP3 (nucleotide-binding domain-like receptor protein 3) inflammasome activation in heart failure. *Circ. Heart Fail.* **13**, e006277 (2020).
112. Mehta, S., Vijayvergiya, R. & Dhawan, V. Activation of NLRP3 inflammasome assembly is associated with smoking status of patients with coronary artery disease. *Int. Immunopharmacol.* **87**, 106820 (2020).
113. Yao, C. et al. Enhanced cardiomyocyte NLRP3 inflammasome signaling promotes atrial fibrillation. *Circulation* **138**, 2227–2242 (2018).
114. Xiao, H. et al. IL-18 cleavage triggers cardiac inflammation and fibrosis upon β-adrenergic insult. *Eur. Heart J.* **39**, 60–69 (2018).
115. Zhuang, Y. T. et al. IL-6 induced lncRNA MALAT1 enhances TNF-α expression in LPS-induced septic cardiomyocytes via activation of SAA3. *Eur. Rev. Med. Pharmacol. Sci.* **21**, 302–309 (2017).
116. Chandrasekar, B., Mummidi, S., Claycomb, W. C., Mestril, R. & Nemer, M. Interleukin-18 is a pro-hypertrophic cytokine that acts through a phosphatidylinositol 3-kinase-phosphoinositide-dependent kinase-1-Akt-GATA4 signaling pathway in cardiomyocytes. *J. Biol. Chem.* **280**, 4553–4567 (2005).
117. Aschar-Sobbi, R. et al. Increased atrial arrhythmia susceptibility induced by intense endurance exercise in mice requires TNFα. *Nat. Commun.* **6**, 6018 (2015).
118. Lakin, R. et al. Inhibition of soluble TNFα prevents adverse atrial remodeling and atrial arrhythmia susceptibility induced in mice by endurance exercise. *J. Mol. Cell Cardiol.* **129**, 165–173 (2019).
119. Scott, L. Jr et al. NLRP3 inflammasome is a key driver of obesity-induced atrial arrhythmias. *Cardiovasc. Res.* **117**, 1746–1759 (2021).
120. Saba, S. et al. Atrial contractile dysfunction, fibrosis, and arrhythmias in a mouse model of cardiomyopathy secondary to cardiac-specific overexpression of tumor necrosis factor-α. *Am. J. Physiol. Heart Circ. Physiol.* **289**, H1456–H1467 (2005).
121. Sawaya, S. E. et al. Downregulation of connexin40 and increased prevalence of atrial arrhythmias in transgenic mice with cardiac-restricted overexpression of tumor necrosis factor. *Am. J. Physiol. Heart Circ. Physiol.* **292**, H1561–H1567 (2007).
122. Lee, S. H. et al. Tumor necrosis factor-α alters calcium handling and increases arrhythmogenesis of pulmonary vein cardiomyocytes. *Life Sci.* **80**, 1806–1815 (2007).
123. He, G. et al. Increased M1 macrophages infiltration is associated with thrombogenesis in rheumatic mitral stenosis patients with atrial fibrillation. *PLoS ONE* **11**, e0149910 (2016).
124. Lazzerini, P. E. et al. Systemic inflammation rapidly induces reversible atrial electrical remodeling: the role of interleukin-6-mediated changes in connexin expression. *J. Am. Heart Assoc.* **8**, e011006 (2019).
125. Li, N. & Brundel, B. Inflammasomes and proteostasis novel molecular mechanisms associated with atrial fibrillation. *Circ. Res.* **127**, 73–90 (2020).
126. Willeford, A. et al. CaMKIIδ-mediated inflammatory gene expression and inflammasome activation in cardiomyocytes initiate inflammation and induce fibrosis. *JCI Insight* https://doi.org/10.1172/jci.insight.97054 (2018).
127. Ling, H. et al. Ca^{2+}/calmodulin-dependent protein kinase II δ mediates myocardial ischemia/reperfusion injury through nuclear factor-κB. *Circ. Res.* **112**, 935–944 (2013).
128. Yao, Y. et al. Targeting CaMKII-δ9 ameliorates cardiac ischemia/reperfusion injury by inhibiting myocardial inflammation. *Circ. Res.* https://doi.org/10.1161/CIRCRESAHA.121.319478 (2022).
129. Joiner, M. L. et al. CaMKII determines mitochondrial stress responses in heart. *Nature* **491**, 269–273 (2012).
130. Dobrev, D. & Dudley, S. C. Oxidative stress: a bystander or a causal contributor to atrial remodelling and fibrillation. *Cardiovasc. Res.* **117**, 2291–2293 (2021).
