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Electroimmunology and cardiac arrhythmia

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Abstract

Conduction disorders and arrhythmias remain difficult to treat and are increasingly prevalent owing to the increasing age and body mass of the general population, because both are risk factors for arrhythmia. Many of the underlying conditions that give rise to arrhythmia — including atrial fibrillation and ventricular arrhythmia, which frequently occur in patients with acute myocardial ischaemia or heart failure — can have an inflammatory component. In the past, inflammation was viewed mostly as an epiphenomenon associated with arrhythmia; however, the recently discovered inflammatory and non-canonical functions of cardiac immune cells indicate that leukocytes can be arrhythmogenic either by altering tissue composition or by interacting with cardiomyocytes; for example, by changing their phenotype or perhaps even by directly interfering with conduction. In this Review, we discuss the electrophysiological properties of leukocytes and how these cells relate to conduction in the heart. Given the thematic parallels, we also summarize the interactions between immune cells and neural systems that influence information transfer, extrapolating findings from the field of neuroscience to the heart and defining common themes. We aim to bridge the knowledge gap between electrophysiology and immunology, to promote conceptual connections between these two fields and to explore promising opportunities for future research.

The clinical presentation of patients with heart rhythm abnormalities ranges from a lack of symptoms to sudden cardiac arrest, which can result in sudden cardiac death (SCD). SCD is a major public health problem, accounting for 50–60% of deaths in patients with

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coronary artery disease. With an incidence between 50 and 100 per 100,000 in the general population, SCD is a leading cause of death worldwide[1–5]. Even when cardiac arrest occurs in a hospital, survival rates are only 3–10%, highlighting an unmet clinical need for risk prediction, prevention and adequate treatment of arrhythmias[6–8].

Classic electrophysiological concepts provide mechanistic insights into the pathophysiology underlying arrhythmogenesis, including abnormal automaticity, triggered activity and re-entry (FIG. 1). Although these mechanisms are well characterized, the prevalence of sudden cardiac arrest remains high. Effective treatment options are mostly limited to implantation of a defibrillator, and rates of SCD remain high, perhaps owing to the lack of preventive therapies. Expanding our understanding of the pathobiology of the arrhythmia beyond electrophysiology might help to develop new approaches to prevention and treatment.

New insights into leukocyte function suggest that immune cell populations might have a role in normal heart rhythm via crosstalk with cardiomyocytes and hypothetically also in the pathophysiology of arrhythmogenesis. Re-entrant arrhythmias, in which anatomical obstacles are arrhythmogenic, are particularly associated with leukocyte recruitment, which, we hypothesize, shapes the composition of the arrhythmogenic substrate. Re-entry is the underlying mechanism for most sustained cardiac arrhythmias and is thought to be based on two components[3]: a trigger, which is often a mild form of arrhythmia such as a premature ventricular complex, and a substrate, leading to sustained and prolonged arrhythmia, including structural remodelling such as scar formation after acute myocardial infarction (MI) or patchy fibrosis in the setting of hypertension and hypertrophy. The underlying structural heart diseases are diverse and range from acute events to chronic processes, each with unique electrophysiological properties. Re-entrant arrhythmias can also cause atrial fibrillation (AF)[9], a common type of arrhythmia[10,11] (TABLE 1). Treating re-entrant arrhythmias often begins with resolving the underlying disease, such as alleviating ischaemia or repairing a valve. However, understanding the specific electrophysiological characteristics of structural heart disease is important for the development of targeted treatment options.

In this Review, we aim to integrate electrophysiology and immunology by focusing on conceptual bridges between these two fields. We summarize basic principles of leukocyte biology, focusing on those that are relevant to conduction in the heart and also in the brain, where resident macrophages (microglia) modulate information transfer by neurons. We discuss the clinical association between leukocyte expansion and arrhythmias and explore emerging mechanistic data on the causal role of leukocytes in arrhythmogenesis. Furthermore, we examine inflammation as a potential therapeutic target and highlight technical developments in immunology and electrophysiology that will facilitate future investigation into the interactions between leukocytes and conducting tissue. We are promoting the case for a more comprehensive consideration of the roles of leukocytes in cardiac conduction and arrhythmia; however, we do not discount the undisputed contributions by other heart cells that have been reviewed previously[12–14].

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Charging leukocytes for defence

The innate immune system

Innate immunity refers to immune responses that are inborn and not learned, as opposed to lymphocyte-based responses that form the adaptive immune system[15]. The innate immune response — a crucial step in the first-line host defence against infectious agents and tissue damage — is mounted by the epithelial and endothelial barriers, neutrophils, macrophages and monocytes, dendritic cells, natural killer cells and mast cells[16]. The innate immune system is activated when Toll-like receptors (TLRs), NOD-like receptors or RIG-I-like receptors recognize pathogen-associated molecular patterns[17]. Some of these receptors also recognize self-derived host molecules called damage-associated molecular patterns, which arise from tissue injury and inflammation[18]. The binding of ligands to these receptors releases cytokines and chemokines, which recruit and activate additional immune cells.

Leukocytes

Leukocytes are the cellular protagonists of immune defence, but also have non-immunological functions that are dependent on the organ in which they reside. In this section, we briefly summarize the functional properties of leukocytes and their subsets, focusing on the heart (BOX 1). Monocytes and macrophages are the most numerous leukocytes in the heart and have pivotal roles in cardiovascular pathophysiology. Monocytes are produced in the bone marrow and circulate in the bloodstream before migrating to tissues where they differentiate into macrophages or dendritic cells[19]. In mice, mature monocytes can be identified by the expression of CD11b and CD115 and distinguished by the surface marker Ly6C. Ly6C^{high} monocytes preferentially accumulate at sites of inflammation and differentiate into macrophages. Ly6C^{low} monocytes patrol the vasculature, remove damaged endothelial cells, and maintain vascular integrity and homeostasis[20,21]. Macrophages reside in almost all tissues. In the murine heart, macrophages constitute 7–8% of non-cardiomyocyte cells[22,23], and single-cell RNA-sequencing data indicate that 5–10% of cells in the human heart are leukocytes[24].

Cardiac macrophage subsets are classified by their surface expression of CC-chemokine receptor 2 (CCR2) and major histocompatibility complex (MHC) class II molecules. Human and mouse hearts contain at least three subpopulations of macrophages: CCR2^{-}MHCII^{low}, CCR2^{-}MHCII^{high} and CCR2^{high}MHCII^{high} (REF.[25]). The two CCR2^{-} macrophage subsets have embryonic origins and are maintained by local proliferation in the myocardium, independent of blood monocytes[26]. CCR2^{-} macrophages reside predominantly in the myocardial wall and participate in coronary vasculature development[27]. The CCR2^{+} macrophage subset (5–15%) is the smallest in healthy hearts and derives from blood monocytes. Single-cell RNA-sequencing studies have revealed additional cardiac macrophage subsets[28–30], but their functional relevance remains to be determined.

Electrophysiology and leukocyte function

Like cardiomyocytes, neurons and many other cell types, leukocytes express various channels to regulate their membrane potential as well as signalling by Ca^{2+} and other ions. These cell features regulate gene expression, cytokine release, cell activation and

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migration[31] and, consequently, inflammation[32,33]. The resting membrane potential of leukocytes ranges from −30 mV to −60 mV (REFs[34–39]) and is determined by the equilibrium potentials of ions such as K^+, Na^+ and Cl^-, which traverse the cell membrane through specific channels.