131. Gawalko, M. et al. Gut microbiota, dysbiosis and atrial fibrillation. Arrhythmogenic mechanisms and potential clinical implications. *Cardiovasc. Res.* https://doi.org/10.1093/cvr/cvab292 (2021).
132. Hu, Y. F., Chen, Y. J., Lin, Y. J. & Chen, S. A. Inflammation and the pathogenesis of atrial fibrillation. *Nat. Rev. Cardiol.* **12**, 230–243 (2015).
133. Yu, L. et al. A potential relationship between gut microbes and atrial fibrillation: trimethylamine N-oxide, a gut microbe-derived metabolite, facilitates the progression of atrial fibrillation. *Int. J. Cardiol.* **255**, 92–98 (2018).
134. Wu, X. et al. Role of NLRP3-inflammasome/caspase-1/galectin-3 pathway on atrial remodeling in diabetic rabbits. *J. Cardiovasc. Transl. Res.* **13**, 731–740 (2020).
135. Hiram, R. et al. Right atrial mechanisms of atrial fibrillation in a rat model of right heart disease. *J. Am. Coll. Cardiol.* **74**, 1332–1347 (2019).
136. Goudis, C. A. Chronic obstructive pulmonary disease and atrial fibrillation: an unknown relationship. *J. Cardiol.* **69**, 699–705 (2017).
137. Hiram, R. et al. The inflammation-resolution promoting molecule resolvin-D1 prevents atrial proarrhythmic remodelling in experimental right heart disease. *Cardiovasc. Res.* **117**, 1776–1789 (2021).
138. Zhang, W. et al. Cardiac fibroblasts contribute to myocardial dysfunction in mice with sepsis: the role of NLRP3 inflammasome activation. *PLoS ONE* **9**, e107639 (2014).
139. Turner, N. A. et al. Mechanism of TNFα-induced IL-1α, IL-1β and IL-6 expression in human cardiac fibroblasts: effects of statins and thiazolidinediones. *Cardiovasc. Res.* **76**, 81–90 (2007).
140. van Nieuwenhoven, F. A., Hemmings, K. E., Porter, K. E. & Turner, N. A. Combined effects of interleukin-1α and transforming growth factor-β1 on modulation of human cardiac fibroblast function. *Matrix Biol.* **32**, 399–406 (2013).
141. Cheng, C. et al. Mutation in NPPA causes atrial fibrillation by activating inflammation and cardiac fibrosis in a knock-in rat model. *FASEB J.* **33**, 8878–8891 (2019).
142. Gawalko, M. et al. Adiposity-associated atrial fibrillation: molecular determinants, mechanisms and clinical significance. *Cardiovasc Res.* https://doi.org/10.1093/cvr/cvac093 (2022).
143. Wong, C. X. et al. Associations of epicardial, abdominal, and overall adiposity with atrial fibrillation. *Circ. Arrhythm. Electrophysiol.* https://doi.org/10.1161/CIRCEP.116.004378 (2016).
144. Mazurek, T. et al. Relation of proinflammatory activity of epicardial adipose tissue to the occurrence of atrial fibrillation. *Am. J. Cardiol.* **113**, 1505–1508 (2014).
145. Shaihov-Teper, O. et al. Extracellular vesicles from epicardial fat facilitate atrial fibrillation. *Circulation* **143**, 2475–2493 (2021).
146. Freire, M. O. & Van Dyke, T. E. Natural resolution of inflammation. *Periodontol 2000* **63**, 149–164 (2013).
147. Weissmann, G., Smolen, J. E. & Korchak, H. M. Release of inflammatory mediators from stimulated neutrophils. *N. Engl. J. Med.* **303**, 27–34 (1980).
148. Serhan, C. N. et al. Resolution of inflammation: state of the art, definitions and terms. *FASEB J.* **21**, 325–332 (2007).
149. Houck, J. C. *Chemical Messengers of the Inflammatory Process* (Elsevier/North-Holland, 1979).
150. Samuelsson, B. From studies of biochemical mechanism to novel biological mediators: prostaglandin endoperoxides, thromboxanes, and leukotrienes. Nobel Lecture, 8 December 1982. *Biosci. Rep.* **3**, 791–813 (1983).
151. Serhan, C. N. et al. The atlas of inflammation resolution (AIR). *Mol. Asp. Med.* **74**, 100894 (2020).
152. Balsinde, J., Winstead, M. V. & Dennis, E. A. Phospholipase A_2 regulation of arachidonic acid mobilization. *FEBS Lett.* **531**, 2–6 (2002).
153. Radmark, O. & Samuelsson, B. 5-Lipoxygenase: mechanisms of regulation. *J. Lipid Res.* **50**, S40–S45 (2009).
154. Takeuchi, O. & Akira, S. Pattern recognition receptors and inflammation. *Cell* **140**, 805–820 (2010).
155. Vestweber, D. How leukocytes cross the vascular endothelium. *Nat. Rev. Immunol.* **15**, 692–704 (2015).
156. Lee, S. et al. NLRP3 inflammasome deficiency protects against microbial sepsis via increased lipoxin B4 synthesis. *Am. J. Respir. Crit. Care Med.* **196**, 713–726 (2017).
157. Singh, N. K. & Rao, G. N. Emerging role of 12/15-lipoxygenase (ALOX15) in human pathologies. *Prog. Lipid Res.* **73**, 28–45 (2019).
158. Ishihara, T., Yoshida, M. & Arita, M. Omega-3 fatty acid-derived mediators that control inflammation and tissue homeostasis. *Int. Immunol.* **31**, 559–567 (2019).
159. El Kebir, D., Gjorstrup, P. & Filep, J. G. Resolvin E1 promotes phagocytosis-induced neutrophil apoptosis and accelerates resolution of pulmonary inflammation. *Proc. Natl Acad. Sci. USA* **109**, 14983–14988 (2012).
160. Pirault, J. & Back, M. Lipoxin and resolvin receptors transducing the resolution of inflammation in cardiovascular disease. *Front. Pharmacol.* **9**, 1273 (2018).
161. Furman, D. et al. Chronic inflammation in the etiology of disease across the life span. *Nat. Med.* **25**, 1822–1832 (2019).
162. Qu, X. et al. Resolvins E1 and D1 inhibit interstitial fibrosis in the obstructed kidney via inhibition of local fibroblast proliferation. *J. Pathol.* **228**, 506–519 (2012).
163. Al-Shaer, A. E., Pal, A. & Shaikh, S. R. Resolvin E1-ChemR23 axis regulates the hepatic metabolic and inflammatory transcriptional landscape in obesity at the whole genome and exon level. *Front. Nutr.* **8**, 799492 (2021).
164. Markworth, J. F. et al. Metabolipidomic profiling reveals an age-related deficiency of skeletal muscle pro-resolving mediators that contributes to maladaptive tissue remodeling. *Aging Cell* **20**, e13393 (2021).

165. Li, G. et al. NLRP3 inflammasome as a novel target for docosahexaenoic acid metabolites to abrogate glomerular injury. *J. Lipid Res.* **58**, 1080–1090 (2017).
166. Younes, R., LeBlanc, C. A. & Hiram, R. Evidence of failed resolution mechanisms in arrhythmogenic inflammation, fibrosis and right heart disease. *Biomolecules* https://doi.org/10.3390/biom12050720 (2022).
167. Chiurchiu, V. et al. Resolution of inflammation is altered in chronic heart failure and entails a dysfunctional responsiveness of T lymphocytes. *FASEB J.* **33**, 909–916 (2019).
168. Artiach, G. et al. Omega-3 polyunsaturated fatty acids decrease aortic valve disease through the resolvin E1 and ChemR23 axis. *Circulation* **142**, 776–789 (2020).
169. Jaen, R. I. et al. BML-111 treatment prevents cardiac apoptosis and oxidative stress in a mouse model of autoimmune myocarditis. *FASEB J.* **34**, 10531–10546 (2020).
170. Keyes, K. T. et al. Resolvin E1 protects the rat heart against reperfusion injury. *Am. J. Physiol. Heart Circ. Physiol.* **299**, H153–H164 (2010).
171. Kain, V. et al. Resolvin D1 activates the inflammation resolving response at splenic and ventricular site following myocardial infarction leading to improved ventricular function. *J. Mol. Cell Cardiol.* **84**, 24–35 (2015).
172. Hiram, R. Resolution-promoting autacoids demonstrate promising cardioprotective effects against heart diseases. *Mol. Biol. Rep.* https://doi.org/10.1007/s11033-022-07230-6 (2022).
173. Gilroy, D. W. et al. Inducible cyclooxygenase may have anti-inflammatory properties. *Nat. Med.* **5**, 698–701 (1999).