In the 1970s, K^+ currents in peritoneal macrophages were first described[34,35,40]. K^+ channels in macrophages include the voltage-gated K^+ channel $K_v1.3$ and the Ca^{2+}-activated K^+ channel $K_{Ca}3.1$, and these channels mainly promote a negative membrane potential. $K_v1.3$ is activated by membrane potential depolarization[41]. Although $K_v1.3$ is the predominant form of voltage-gated K^+ channel, $K_v1.5$ is also present in myeloid cells and can form heterotetramers with $K_v1.3$. The ratio of $K_v1.3$ to $K_v1.5$ in the K_v complex can vary, leading to biophysically and pharmacologically distinct channels[42,43]. Interestingly, cell activation with either the bacterial wall component lipopolysaccharide or tumour necrosis factor (TNF) increases $K_v1.3$ activity in macrophages[42,44]. By contrast, anti-inflammatory signals such as glucocorticoids downregulate $K_v1.3$ and increase the presence of $K_v1.5$ in the heteromeric K_v channels[42,44]. Unlike $K_v1.3$, $K_{Ca}3.1$ is voltage-independent and is activated by the binding of Ca^{2+} to calmodulin, which is associated with the C terminus of the $K_{Ca}3.1$ channel[45]. Opening of $K_{Ca}3.1$ channels hyperpolarizes the membrane potential following an increase in the intracellular Ca^{2+} concentration.

In lymphocytes, the relative contributions of $K_v1.3$ and $K_{Ca}3.1$ to Ca^{2+} influx are determined by their expression levels, which depend on the lymphocyte subset and on cell activation[33,46,47]. Under resting conditions, naive T cells predominantly express the $K_v1.3$ channel[46]. Following activation, T cells transcriptionally upregulate $K_{Ca}3.1$, which sustains Ca^{2+} signalling[47]. T helper 1 and T helper 2 lymphocytes predominantly express $K_{Ca}3.1$ and depend on $K_{Ca}3.1$ for cytokine production, whereas T helper 17 cells mainly express $K_v1.3$, which regulates IL-17 production[33]. Taken together, activation of $K_v1.3$ by depolarization and of $K_{Ca}3.1$ by Ca^{2+} preserves the negative membrane potential required for Ca^{2+} entry.

Transient receptor potential cation channel subfamily M member 4 (TRPM4) is another essential regulator of the membrane potential of leukocytes and is much more permeable to Na^+ than to Ca^{2+} (REF.[48]). TRPM4 channels are activated by increases in intracellular Ca^{2+} concentration, resulting in Na^+ influx and membrane depolarization, which then limits Ca^{2+} influx because of the reduction in the electrochemical gradient.

Ca^{2+} is a second messenger that regulates proliferation, gene expression and motility in leukocytes. Ca^{2+} release-activated Ca^{2+} (CRAC) channels (ORAI1, ORAI2 and ORAI3), known as store-operated Ca^{2+} channels, are present in most leukocytes. Activation of CRAC channels is mediated by stromal interaction molecule 1 (STIM1) and STIM2, which are located in the endoplasmic reticulum membrane. Following the depletion of endoplasmic reticulum Ca^{2+} stores, STIM1 and STIM2 activate, oligomerize and translocate to the junctions between the endoplasmic reticulum and the plasma membrane, into which ORAI1 is recruited, resulting in Ca^{2+} influx[49–51]. The importance of ion channels for inflammation is exemplified by the observation that $CD4^+$ and $CD8^+$ T cells from mice and humans that are deficient in ORAI1 and/or STIM1 have defective production of many cytokines, including IL-2, IL-4, IL-17, IFNγ and TNF[52,53]. Moreover, B cells from mice lacking either

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ORAI1 or STIM1 and STIM2 have less B cell receptor-induced proliferation[54]. The crucial roles of CRAC channels in adaptive immune responses are well established, but little is known about their function in innate immunity.

Ionotropic P2X receptors are ligand-gated, non-selective cation channels that are activated by extracellular ATP and facilitate the influx of Na^+, Ca^{2+} and other cations[55]. P2X receptor opening causes Ca^{2+} influx and activates downstream signalling, leading to the proliferation of T cells and B cells[56,57]. Ion and connexin channel expression in leukocytes based on data from the Immunological Genome Project[58] is summarized in TABLE 2, and their known functions are summarized in Supplementary Table 1. Taken together, these data indicate that leukocyte functions — and inflammation as a consequence[32,33] — are regulated by ion flux across the leukocyte plasma membrane and the resulting changes in membrane potential. Of note, leukocytes and cardiomyocytes share several ion channels, such as ORAI1 and its activator STIM1. Genetic variants in *ORAI1* or *STIM1* in humans that lead to the expression of non-functional ORAI1 or STIM1 protein or a complete lack of the protein are associated with a clinical phenotype characterized by immunodeficiency[59]. Because individuals who lack ORAI1 or STIM1 have lethal immunodeficiency and die in their first years of life, the influence of a sustained lack of these proteins on the heart might not be apparent. However, cardiomyocyte-restricted *Stim1*-knockdown mice have a proclivity for arrhythmia, involving decreased conduction velocity and increased action potential duration (APD)[60]. How cardiac immune cell functions are influenced by the regular depolarization and repolarization of the surrounding myocardium, electrolyte imbalance or even arrhythmia is so far unknown. Given that the heart has a sizeable population of resident immune cells that might affect cardiomyocyte health[61] and extracellular matrix composition, this question merits further investigation.

Leukocytes in cardiac conduction

Gap junctions, formed by the connexin protein family, allow cytoplasmic exchange of ions, nucleotides, metabolites and electrical signals between connected cells[62]. Connexins are present in almost all cells, including cardiomyocytes and leukocytes. In the healthy heart, gap junctions provide pathways for intercellular current flow, enabling coordinated propagation of the action potential[63,64]. Direct macrophage–cardiomyocyte interaction through connexin 43 (Cx43)-containing gap junctions was found in mouse and human hearts[37]. This contact enables electrical coupling between the two cell types. Patch-clamp experiments revealed that many macrophages rhythmically depolarize when they are coupled to cardiomyocytes. In vitro coupling rendered the resting membrane potential of cardiomyocytes more positive — a change that was reversed by pharmacological blockade of Cx43 (REF.[37]). Computational modelling indicated that coupling of higher numbers of macrophages to one cardiomyocyte (a reasonable assumption given that cardiomyocytes are much larger than macrophages) lowers the action potential upstroke and overshoot, leading to earlier repolarization and a shorter refractory period[37].

Optical clearing of mouse and human heart samples followed by confocal fluorescence microscopy documented that macrophages are concentrated not only in the distal atrioventricular node, which electrically connects the atria and the ventricles, but also in

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the sinus node[37]. In vivo, macrophage-specific genetic ablation of *Cx43* (also known as *Gja1*) delayed conduction through the atrioventricular node, and depletion of myeloid cells in CD11bDTR mice resulted in progressive atrioventricular block[37]. Collectively, these findings suggest that macrophages support normal electrical conduction and influence cardiac conduction through gap junctions. In addition to questions about whether this communication might hypothetically shape arrhythmias, which we discuss below, we speculate that immune cells can affect electrical communication between cardiomyocytes and influence conduction via currently unknown mechanisms, perhaps by shaping the development of the conduction system, regulating turnover of insulating extracellular matrix, interfering with gap junction communication between cardiomyocytes, or regulating ion channel expression and function in cardiomyocytes. The abundance of macrophages in cardiac conduction system structures[37] suggests that they have undiscovered roles. Single-cell RNA-sequencing analysis of mouse atrioventricular node samples[37] indicated that macrophages in the atrioventricular node cluster according to the typical subset markers MHC class II and CCR2 and express conduction-related genes, including those encoding ion channels, such as *Cacna1c* ($Ca_v1.2$), *Kcnj2* ($K_{ir}2.1$), *Kcnq1* ($K_v7.1$), *Hcn2* (HCN2) and *Kcnh2* ($K_v11.1$) (TABLE 2; Supplementary Table 1). This single-cell RNA-sequencing study contains data on 76 macrophages isolated by microdissection of the atrioventricular node but lacks a comparison with macrophages from a remote control region[37]. Whether atrioventricular node macrophages differ from other macrophages located in the atria or ventricles remains unresolved. Another important question is which of these ion channels are functional in cardiac macrophages. Furthermore, whether other immune cells, although less numerous than macrophages, also couple to cardiomyocytes is worth exploring.