174. Hua, K. F. et al. Cyclooxygenase-2 regulates NLRP3 inflammasome-derived IL-1β production. *J. Cell Physiol.* **230**, 863–874 (2015).
175. Chan, M. M. & Moore, A. R. Resolution of inflammation in murine autoimmune arthritis is disrupted by cyclooxygenase-2 inhibition and restored by prostaglandin E2-mediated lipoxin A4 production. *J. Immunol.* **184**, 6418–6426 (2010).
176. Levy, B. D., Clish, C. B., Schmidt, B., Gronert, K. & Serhan, C. N. Lipid mediator class switching during acute inflammation: signals in resolution. *Nat. Immunol.* **2**, 612–619 (2001).
177. Patrono, C. Cardiovascular effects of cyclooxygenase-2 inhibitors: a mechanistic and clinical perspective. *Br. J. Clin. Pharmacol.* **82**, 957–964 (2016).
178. Hocherl, K., Endemann, D., Kammerl, M. C., Grobecker, H. F. & Kurtz, A. Cyclo-oxygenase-2 inhibition increases blood pressure in rats. *Br. J. Pharmacol.* **136**, 1117–1126 (2002).
179. Qi, Z. et al. Opposite effects of cyclooxygenase-1 and -2 activity on the pressor response to angiotensin II. *J. Clin. Invest.* **110**, 61–69 (2002).
180. Izhar, M., Alausa, T., Folker, A., Hung, E. & Bakris, G. L. Effects of COX inhibition on blood pressure and kidney function in ACE inhibitor-treated blacks and Hispanics. *Hypertension* **43**, 573–577 (2004).
181. Shiroshita-Takeshita, A., Brundel, B. J., Lavoie, J. & Nattel, S. Prednisone prevents atrial fibrillation promotion by atrial tachycardia remodeling in dogs. *Cardiovasc. Res.* **69**, 865–875 (2006).
182. Nomani, H., Mohammadpour, A. H., Moallem, S. M. H. & Sahebkar, A. Anti-inflammatory drugs in the prevention of post-operative atrial fibrillation: a literature review. *Inflammopharmacology* **28**, 111–129 (2020).
183. Zhou, X. et al. Aspirin alleviates endothelial gap junction dysfunction through inhibition of NLRP3 inflammasome activation in LPS-induced vascular injury. *Acta Pharm. Sin. B* **9**, 711–723 (2019).
184. Ofman, P. et al. Aspirin use and risk of atrial fibrillation in the Physicians' Health Study. *J. Am. Heart Assoc.* https://doi.org/10.1161/JAHA.113.000763 (2014).
185. Liu, Y. et al. Glucocorticoids promote nonphlogistic phagocytosis of apoptotic leukocytes. *J. Immunol.* **162**, 3639–3646 (1999).
186. Giles, K. M. et al. Glucocorticoid augmentation of macrophage capacity for phagocytosis of apoptotic cells is associated with reduced p130Cas expression, loss of paxillin/pyk2 phosphorylation, and high levels of active Rac. *J. Immunol.* **167**, 976–986 (2001).
187. Birnbaum, Y. et al. Augmentation of myocardial production of 15-epi-lipoxin-A_4 by pioglitazone and atorvastatin in the rat. *Circulation* **114**, 929–935 (2006).
188. Lucas, C. D. et al. Downregulation of Mcl-1 has anti-inflammatory pro-resolution effects and enhances bacterial clearance from the lung. *Mucosal Immunol.* **7**, 857–868 (2014).
189. Busillo, J. M., Azzam, K. M. & Cidlowski, J. A. Glucocorticoids sensitize the innate immune system through regulation of the NLRP3 inflammasome. *J. Biol. Chem.* **286**, 38703–38713 (2011).
190. Panoulas, V. F. et al. Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. *Rheumatology* **47**, 72–75 (2008).
191. Tripathi, R. C., Parapuram, S. K., Tripathi, B. J., Zhong, Y. & Chalam, K. V. Corticosteroids and glaucoma risk. *Drugs Aging* **15**, 439–450 (1999).
192. Nashel, D. J. Is atherosclerosis a complication of long-term corticosteroid treatment? *Am. J. Med.* **80**, 925–929 (1986).
193. Xu, Y. et al. Multiple-modulation effects of Oridonin on the production of proinflammatory cytokines and neurotrophic factors in LPS-activated microglia. *Int. Immunopharmacol.* **9**, 360–365 (2009).
194. Perregaux, D. G. et al. Identification and characterization of a novel class of interleukin-1 post-translational processing inhibitors. *J. Pharmacol. Exp. Ther.* **299**, 187–197 (2001).
195. Zahid, A., Li, B., Kombe, A. J. K., Jin, T. & Tao, J. Pharmacological inhibitors of the NLRP3 inflammasome. *Front. Immunol.* **10**, 2538 (2019).
196. Gao, R. F. et al. The covalent NLRP3-inflammasome inhibitor Oridonin relieves myocardial infarction induced myocardial fibrosis and cardiac remodeling in mice. *Int. Immunopharmacol.* **90**, 107133 (2021).
197. Wei, Z. et al. Loss of Camk2n1 aggravates cardiac remodeling and malignant ventricular arrhythmia after myocardial infarction in mice via NLRP3 inflammasome activation. *Free Radic. Biol. Med.* **167**, 243–257 (2021).
198. Brucato, A. et al. Effect of anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence: the AIRTRIP randomized clinical trial. *JAMA* **316**, 1906–1912 (2016).
199. Abbate, A. et al. Interleukin-1 blockade with anakinra and heart failure following ST-segment elevation myocardial infarction: results from a pooled analysis of the VCUART clinical trials. *Eur. Heart J. Cardiovasc. Pharmacother.* https://doi.org/10.1093/ehjcvp/pvab075 (2021).
200. Van Tassell, B. W. et al. Interleukin-1 blockade in recently decompensated systolic heart failure: results from REDHART (Recently Decompensated Heart Failure Anakinra Response Trial). *Circ. Heart Fail.* https://doi.org/10.1161/CIRCHEARTFAILURE.117.004373 (2017).
201. Klein, A. L. et al. Phase 3 trial of interleukin-1 trap rilonacept in recurrent pericarditis. *N. Engl. J. Med.* **384**, 31–41 (2021).
202. Everett, B. M. et al. Anti-inflammatory therapy with canakinumab for the prevention of hospitalization for heart failure. *Circulation* **139**, 1289–1299 (2019).
203. Thul, S., Labat, C., Temmar, M., Benetos, A. & Back, M. Low salivary resolvin D1 to leukotriene B4 ratio predicts carotid intima media thickness: a novel biomarker of non-resolving vascular inflammation. *Eur. J. Prev. Cardiol.* **24**, 903–906 (2017).
204. Bazan, H. A. et al. Circulating inflammation-resolving lipid mediators RvD1 and DHA are decreased in patients with acutely symptomatic carotid disease. *Prostaglandins Leukot. Essent. Fat. Acids* **125**, 43–47 (2017).
205. Fredman, G. Can inflammation-resolution provide clues to treat patients according to their plaque phenotype. *Front. Pharmacol.* **10**, 205 (2019).
206. Petri, M. H. et al. Aspirin-triggered lipoxin A4 inhibits atherosclerosis progression in apolipoprotein E(-/-) mice. *Br. J. Pharmacol.* **174**, 4043–4054 (2017).
207. Viola, J. R. et al. Resolving lipid mediators maresin 1 and resolvin D2 prevent atheroprogression in mice. *Circ. Res.* **119**, 1030–1038 (2016).
208. Zhang, J. et al. The anti-inflammatory mediator resolvin E1 protects mice against lipopolysaccharide-induced heart injury. *Front. Pharmacol.* **11**, 203 (2020).
209. Halade, G. V., Kain, V., Black, L. M., Prabhu, S. D. & Ingle, K. A. Aging dysregulates D- and E-series resolvins to modulate cardiosplenic and cardiorenal network following myocardial infarction. *Aging* **8**, 2611–2634 (2016).
210. Halade, G. V. & Lee, D. H. Inflammation and resolution signaling in cardiac repair and heart failure. *EBioMedicine* **79**, 103992 (2022).
211. El-Sharkawy, L. Y., Brough, D. & Freeman, S. Inhibiting the NLRP3 Inflammasome. *Molecules* https://doi.org/10.3390/molecules25235533 (2020).
212. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT04338997 (2020).
213. European Medicines Agency. *EU Clinical Trials Register* https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-000489-40/GB (2020).
214. Van Tassell, B. W. et al. Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART pilot study). *Am. J. Cardiol.* **113**, 321–327 (2014).