Leukocytes and neural function

Similar to the population of macrophages resident in the heart, the brain contains a large population of resident innate immune cells. Another similarity inviting a comparison of these organ systems is illustrated by electrophysiological studies showing that the behaviour of cardiac Purkinje fibres is electrically similar to that of nerve axons[65]. Both the heart and the brain contain a massive number of electrically excitable cells (cardiomyocytes and neurons, respectively), which rely on an organized conduction system to function. In the brain, axonal projections from different neuronal subtypes propagate electrical impulses to specific anatomical locations. Microglia, the brain's equivalent of tissue-resident macrophages, interact with almost all cell types in the central nervous system to mediate developmental programmes and maintain homeostasis[66].

Microglia have essential roles in excitatory networks in the brain. During development, microglia engulf synapse components and actively participate in synapse maturation[67,68], raising the question as to whether cardiac macrophages participate in the development of the cardiac conduction system. IL-33 produced by astrocytes in the brain promotes microglial synapse engulfment, indicating that astrocyte–microglia communication is required for synapse homeostasis during development[69]. Moreover, microglia contact with dendrites induces filopodia formation in the developing somatosensory cortex[70]. Microglia are also required for the development of oligodendrocytes, their progenitors and the subsequent myelination process[71]. In adults, microglia maintain the oligodendrocyte progenitor pool

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and modulate synaptic neurotransmission via microglia–astrocyte crosstalk. Activation of microglia by lipopolysaccharide induces a rapid increase in spontaneous excitatory post-synaptic currents in hippocampal slice preparations[72]. These activated microglia release small amounts of ATP, which targets P2Y1 receptors located on astrocytes, leading to glutamate release; subsequently, glutamate acts on neuronal receptors[72].

Connexin expression by microglia depends heavily on the context of cell activation, which has not been explored in cardiac macrophages. Whereas Cx32 and Cx36 are expressed in the resting surveillance state[73,74], Cx43 expression is rarely detected in steady-state microglia. Intercellular electrical coupling was observed between cultured microglia and neurons through Cx36 gap junctions[73]. Approximately one-third of co-cultured microglia and neuron pairs showed evidence of electrical coupling, with small unitary conductance and very low voltage sensitivity, which is consistent with the characteristics of Cx36 channels. This situation is reminiscent of the coupling between cardiac macrophages and cardiomyocytes via Cx43 (REF.[37]). Likewise, Cx36 is involved in coupling between microglial pairs[73], raising the question as to whether cardiac macrophages couple to each other. Of note, >2 weeks of co-culture might have affected the native characteristics of microglia–neuron crosstalk, especially given that Cx36 expression is low in non-cultured naive microglia, as reported by the Immunological Genome Project[58]. Nevertheless, the findings support the notion that brain tissue-resident macrophages couple with excitable cells and contribute to electrical conduction in the brain, just as in the heart.

Despite the obvious differences between the brain and the heart, both are organs in which the primary function directly depends on electrical activity; therefore, comparing them might be instructive. Direct electrical coupling between tissue-resident macrophages and cardiomyocytes[37] or neurons[73] has been observed in culture, but in vivo data on coupling are currently available only for the heart[37]. Extrapolating the observation that microglia influence synaptic neuron-to-neuron communication leads us to wonder whether cardiac macrophages might have similar roles. We speculate that cardiac macrophages might modulate the excitation transfer between two neighbouring cardiomyocytes, perhaps by influencing gap junction abundance or deposition of insulating extracellular matrix by fibroblasts. One question arising from the microglia data on synaptic pruning[67,68] is whether macrophages influence the embryonic development of the conduction system. These conceptual connections underscore the value of neuroscience tools for research on cardiac conduction, as indicated by the use of optogenetics[37] and in vivo heart microscopy[75] in conjunction with ion and voltage reporters[76,77] (BOX 2).

Inflammation and arrhythmias

Clinical associations

AF is a prevalent condition, with a rising incidence in elderly individuals[10,78]. The lack of organized atrial contraction causes blood stasis, which increases the risk of thrombus formation and stroke[79]. Moreover, during AF, the ventricles might not fill adequately, reducing cardiac output and elevating the risk of heart failure (HF), cardiovascular death and SCD[80]. Repetitive high-frequency ectopy and re-entry are thought to be the major AF-maintaining mechanisms in atria with vulnerable morphological substrates[81,82].

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More than 20 years of research point to an association between inflammation and AF[83–85]. Leukocyte recruitment occurs in the atria of patients with AF[86–88]. Among immune cells, $CD68^+$ macrophages are more numerous than adaptive immune cells such as $CD3^+$ T lymphocytes in the atria of patients with AF[89]. Leukocytes have an important role in local inflammation in releasing cytokines and chemokines, such as interleukins and TNF, and activating innate signalling pathways, such as the inflammasome[90]. These actions contribute to structural, electrical and mechanical heterogeneity in the atrial myocardium and thereby facilitate the pathogenesis of arrhythmogenesis (see Inflammatory mechanisms below). Case–control studies have shown elevated circulating levels of inflammatory molecules (C-reactive protein (CRP), heat shock protein 27, IL-6 and TNF) in patients with AF[91–93]. CRP has been linked to the development of AF[94,95]: in the Cardiovascular Health Study[96] involving 5,806 participants, higher circulating CRP levels were associated with the presence and future development of AF. Anti-inflammatory therapy reduced the burden of AF in a dog model of sterile pericarditis and in patients after cardiac surgery[97–100]. Profiling inflammatory biomarkers and other signalling molecules might help to predict the risk of AF in patients[101,102].

Multiple major cardiovascular risk factors and inflammation-associated conditions, including hypertension, coronary artery disease, HF and obesity, are linked to AF[103–105]. Although various pathological mechanisms, including endothelial dysfunction and myocardial ischaemia, underlie these risk factors, they might converge on a final common pathway: leukocyte expansion in the atrial myocardium and consequent production of pro-inflammatory cytokines.

The interconnected development of HF and AF involves inflammatory components that probably interact with neurohumoral activation, morphological remodelling, fibrosis and disruption of cardiomyocyte energy metabolism; together, these actions alter the myocardial substrate, leading to arrhythmogenesis. In patients with AF, the arrhythmogenic substrate involves three electrophysiological mechanisms: abnormal automaticity[106], triggered activity[107,108] and re-entry[109]. The most common underlying mechanisms for ventricular tachycardia (VT) or ventricular fibrillation (VF) are early or delayed afterdepolarizations, which can affect the cardiomyocyte APD. Several inflammatory mechanisms might contribute to ventricular dysfunction (reviewed previously[110]).

New-onset AF is common in patients with acute sepsis[111]. The pathogenesis of sepsis includes the interaction between pro-inflammatory cytokines and stress hormones, autonomic dysfunction, extravascular volume shifts and cardiovascular compromise[112], all of which can beget AF. Signs of systemic inflammation consist of changes in leukocyte count, fever and elevated heart rate[113]. AF commonly occurs in patients with severe sepsis[114–116] and results in increased morbidity and mortality[117,118]. Higher CRP levels occur before AF in patients with septic shock[116], which suggests that systemic inflammation might trigger AF. In support of this hypothesis, hydrocortisone therapy was associated with a lower risk of AF and reduced production of pro-inflammatory cytokines in patients with septic shock[119,120].

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In contrast to AF, third-degree atrioventricular block or severe arrhythmia affecting the ventricles can have acute and marked haemodynamic consequences, resulting in high mortality[121] (TABLE 1). Patients presenting with ventricular tachyarrhythmias have a substantially increased mortality, regardless of the underlying disease[122–125]. The electrophysiological origins of VT and VF include abnormal automaticity, triggered activity and re-entry[126–128]. Ventricular arrhythmias have multifactorial origins and various combinations of derangements in ion channel distribution and expression patterns, intracellular ion dynamics, anatomical features and metabolic pathways (reviewed previously[129–131]).