215. Marchetti, C. et al. OLT1177, a β-sulfonyl nitrile compound, safe in humans, inhibits the NLRP3 inflammasome and reverses the metabolic cost of inflammation. *Proc. Natl Acad. Sci. USA* **115**, E1530–E1539 (2018).
216. Wohlford, G. F. et al. Phase 1B, randomized, double-blinded, dose escalation, single-center, repeat dose safety and pharmacodynamics study of the oral NLRP3 inhibitor dapansutrile in subjects with NYHA II-III systolic heart failure. *J. Cardiovasc. Pharmacol.* **77**, 49–60 (2020).
217. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02272946 (2021).
218. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03939520 (2022).
219. Martin, J. et al. Tranilast attenuates cardiac matrix deposition in experimental diabetes: role of transforming growth factor-β. *Cardiovasc. Res.* **65**, 694–701 (2005).
220. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03490708 (2018).
221. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03923140 (2019).
222. Li, Y. et al. Pirfenidone ameliorates lipopolysaccharide-induced pulmonary inflammation and fibrosis by blocking NLRP3 inflammasome activation. *Mol. Immunol.* **99**, 134–144 (2018).
223. Aimo, A. et al. Pirfenidone as a novel cardiac protective treatment. *Heart Fail. Rev.* **27**, 525–532 (2022).
224. Ridker, P. M. et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N. Engl. J. Med.* **377**, 1119–1131 (2017).
225. Lyu, H. et al. VX-765 prevents intestinal ischemia-reperfusion injury by inhibiting NLRP3 inflammasome. *Tissue Cell* **75**, 101718 (2022).
226. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT05164120 (2022).
227. Toldo, S. et al. Targeting the NLRP3 inflammasome in cardiovascular diseases. *Pharmacol. Ther.* **236**, 108053 (2021).
228. Samuel, M. et al. Colchicine for secondary prevention of cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials. *Can. J. Cardiol.* **37**, 776–785 (2021).
229. Varghese, B. et al. Inflammation, atrial fibrillation, and the potential role for colchicine therapy. *Heart Rhythm O2* **2**, 298–303 (2021).
230. Tabbalat, R. A. et al. Effect of low-dose colchicine on the incidence of atrial fibrillation in open heart surgery patients: END-AF low dose trial. *J. Int. Med. Res.* **48**, 300060520939832 (2020).
231. Tabbalat, R. A. et al. Effect of colchicine on the incidence of atrial fibrillation in open heart surgery patients: END-AF trial. *Am. Heart J.* **178**, 102–107 (2016).
232. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03310125 (2022).
233. Aguilar, M., Heijman, J., Dobrev, D. & Nattel, S. One ring to rule them all: continuous monitoring of patients with secondary atrial fibrillation points to a unifying underlying mechanism. *Can. J. Cardiol.* **37**, 686–689 (2021).
234. Tucker, N. R. et al. Transcriptional and cellular diversity of the human heart. *Circulation* **142**, 466–482 (2020).
235. Moreira, L. M. et al. Paracrine signalling by cardiac calcitonin controls atrial fibrogenesis and arrhythmia. *Nature* **587**, 460–465 (2020).
236. Litvinukova, M. et al. Cells of the adult human heart. *Nature* **588**, 466–472 (2020).
237. Zhang, Y. et al. Gut microbiota dysbiosis promotes age-related atrial fibrillation by lipopolysaccharide and glucose-induced activation of NLRP3-inflammasome. *Cardiovasc. Res.* **118**, 785–797 (2022).

238. Rong, J. et al. Loss of hepatic angiotensinogen attenuates sepsis-induced myocardial dysfunction. *Circ. Res.* **129**, 547–564 (2021).
239. Shi, H. et al. GSDMD-mediated cardiomyocyte pyroptosis promotes myocardial I/R injury. *Circ. Res.* **129**, 383–396 (2021).
240. Takahashi, M. Role of NLRP3 inflammasome in cardiac inflammation and remodeling after myocardial infarction. *Biol. Pharm. Bull.* **42**, 518–523 (2019).
241. Walkey, A. J., Evans, S. R., Winter, M. R. & Benjamin, E. J. Practice patterns and outcomes of treatments for atrial fibrillation during sepsis: a propensity-matched cohort study. *Chest* **149**, 74–83 (2016).
242. Spodick, D. H. Frequency of arrhythmias in acute pericarditis determined by Holter monitoring. *Am. J. Cardiol.* **53**, 842–845 (1984).
243. Talreja, D. R. et al. Constrictive pericarditis in 26 patients with histologically normal pericardial thickness. *Circulation* **108**, 1852–1857 (2003).
244. Syed, F. F. et al. Atrial fibrillation as a consequence of tuberculous pericardial effusion. *Int. J. Cardiol.* **158**, 152–154 (2012).
245. Larsen, B. T. et al. Atrial giant cell myocarditis: a distinctive clinicopathologic entity. *Circulation* **127**, 39–47 (2013).
246. Anderson, B. R., Silver, E. S., Richmond, M. E. & Liberman, L. Usefulness of arrhythmias as predictors of death and resource utilization in children with myocarditis. *Am. J. Cardiol.* **114**, 1400–1405 (2014).
247. Blagova, O. V. et al. Myocardial biopsy in "idiopathic" atrial fibrillation and other arrhythmias: nosological diagnosis, clinical and morphological parallels, and treatment. *J. Atr. Fibrillation* **9**, 24–30 (2016).
248. Subahi, A. et al. Impact of atrial fibrillation on patients hospitalized for acute myocarditis: insights from a nationally-representative United States cohort. *Clin. Cardiol.* **42**, 26–31 (2019).
249. Rasal, G. et al. Arrhythmia spectrum and outcome in children with myocarditis. *Ann. Pediatr. Cardiol.* **14**, 366–371 (2021).
250. Dunbar, D. N. et al. Intracavitary electrode catheter cardioversion of atrial tachyarrhythmias in the dog. *J. Am. Coll. Cardiol.* **7**, 1015–1027 (1986).
251. Kumagai, K., Yamanouchi, Y., Tashiro, N., Hiroki, T. & Arakawa, K. Low energy synchronous transcatheter cardioversion of atrial flutter/fibrillation in the dog. *J. Am. Coll. Cardiol.* **16**, 497–501 (1990).
252. Ali, I. M., Butler, C. K., Armour, J. A. & Murphy, D. A. Modification of supraventricular tachyarrhythmias by stimulating atrial neurons. *Ann. Thorac. Surg.* **50**, 251–256 (1990).
253. Yamanouchi, Y., Kumagai, K., Tashiro, N., Hiroki, T. & Arakawa, K. Transesophageal low-energy synchronous cardioversion of atrial flutter/fibrillation in the dog. *Am. Heart J.* **123**, 417–420 (1992).
254. Ortiz, J. et al. Mechanism of spontaneous termination of stable atrial flutter in the canine sterile pericarditis model. *Circulation* **88**, 1866–1877 (1993).
255. Ortiz, J. et al. Atrial defibrillation using temporary epicardial defibrillation stainless steel wire electrodes: studies in the canine sterile pericarditis model. *J. Am. Coll. Cardiol.* **26**, 1356–1364 (1995).
256. Cmolik, B. L. et al. Successful atrial defibrillation with very-low-energy shocks by means of temporary epicardial wire electrodes. *J. Thorac. Cardiovasc. Surg.* **111**, 392–397 (1996). discussion 397-398.
257. Kumagai, K., Khrestian, C. & Waldo, A. L. Simultaneous multisite mapping studies during induced atrial fibrillation in the sterile pericarditis model. Insights into the mechanism of its maintenance. *Circulation* **95**, 511–521 (1997).
258. Sokoloski, M. C. et al. Safety of transvenous atrial defibrillation: studies in the canine sterile pericarditis model. *Circulation* **96**, 1343–1350 (1997).
259. Kumagai, K., Uno, K., Khrestian, C. & Waldo, A. L. Single site radiofrequency catheter ablation of atrial fibrillation: studies guided by simultaneous multisite mapping in the canine sterile pericarditis model. *J. Am. Coll. Cardiol.* **36**, 917–923 (2000).
260. Becker, R. et al. Suppression of atrial fibrillation by multisite and septal pacing in a novel experimental model. *Cardiovasc. Res.* **54**, 476–481 (2002).
261. Kumagai, K., Nakashima, H., Gondo, N. & Saku, K. Antiarrhythmic effects of JTV-519, a novel cardioprotective drug, on atrial fibrillation/flutter in a canine sterile pericarditis model. *J. Cardiovasc. Electrophysiol.* **14**, 880–884 (2003).
262. Goldstein, R. N., Khrestian, C., Carlsson, L. & Waldo, A. L. Azd7009: a new antiarrhythmic drug with predominant effects on the atria effectively terminates and prevents reinduction of atrial fibrillation and flutter in the sterile pericarditis model. *J. Cardiovasc. Electrophysiol.* **15**, 1444–1450 (2004).