Myocarditis remains a major cause of SCD in young individuals[132] and is usually caused by viral infections or autoimmunity leading to heterogeneous clinical manifestations, including life-threatening ventricular tachyarrhythmias[133]. Acute myocarditis is associated with massive cardiac recruitment of macrophages and T lymphocytes, oedema and cell necrosis, all of which can contribute to electrical instability[134–137]. Mild symptoms of infection, elevated leukocyte count and increased CRP levels often precede the onset of life-threatening ventricular arrhythmias and sudden cardiac arrest[138]. Polymorphic and irregular ventricular arrhythmias are common during the active phase, whereas monomorphic, regular-shaped tachyarrhythmias are associated with healed myocarditis[139]. The underlying mechanisms remain elusive, and hypotheses range from abnormal Ca^{2+} handling[140] to long-lasting, disturbed expression patterns of gap junctions[141]. A series of patients with viral myocarditis complicated by VF showed electrocardiographic features of Brugada syndrome, a genetic disorder caused by genetic variation in *SCN5A*, encoding the cardiac Na^+ channel ($Na_v1.5$), and associated with ST-segment elevation and right bundle branch block[124]. These patients showed electrocardiogram (ECG) changes that persisted after acute myocardial inflammation had subsided, suggesting structural and electrical remodelling of the ventricular substrate. For patients with Brugada syndrome, temperature-dependent alteration of ion-channel function might trigger ventricular arrhythmias during infection, indicating that fever might be arrhythmogenic[142]. This association aligns with previous findings linking febrile illness with infectious aetiology to increased vulnerability to VT and VF, not only in patients with Brugada syndrome[143–145] but also in patients without known repolarization abnormalities[146–148]. Taken together, these data support the hypothesis that infection and fever might initiate life-threatening ventricular arrhythmias. Although no mechanistic data are available, we speculate that leukocytes recruited to the myocardium contribute to the occurrence of arrhythmia, especially in patients with myocarditis.

VF often occurs after MI[149,150]. The onset of ventricular arrhythmias after MI follows certain temporal dynamics: the first 3 days constitute an acute phase, and a subsequent chronic phase is dominated by ventricular remodelling[151]. The ischaemia-induced cardiomyocyte death causes a rapid, massive infiltration of monocytes and neutrophils. The resulting increase in tissue heterogeneity might contribute to the markedly higher risk of ventricular arrhythmias early after MI[122,152–155], when the electrophysiological properties of the ventricular substrate change profoundly and in a layer-specific manner[156]. The tissue heterogeneity in the peri-infarct region, which is particularly rich in leukocytes, favours arrhythmogenesis by forming re-entrant circuits with zones of slow conduction or complete block, leading to sustained monomorphic VTs[157,158]. Very large, acute ischaemic

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zones might create the substrate for a transiently stable re-entrant circuit that can sustain a monomorphic re-entrant tachycardia[159]. In subacute MI, the physiological substrate continues to change. Whereas macrophages and cardiomyocytes produce varying amounts of inflammatory cytokines and chemokines, such as IL-1, IL-6, TNF and CC-chemokine ligand 2 (REFs[160–162]), cardiac fibroblasts release haematopoietic growth factors, such as granulocyte–macrophage colony-stimulating factor[163], and endothelial cells become activated, possibly also contributing to conduction heterogeneity in the ventricular substrate. During the subsequent development of myocardial scar tissue and inflammation-associated HF, ventricular arrhythmias and sudden cardiac arrest can occur[164]. To address the increased risk of SCD, patients who experience VT or VF episodes >48 h after MI are implanted with defibrillators that effectively terminate life-threatening arrhythmias[165]. Selection criteria for this treatment are weak, given that 80% of patients experiencing SCD do not meet the criteria for implantation of a defibrillator[166,167]. Inflammatory biomarkers might improve risk prediction for ventricular arrhythmias and guide patient selection for device implantation, if further research documents a robust association between these biomarkers and SCD.

Inflammatory mechanisms

In accordance with the associations described above, emerging data suggest a causal relationship between inflammation and arrhythmia. We postulate that four distinct electroimmunological pathways can lead to arrhythmia: leukocyte release of cytokines that act on cardiomyocytes; altered electrotonic gap junction communication between conducting cells and leukocytes; leukocyte-instigated, insulating fibrosis; and autoimmune channelopathies.

Inflammatory mediators acting on cardiomyocytes.

The secretion of inflammatory cytokines by leukocytes can affect the capacity of cardiomyocytes to conduct properly. Clinical data associate arrhythmias with elevated levels of IL-1β[168,169], IL-6 (REFs[170–172]), IL-8 (REF.[173]), IL-10 (REF.[173]), IL-17 (REFs[174–176]) and TNF[168,169,177]. Data obtained in mouse and dog models of AF indicate that macrophages, which are a major source of cytokines, have a causal role in the pathogenesis of AF; specifically, lipopolysaccharide-stimulated pro-inflammatory macrophages were shown to induce atrial electrical remodelling, increase AF inducibility and decrease atrial effective refractory period[178]. Macrophage depletion with clodronate liposomes protected mouse atria from lipopolysaccharide-triggered electrical remodelling[178]. Macrophage-specific *Il1b* knockout reversed lipopolysaccharide-mediated phenotypes in atrial myocytes[178]. Macrophage-derived IL-1β also prolonged the APD and lowered K^+ currents in diabetic mice, changes that increased the susceptibility to arrhythmia[179]. IL-1β reduced L-type Ca^{2+} current density in neonatal mouse ventricular myocytes by activating protein kinase C[180]. In agreement with these findings, IL-1 receptor inhibition raised conduction velocity and curtailed spontaneous and inducible ventricular arrhythmias in mice with acute MI[181].

These preclinical data are particularly interesting when viewed together with the CANTOS trial[182], which demonstrated that anti-inflammatory therapy targeting the IL-1β pathway

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with canakinumab led to significantly lower rates of recurrent cardiovascular events. IL-1β and IL-6, which is downstream of Il-1β, both affect cardiomyocyte Ca^{2+} regulation; although both cytokines prolonged the APD, IL-6 worsened Ca^{2+}-mediated arrhythmia substrates more than IL-1β[183]. Elevated circulating levels of IL-6 have been observed in both AF[184] and polymorphic VT[185]. Data from humans suggest that increased circulating levels of IL-6 rapidly induce atrial electrical remodelling by downregulation of cardiac connexins[184]. Anti-IL-6 treatment had beneficial effects in patients with rheumatoid arthritis and systemic inflammation, typically associated with long QT intervals and increased rates of SCD[186]. Treatment with tocilizumab, an anti-IL-6 receptor antibody, shortened QTc intervals, which correlated with reduced CRP and TNF levels, suggesting a potential anti-arrhythmic effect of anti-IL-6 treatment.

Increased circulating levels of leukocyte-released IL-17A have been linked with AF[176]. Moreover, IL-17A levels in the plasma were positively correlated with left atrial diameter, suggesting the functional relevance of IL-17 signalling in the pathogenesis of AF[174]. This hypothesis is supported by preclinical studies demonstrating that IL-17 mediates inflammation by inducing increased cytokine release (IL-1β and IL-6) and collagen deposition, thereby shaping the arrhythmogenic substrate of the atria[175]. IL-17 inhibition with an extract from *Rhodiola crenulata* suppressed atrial fibrosis, cardiomyocyte apoptosis and the incidence of ventricular arrhythmias in a dog model of HF[187], suggesting that targeting the IL-17 pathway has therapeutic potential.

Although we are only beginning to understand the multifaceted effects of leukocyte-released cytokines on conduction, these effects have already been partially shown for TNF, which alters the expression and distribution patterns of Cx40 and Cx43 in cardiomyocytes through the transforming growth factor-β (TGFβ)–SMAD signalling pathway, activates myofibroblasts, increases collagen deposition and ultimately shapes an arrhythmogenic substrate for AF[188,189]. TNF might affect Ca^{2+} handling in cardiomyocytes by electrical remodelling, such as by decreasing sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a expression[190–192]. Finally, TNF induces cardiomyocyte apoptosis via cell death pathways[193], creating conduction heterogeneity (FIG. 2).

Upstream of cytokine release, nuclear factor-κB (NF-κB) signalling and the NLRP3 inflammasome cause cardiac arrhythmias. NF-κB facilitates transcription of IL-1, IL-6, IL-8 and TNF in response to damage-associated molecular patterns[194]. A common mechanism for NF-κB signalling is the TLR4–MYD88 pathway[195,196]. NF-κB, TLR4 and MYD88 protein expression increase in the atrial tissue of individuals with AF[197], while TLR4 activation also promotes cardiac arrhythmias by IRF3-dependent, but MYD88-independent, pathways[198]. Moreover, NF-κB suppresses the transcription of genes encoding cardiac Na^{+} channels in response to oxidative stress, a hallmark of AF, and therefore also acts on electrical remodelling of the cardiac substrate[199].

NLRP3 inflammasome activation leads to atrial electrical and structural remodelling, frequent atrial ectopy and pacing-induced AF[200,201]. Underlying mechanisms might include abnormal release of Ca^{2+} from the sarcoplasmic reticulum[202], shortening of the APD or atrial hypertrophy. Activation of the NLRP3 inflammasome and Ca^{2+}/calmodulin-

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dependent protein kinase II signalling was evident in atrial cardiomyocytes from patients who subsequently developed postoperative AF compared with postoperative samples from patients without AF[203]. These inflammatory mediators sensitized cardiomyocytes to spontaneous release of Ca^{2+} from the sarcoplasmic reticulum and arrhythmogenic afterdepolarizations[200].

Altered electrotonic gap junction communication between cardiomyocytes and leukocytes.

Similar to stromal cells, macrophages communicate with cardiomyocytes through Cx43-containing gap junctions[37,204,205]. The functional relevance of heterocellular coupling has been indicated by synchronized electrical activity and electronic interactions between cardiomyocytes and stromal cells in the steady state[206–208] and in ventricular infarct border zones[209,210]. In the diseased heart, Cx43 is expressed at lower levels and heterogeneously redistributed to the lateral sides of cardiomyocytes[211]. Reverse remodelling of reduced Cx43 expression can restore electrical stability[211]. In the steady state, macrophage coupling affects cardiomyocyte action potentials, producing a more positive resting membrane potential as well as a decrease in APD and refractory period[37]. This contribution to physiological conduction might depend on macrophage number and phenotype, and we speculate that a change in these parameters might be arrhythmogenic. Data from mice with acute MI indicate that inflammation induced by lipopolysaccharide injections or atherosclerosis leads to inducible non-sustained VTs that were attributed to slower conduction[205]. In this model, macrophage expansion areas colocalized with regions of Cx43 degradation and decreased Cx43 expression[205]. In the setting of acute MI, resident cardiac macrophages, which stabilize physiological conduction[37], die alongside ischaemic cardiomyocytes[212]. We hypothesize that the loss of these cardiomyocyte-coupled resident macrophages might alter conduction. Recruited, phenotypically distinct monocyte-derived macrophages boost macrophage numbers by an order of magnitude in the ischaemic myocardium and simultaneously are likely to increase conduction heterogeneity.

In support of this hypothesis, a report suggested that cardiomyocyte–macrophage coupling occurs in MI border zones of mice and humans[213] (FIG. 3). Patients with arrhythmia after MI have more pro-inflammatory mononuclear cells in the circulation than patients with MI who do not have arrhythmia[213]. In vitro macrophage co-culture with cardiomyocytes demonstrated that cardiomyocyte APD differs depending on the macrophage phenotype and their gap junction status[213]. The concept of gap junction communication between cardiomyocytes and non-excitable cells has been promoted since the 1990s by Kohl and Noble[214,215] and is supported by a study testing whether lentivirus-mediated delivery of *Cx43* into acute myocardial lesions increased electrical signal propagation[216]. Gene therapy with *Cx43* led to expression of Cx43 in (myo)fibroblasts and $CD45^{+}$ leukocytes in the infarct region and prevented arrhythmia[216]. Optical mapping of Cx43-overexpressing hearts revealed amplified conduction velocity within the scar, indicating that the therapy increased Cx43-mediated coupling between cardiomyocytes and non-cardiomyocytes[216].

Taken together, an emerging body of evidence suggests that leukocytes directly participate in conduction in healthy and diseased hearts. In HF[26], myocarditis[217], sepsis[218] and acute MI[154], macrophage numbers increase and phenotypes are altered. Hypothetically,

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these changes could directly influence the action potential in cardiomyocytes, perhaps contributing to arrhythmia. Although we are only beginning to understand immune cell coupling to cardiomyocytes, we believe this field of research will reveal new therapeutic options for conduction disorders and arrhythmia.

Leukocyte-instigated, insulating fibrosis.

Leukocyte-mediated extracellular matrix deposition might disturb the capacity of cardiomyocytes to conduct properly because insulating extracellular matrix slows or even blocks conduction. Leukocytes orchestrate the formation of extracellular matrix in acute MI[219], HF[220] and angiotensin II-induced cardiomyocyte hypertrophy[221]. Macrophages modulate the extracellular matrix by releasing interleukins and TGFβ[222–224], thereby activating cardiac fibroblasts. The differentiation of fibroblasts into secretory and contractile myofibroblasts is a cellular hallmark of cardiac fibrosis, replacing dead cardiomyocytes with non-contractile scar tissue. Macrophages reside in close proximity to patchy fibrosis and myofibroblasts in ischaemic hearts, and their abundance increases in segments with contractile dysfunction[225,226]. Indeed, the release of cytokines by macrophages might influence the activation and phenoconversion of cardiac fibroblasts into myofibroblasts[227,228], which deposit collagen to form scar tissue[229]. Myofibroblasts increase Cx43 expression in cardiac injury, which could have direct implications for heterocellular coupling between conducting cells[230]. Moreover, macrophages might themselves produce extracellular matrix[229], although the relative importance of this direct contribution to fibrosis is unclear.

Only a few studies have addressed the possible causal relationship between leukocytes and AF via fibrosis. An experimental and clinical study of the haem enzyme myeloperoxidase (MPO), which is typically expressed by neutrophils, mechanistically demonstrated leukocyte involvement in the pathogenesis of atrial fibrosis and AF[231]. Leukocyte-derived MPO generates hypochlorous acid, which modulates matrix metalloproteinase (MMP) activity and, therefore, extracellular matrix turnover[232]. MPO-deficient mice were protected against the development of AF, which was reversed when MPO abundance was restored[231]. Patients with AF had higher plasma concentrations of MPO and higher MPO levels in the right atria[231]. Subsequent trials confirmed these results[233,234]. Attenuated infiltration of neutrophils into the atria decreased atrial fibrosis and prevented AF episodes after angiotensin II infusion in CD11b-deficicent mice, providing further evidence for leukocyte-mediated fibrosis formation in AF[235].

Additional research demonstrated a positive correlation between atrial fibrosis and higher numbers of macrophages and myofibroblasts in epicardial adipose tissue[236], which produces inflammatory cytokines[237] and has previously been linked to the pathogenesis of AF[238]. Left atrial collagen content correlated with the abundance of IL-6, MMPs and TNF in epicardial adipose tissue[236]. These data suggest that macrophages in the peri-atrial adipose tissue trigger atrial fibrosis and thereby shape the arrhythmogenic substrate[236].

Macrophages also mediate the resolution of fibrosis by producing MMPs, removing apoptotic myofibroblasts or suppressing fibroblast activation[239–243]. For instance, MMP7 is produced by macrophages[244] and cardiomyocytes[245] during the acute phase after MI,

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and this protease can cleave extracellular matrix substrates. Interestingly, deletion of *Mmp7* in mice resulted in improved survival after MI and decreased the degradation of Cx43, which in turn influenced electrical remodelling of the ventricular substrate[246]. Although the mediating effects of leukocytes on fibrosis are well established in many settings, data on leukocyte-mediated fibrosis in arrhythmogenesis are mostly associative at this time, indicating a need for mechanistic studies.