263. Ryu, K. et al. Characterization of the critical cycle length of a left atrial driver which causes right atrial fibrillatory conduction. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **2004**, 3960–3963 (2004).
264. Ryu, K., Sahadevan, J., Khrestian, C. M., Stambler, B. S. & Waldo, A. L. Use of fast Fourier transform analysis of atrial electrograms for rapid characterization of atrial activation – implications for delineating possible mechanisms of atrial tachyarrhythmias. *J. Cardiovasc. Electrophysiol.* **17**, 198–206 (2006).
265. Tselentakis, E. V., Woodford, E., Chandy, J., Gaudette, G. R. & Saltman, A. E. Inflammation effects on the electrical properties of atrial tissue and inducibility of postoperative atrial fibrillation. *J. Surg. Res.* **135**, 68–75 (2006).
266. Bui, H. M., Khrestian, C. M., Ryu, K., Sahadevan, J. & Waldo, A. L. Fixed intercaval block in the setting of atrial fibrillation promotes the development of atrial flutter. *Heart Rhythm.* **5**, 1745–1752 (2008).
267. Ryu, K., Sahadevan, J., Khrestian, C. M., Stambler, B. S. & Waldo, A. L. Frequency analysis of atrial electrograms identifies conduction pathways from the left to the right atrium during atrial fibrillation – studies in two canine models. *J. Cardiovasc. Electrophysiol.* **20**, 667–674 (2009).
268. Rossman, E. I. et al. The gap junction modifier, GAP-134 [(2S,4R)-1-(2-aminoacetyl)-4-benzamido-pyrrolidine-2-carboxylic acid], improves conduction and reduces atrial fibrillation/flutter in the canine sterile pericarditis model. *J. Pharmacol. Exp. Ther.* **329**, 1127–1133 (2009).
269. Matsumoto, N. et al. Vanoxerine, a new drug for terminating atrial fibrillation and flutter. *J. Cardiovasc. Electrophysiol.* **21**, 311–319 (2010).
270. Cakulev, I. et al. Oral vanoxerine prevents reinduction of atrial tachyarrhythmias: preliminary results. *J. Cardiovasc. Electrophysiol.* **22**, 1266–1273 (2011).
271. Bhimani, A. A. et al. Ranolazine terminates atrial flutter and fibrillation in a canine model. *Heart Rhythm.* **11**, 1592–1599 (2014).
272. Sadrpour, S. A. et al. Termination of atrial flutter and fibrillation by K201's metabolite M-II: studies in the canine sterile pericarditis model. *J. Cardiovasc. Pharmacol.* **65**, 494–499 (2015).
273. Goldstein, R. N., Ryu, K., Khrestian, C., van Wagoner, D. R. & Waldo, A. L. Prednisone prevents inducible atrial flutter in the canine sterile pericarditis model. *J. Cardiovasc. Electrophysiol.* **19**, 74–81 (2008).
274. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT04575753 (2020).
275. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT04997057 (2022).
276. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03609541 (2022).
277. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT04697719 (2022).
278. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02322073 (2021).

Acknowledgements
The authors thank T. Poppenborg (Institute of Pharmacology, University Duisburg-Essen, Germany) for help with preparing the figures for initial submission and A. Saljic (Institute of Pharmacology, University Duisburg-Essen, Germany) for critical review of the tables. The authors are supported by funding from the National Institutes of Health (R01HL136389, R01HL131517, R01HL089598 and R01HL163277 to D.D.; R01HL136389, R01HL147108 and R01HL163277 to N.L.), the German Research Foundation (DFG, Do 769/4-1 to D.D.), the European Union (large-scale integrative project MAESTRIA, no. 965286 to D.D.), the Netherlands Organization for Scientific Research (NWO/ZonMW Vidi 09150171910029 to J.H.), the Montreal Heart Institute Foundation (4800 to R.H.), the Canada Foundation for Innovation (42228 to S.N. and R.H.), the Canadian Institutes of Health Research (148401 to S.N.), and the AHA (Established Investigator Award 936111 to N.L).

Author contributions
All the authors contributed substantially to all aspects of the article.

Competing interests
The authors declare no competing interests.

Peer review information
Nature Reviews Cardiology thanks Antonio Abbate, Shih-Ann Chen and David van Wagoner for their contribution to the peer review of this work.

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