Autoimmune channelopathies.

The absence of morphological substrates and ion channel mutations in some patients with SCD led to the recognition of arrhythmia caused by autoantibodies[247,248] that target β_1-adrenergic receptors[249] or Na^+, K^+ or Ca^{2+} channels[250]. Cardiac inflammation and its resolution are believed to trigger the release of proteins (such as ion channels) that can become 'self antigens', provoking immune system humoral responses that cause plasma cells to generate autoantibodies. Given that potential self antigens are present in virtually unlimited supply, the results can be chronic autoimmunity and cardiac inflammation.

Long QT syndrome, an ECG abnormality with a prolonged repolarization phase (the QT interval) and extended APD, predisposes individuals to life-threatening tachyarrhythmias[251]. This channelopathy arises from either genetic variants[252] or drugs that prolong the QT interval[253]. Antibodies reacting with K^+ channels ($K_v1.4$) can induce an autoimmune version of the long QT syndrome[254,255] (FIG. 4a). By directly binding to a channel subunit, antibodies limit K^+ currents (the rapid component of the delayed rectifier K^+ current (I_{Kr}) or the transient outward K^+ current (I_{to})), thereby prolonging the APD[254]. Injecting guinea pigs with a peptide corresponding to an extracellular subunit of the hERG K^+ channel produced autoantibodies that inhibited I_{Kr} and lengthened the QT interval[256].

Autoantibodies causing short QT syndrome in patients with dilated cardiomyopathy activate $K_v7.1$ K^+ channels, increase the slow component of the delayed rectifier K^+ current (I_{Ks}) and shorten the APD, which is associated with ventricular arrhythmias and AF[257,258] (FIG. 4a). Cardiomyocytes isolated from rabbits injected with patient serum containing antibodies targeting $K_v7.1$ had a shortened APD, increased I_{Ks} and an increased likelihood of arrhythmia[258]. Autoantibodies specific for Ro proteins (also known as Sjögren syndrome-related antigen A; SSA)[259,260], which are associated with systemic lupus and Sjögren syndrome, were found to be present in 60% of patients with torsades de pointes[261] and can also trigger congenital heart block[262,263]. Congenital heart block is associated with the transplacental transfer of maternal anti-Ro/SSA antibodies to the embryo as early as week 11 of gestation, leading to atrioventricular block, sinus bradycardia, inflammation, calcification and fibrosis (also referred to as neonatal lupus)[264]. The major arrhythmic manifestation of congenital heart block is a third-degree atrioventricular block[265,266]; other ECG abnormalities, such as a long QT interval, sinus node dysfunction and atrial flutter, have occasionally been reported. These conduction abnormalities in the fetal heart result from autoantibodies targeting L-type and T-type voltage-gated Ca^{2+} channel α-subunits ($Ca_v1.2$, $Ca_v1.3$, $Ca_v3.1$ and $Ca_v3.2$), causing inhibitory effects on the L-type Ca^{2+} channel current (I_{CaL}) and T-type Ca^{2+} channel current (I_{CaT})[267,268] (FIG. 4b). A small clinical trial demonstrated that autoantibody-related second-degree congenital heart block can

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be ameliorated to first-degree congenital heart block or even to normal atrioventricular conduction with the use of a combined anti-inflammatory therapy involving plasmapheresis, intravenous immunoglobulins and betamethasone[269].

Some patients with idiopathic atrioventricular block have autoantibodies against $Na_v1.5$ (REF.[270]). These autoantibodies inhibit Na^+ channel function and consequently decrease I_{Na} currents but can also lower protein expression levels of the $Na_v1.5$ channel. Profiling autoantibody signatures in patients with idiopathic cardiac arrest identified autoantibodies against the L-type Ca^{2+} channels as a biomarker for sudden cardiac arrest, whereas autoantibodies against K^+ channel subfamily K member 2 (KCNK2; also known as TREK1) were found in both patients with ischaemic cardiac arrest and healthy control individuals[271]. Autoantibody-induced arrhythmias have been reviewed in detail previously[250].

Immune modulation and arrhythmia

Twentieth century research into electrophysiology gave rise to implantable defibrillators, anti-tachycardiac pacing terminating life-threatening VTs and VFs, catheter ablation of arrhythmic foci and antiarrhythmic drugs. However, arrhythmia-associated mortality remains high, and the use of some channel inhibitors was abandoned due to pro-arrhythmic and other adverse effects. We speculate that anti-inflammatory therapeutics might help to overcome these problems. Emerging data indicate that this approach is promising, such as the effects of low-dose hydrocortisone on AF in patients with sepsis[119], IL-1 receptor inhibition in mice with acute MI[181] or antibodies against KCNQ1 that suppress arrhythmic activities in ex vivo models of long QT syndrome[272]. We concede that this development is still in its early stages, which is unsurprising given that cardiac immune cells were virtually unknown a decade ago. The next steps involve carefully dissecting the hypothetical inflammatory pathways that lead to arrhythmia, followed by selecting immune targets that are safe — that is, inhibiting them would not compromise host immune defence. The increasing availability of high-resolution data, especially single-cell RNA-sequencing data sets, on cardiac immune cells will aid this development. Fortunately, immunomodulatory therapy has been successful in many diseases, including cancer, leading to optimism that similar objectives can be accomplished for cardiovascular disease and cardiac arrhythmias. Particularly promising platforms include neutralizing antibodies against cells or secreted proteins[182], nanoparticle drug delivery to phagocytic cells such as macrophages[273] and liposome-enabled RNA interference[274]. Cell therapy might also be an option, as indicated by data on $CD8^+$ T cells targeting fibroblast activation protein, which reduced cardiac fibrosis in mice[275]. On the basis of these and other studies, we believe understanding the role of immunity in physiological conduction and exploring electroimmunological contributions to arrhythmias will provide a foundation for the development of next-generation drugs to correct abnormal conduction. Of note, immune cell-targeted therapeutics can also elicit unwanted pro-arrhythmic adverse effects. For instance, immune checkpoint inhibitors can lead to myocarditis and arrhythmia[276,277].

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Conclusions

Growing preclinical and clinical evidence demonstrates that immunity has a role in the pathophysiology of arrhythmia. Emerging findings obtained by understanding leukocyte electrophysiology provide insights into non-canonical leukocyte function associated with physiological and abnormal conduction. By extrapolating findings on the interaction between microglia and neurons, we suspect that cardiac macrophages might also have additional, currently unknown functions modulating the cardiac conduction system. Targeting inflammatory processes might be central to preventing and treating arrhythmias, but comprehensively understanding leukocyte heterogeneity, immune cell subtypes and their functions is necessary for the development of future therapeutic strategies for arrhythmia and SCD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Adabag AS, Luepker RV, Roger VL & Gersh BJ Sudden cardiac death: epidemiology and risk factors. Nat. Rev. Cardiol 7, 216–225 (2010). [PubMed: 20142817]
2. Byrne R et al. Multiple source surveillance incidence and aetiology of out-of-hospital sudden cardiac death in a rural population in the West of Ireland. Eur. Heart J 29, 1418–1423 (2008). [PubMed: 18424446]
3. Dalia AA et al. A narrative review for anesthesiologists of the 2017 American Heart Association/ American College of Cardiology/Heart Rhythm Society Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. J. Cardiothorac. Vasc. Anesth 33, 1722–1730 (2019). [PubMed: 30685157]
4. Vaillancourt C, Stiell IG & Canadian Cardiovascular Outcomes Research Team. Cardiac arrest care and emergency medical services in Canada. Can. J. Cardiol 20, 1081–1090 (2004). [PubMed: 15457303]
5. Chugh SS et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large US community. J. Am. Coll. Cardiol 44, 1268–1275 (2004). [PubMed: 15364331]
6. Nichol G et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA 300, 1423–1431 (2008). [PubMed: 18812533]
7. Bloom HL et al. Long-term survival after successful inhospital cardiac arrest resuscitation. Am. Heart J 153, 831–836 (2007). [PubMed: 17452161]
8. Yan S et al. The global survival rate among adult out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation: a systematic review and meta-analysis. Crit. Care Lond. Engl 24, 61 (2020).
9. Iwasaki Y, Nishida K, Kato T & Nattel S Atrial fibrillation pathophysiology: implications for management. Circulation 124, 2264–2274 (2011). [PubMed: 22083148]

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10. Chugh SS et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation 129, 837–847 (2014). [PubMed: 24345399]
11. Naccarelli GV, Varker H, Lin J & Schulman KL Increasing prevalence of atrial fibrillation and flutter in the United States. Am. J. Cardiol 104, 1534–1539 (2009). [PubMed: 19932788]
12. Jousset F, Maguy A, Rohr S & Kucera JP Myofibroblasts electrotonically coupled to cardiomyocytes alter conduction: insights at the cellular level from a detailed in silico tissue structure model. Front. Physiol 7, 496 (2016). [PubMed: 27833567]
13. Klabunde RE Cardiac electrophysiology: normal and ischemic ionic currents and the ECG. Adv. Physiol. Educ 41, 29–37 (2017). [PubMed: 28143820]
14. Kohl P & Gourdie RG Fibroblast-myocyte electrotonic coupling: does it occur in native cardiac tissue? J. Mol. Cell. Cardiol 70, 37–46 (2014). [PubMed: 24412581]
15. Medzhitov R & Janeway CA Innate immunity: the virtues of a nonclonal system of recognition. Cell 91, 295–298 (1997). [PubMed: 9363937]
16. Hoffmann J & Akira S Innate immunity. Curr. Opin. Immunol 25, 1–3 (2013). [PubMed: 23452839]
17. Kumar H, Kawai T & Akira S Pathogen recognition by the innate immune system. Int. Rev. Immunol 30, 16–34 (2011). [PubMed: 21235323]
18. Sirisinha S Insight into the mechanisms regulating immune homeostasis in health and disease. Asian Pac. J. Allergy Immunol 29, 1–14 (2011). [PubMed: 21560483]
19. Coillard A & Segura E In vivo differentiation of human monocytes. Front. Immunol 10, 1907 (2019).
20. Auffray C et al. Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior. Science 317, 666–670 (2007). [PubMed: 17673663]
21. Carlin LM et al. Nr4a1-dependent $Ly6C^{low}$ monocytes monitor endothelial cells and orchestrate their disposal. Cell 153, 362–375 (2013). [PubMed: 23582326]
22. Heidt T et al. Differential contribution of monocytes to heart macrophages in steady-state and after myocardial infarction. Circ. Res 115, 284–295 (2014). [PubMed: 24786973]
23. Pinto AR et al. Revisiting cardiac cellular composition. Circ. Res 118, 400–409 (2016). [PubMed: 26635390]
24. Litviňuková M et al. Cells of the adult human heart. Nature 588, 466–472 (2020). [PubMed: 32971526]
25. Bajpai G et al. The human heart contains distinct macrophage subsets with divergent origins and functions. Nat. Med 24, 1234–1245 (2018).
26. Epelman S et al. Embryonic and adult-derived resident cardiac macrophages are maintained through distinct mechanisms at steady state and during inflammation. Immunity 40, 91–104 (2014). [PubMed: 24439267]
27. Leid J et al. Primitive embryonic macrophages are required for coronary development and maturation. Circ. Res 118, 1498–1511 (2016). [PubMed: 27009605]
28. Martini E et al. Single-cell sequencing of mouse heart immune infiltrate in pressure overload-driven heart failure reveals extent of immune activation. Circulation 140, 2089–2107 (2019). [PubMed: 31661975]
29. Dick SA et al. Self-renewing resident cardiac macrophages limit adverse remodeling following myocardial infarction. Nat. Immunol 20, 29–39 (2019). [PubMed: 30538339]
30. Skelly DA et al. Single-cell transcriptional profiling reveals cellular diversity and intercommunication in the mouse heart. Cell Rep 22, 600–610 (2018). [PubMed: 29346760]
31. Cahalan MD & Chandy KG The functional network of ion channels in T lymphocytes. Immunol. Rev 231, 59–87 (2009). [PubMed: 19754890]
32. Chen Y-J, Nguyen HM, Maezawa I, Jin L-W & Wulff H Inhibition of the potassium channel Kv1.3 reduces infarction and inflammation in ischemic stroke. Ann. Clin. Transl. Neurol 5, 147–161 (2018). [PubMed: 29468176]
33. Di L et al. Inhibition of the K^+ channel $K_{Ca}3.1$ ameliorates T cell-mediated colitis. Proc. Natl Acad. Sci. USA 107, 1541–1546 (2010). [PubMed: 20080610]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

34. Gallin EK & Gallin JI Interaction of chemotactic factors with human macrophages. Induction of transmembrane potential changes. J. Cell Biol 75, 277–289 (1977). [PubMed: 410816]
35. Gallin EK & Livengood DR Nonlinear current-voltage relationships in cultured macrophages. J. Cell Biol 85, 160–165 (1980). [PubMed: 7364871]
36. Mackenzie AB, Chirakkal H & North RA Kv1.3 potassium channels in human alveolar macrophages. Am. J. Physiol. Lung Cell. Mol. Physiol 285, L862–L868 (2003). [PubMed: 12909584]
37. Hulsmans M et al. Macrophages facilitate electrical conduction in the heart. Cell 169, 510–522.e20 (2017). [PubMed: 28431249]
38. Rink TJ, Montecucco C, Hesketh TR & Tsien RY Lymphocyte membrane potential assessed with fluorescent probes. Biochim. Biophys. Acta 595, 15–30 (1980). [PubMed: 6153065]
39. Mello de Queiroz F, Ponte CG, Bonomo A, Vianna-Jorge R & Suarez-Kurtz G Study of membrane potential in T lymphocytes subpopulations using flow cytometry. BMC Immunol 9, 63 (2008).
40. Gallin EK, Wiederhold ML, Lipsky PE & Rosenthal AS Spontaneous and induced membrane hyperpolarizations in macrophages. J. Cell. Physiol 86, 653–661 (1975). [PubMed: 811677]
41. Cahalan MD, Chandy KG, DeCoursey TE & Gupta S A voltage-gated potassium channel in human T lymphocytes. J. Physiol 358, 197–237 (1985). [PubMed: 2580081]
42. Vicente R et al. Association of Kv1.5 and Kv1.3 contributes to the major voltage-dependent K_+ channel in macrophages. J. Biol. Chem 281, 37675–37685 (2006). [PubMed: 17038323]
43. Villalonga N et al. Kv1.3/Kv1.5 heteromeric channels compromise pharmacological responses in macrophages. Biochem. Biophys. Res. Commun 352, 913–918 (2007). [PubMed: 17157812]
44. Villalonga N et al. Immunomodulation of voltage-dependent K^+ channels in macrophages: molecular and biophysical consequences. J. Gen. Physiol 135, 135–147 (2010). [PubMed: 20100893]
45. Xia XM et al. Mechanism of calcium gating in small-conductance calcium-activated potassium channels. Nature 395, 503–507 (1998). [PubMed: 9774106]
46. Leonard RJ, Garcia ML, Slaughter RS & Reuben JP Selective blockers of voltage-gated K^+ channels depolarize human T lymphocytes: mechanism of the antiproliferative effect of charybdotoxin. Proc. Natl Acad. Sci. USA 89, 10094–10098 (1992). [PubMed: 1279670]
47. Ghanshani S et al. Up-regulation of the IKCa1 potassium channel during T-cell activation. Molecular mechanism and functional consequences. J. Biol. Chem 275, 37137–37149 (2000). [PubMed: 10961988]
48. Launay P et al. TRPM4 regulates calcium oscillations after T cell activation. Science 306, 1374–1377 (2004). [PubMed: 15550671]
49. Luik RM, Wang B, Prakriya M, Wu MM & Lewis RS Oligomerization of STIM1 couples ER calcium depletion to CRAC channel activation. Nature 454, 538–542 (2008). [PubMed: 18596693]
50. Stathopulos PB, Zheng L, Li G-Y, Plevin MJ & Ikura M Structural and mechanistic insights into STIM1-mediated initiation of store-operated calcium entry. Cell 135, 110–122 (2008). [PubMed: 18854159]
51. Wu MM, Buchanan J, Luik RM & Lewis RS Ca^{2+} store depletion causes STIM1 to accumulate in ER regions closely associated with the plasma membrane. J. Cell Biol 174, 803–813 (2006). [PubMed: 16966422]
52. Feske S ORAI1 and STIM1 deficiency in human and mice: roles of store-operated Ca^{2+} entry in the immune system and beyond. Immunol. Rev 231, 189–209 (2009). [PubMed: 19754898]
53. Feske S, Giltnane J, Dolmetsch R, Staudt LM & Rao A Gene regulation mediated by calcium signals in T lymphocytes. Nat. Immunol 2, 316–324 (2001). [PubMed: 11276202]
54. Matsumoto M et al. The calcium sensors STIM1 and STIM2 control B cell regulatory function through interleukin-10 production. Immunity 34, 703–714 (2011). [PubMed: 21530328]
55. Cekic C & Linden J Purinergic regulation of the immune system. Nat. Rev. Immunol 16, 177–192 (2016). [PubMed: 26922909]
56. Baricordi OR et al. An ATP-activated channel is involved in mitogenic stimulation of human T lymphocytes. Blood 87, 682–690 (1996). [PubMed: 8555491]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

57. Padeh S, Cohen A & Roifman CM ATP-induced activation of human B lymphocytes via P2-purinoceptors. J. Immunol 146, 1626–1632 (1991). [PubMed: 1847168]
58. Shay T & Kang J Immunological Genome Project and systems immunology. Trends Immunol 34, 602–609 (2013). [PubMed: 23631936]
59. Picard C et al. STIM1 mutation associated with a syndrome of immunodeficiency and autoimmunity. N. Engl. J. Med 360, 1971–1980 (2009). [PubMed: 19420366]
60. Cacheux M et al. Cardiomyocyte-specific STIM1 (stromal interaction molecule 1) depletion in the adult heart promotes the development of arrhythmogenic discordant alternans. Circ. Arrhythm. Electrophysiol 12, e007382 (2019). [PubMed: 31726860]
61. Nicolás-Ávila JA et al. A network of macrophages supports mitochondrial homeostasis in the heart. Cell 183, 94–109.e23 (2020). [PubMed: 32937105]
62. Evans WH & Martin PEM Gap junctions: structure and function (Review). Mol. Membr. Biol 19, 121–136 (2002). [PubMed: 12126230]
63. Rohr S Role of gap junctions in the propagation of the cardiac action potential. Cardiovasc. Res 62, 309–322 (2004). [PubMed: 15094351]
64. Jongsma HJ & Wilders R Gap junctions in cardiovascular disease. Circ. Res 86, 1193–1197 (2000). [PubMed: 10864907]
65. Weidmann S The electrical constants of Purkinje fibres. J. Physiol 118, 348–360 (1952). [PubMed: 13000763]
66. Li Q & Barres BA Microglia and macrophages in brain homeostasis and disease. Nat. Rev. Immunol 18, 225–242 (2018). [PubMed: 29151590]
67. Schafer DP et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron 74, 691–705 (2012). [PubMed: 22632727]
68. Paolicelli RC et al. Synaptic pruning by microglia is necessary for normal brain development. Science 333, 1456–1458 (2011). [PubMed: 21778362]
69. Vainchtein ID et al. Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. Science 359, 1269–1273 (2018). [PubMed: 29420261]
70. Miyamoto A et al. Microglia contact induces synapse formation in developing somatosensory cortex. Nat. Commun 7, 12540 (2016). [PubMed: 27558646]
71. Hagemeyer N et al. Microglia contribute to normal myelinogenesis and to oligodendrocyte progenitor maintenance during adulthood. Acta Neuropathol 134, 441–458 (2017). [PubMed: 28685323]
72. Pascual O, Ben Achour S, Rostaing P, Triller A & Bessis A Microglia activation triggers astrocyte-mediated modulation of excitatory neurotransmission. Proc. Natl Acad. Sci. USA 109, E197–E205 (2012). [PubMed: 22167804]
73. Dobrenis K et al. Human and mouse microglia express connexin36, and functional gap junctions are formed between rodent microglia and neurons. J. Neurosci. Res 82, 306–315 (2005). [PubMed: 16211561]
74. Maezawa I & Jin L-W Rett syndrome microglia damage dendrites and synapses by the elevated release of glutamate. J. Neurosci 30, 5346–5356 (2010). [PubMed: 20392956]
75. Vinegoni C, Aguirre AD, Lee S & Weissleder R Imaging the beating heart in the mouse using intravital microscopy techniques. Nat. Protoc 10, 1802–1819 (2015). [PubMed: 26492138]
76. Chen T-W et al. Ultrasensitive fluorescent proteins for imaging neuronal activity. Nature 499, 295–300 (2013). [PubMed: 23868258]
77. Ahrens MB, Orger MB, Robson DN, Li JM & Keller PJ Whole-brain functional imaging at cellular resolution using light-sheet microscopy. Nat. Methods 10, 413–420 (2013). [PubMed: 23524393]
78. Heeringa J et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur. Heart J 27, 949–953 (2006). [PubMed: 16527828]
79. Wolf PA, Dawber TR, Thomas HE & Kannel WB Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology 28, 973–977 (1978). [PubMed: 570666]
80. Odutayo A et al. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ 354, i4482 (2016). [PubMed: 27599725]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

81. Heijman J, Voigt N, Nattel S & Dobrev D Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. Circ. Res 114, 1483–1499 (2014). [PubMed: 24763466]
82. Workman AJ, Kane KA & Rankin AC Cellular bases for human atrial fibrillation. Heart Rhythm 5, S1–S6 (2008). [PubMed: 18456193]
83. Zhang H et al. Association of systemic inflammation score with atrial fibrillation: a case-control study with propensity score matching. Heart Lung Circ 27, 489–496 (2018). [PubMed: 28579228]
84. Bruins P et al. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. Circulation 96, 3542–3548 (1997). [PubMed: 9396453]
85. 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). [PubMed: 25622848]
86. Chen M-C et al. Increased inflammatory cell infiltration in the atrial myocardium of patients with atrial fibrillation. Am. J. Cardiol 102, 861–865 (2008). [PubMed: 18805111]
87. Smorodinova N et al. Analysis of immune cell populations in atrial myocardium of patients with atrial fibrillation or sinus rhythm. PLoS ONE 12, e0172691 (2017). [PubMed: 28225836]
88. Abdelhadi RH, Gurm HS, Van Wagoner DR & Chung MK Relation of an exaggerated rise in white blood cells after coronary bypass or cardiac valve surgery to development of atrial fibrillation postoperatively. Am. J. Cardiol 93, 1176–1178 (2004). [PubMed: 15110218]
89. Yamashita T et al. Recruitment of immune cells across atrial endocardium in human atrial fibrillation. Circ. J 74, 262–270 (2010). [PubMed: 20009387]
90. Frangogiannis NG Regulation of the inflammatory response in cardiac repair. Circ. Res 110, 159–173 (2012). [PubMed: 22223212]
91. Patel P, Dokainish H, Tsai P & Lakkis N Update on the association of inflammation and atrial fibrillation. J. Cardiovasc. Electrophysiol 21, 1064–1070 (2010). [PubMed: 20455973]
92. Jacob KA et al. Inflammation in new-onset atrial fibrillation after cardiac surgery: a systematic review. Eur. J. Clin. Invest 44, 402–428 (2014). [PubMed: 24387767]
93. Hu Y-F et al. Electrophysiological correlation and prognostic impact of heat shock protein 27 in atrial fibrillation. Circ. Arrhythm. Electrophysiol 5, 334–340 (2012). [PubMed: 22354927]
94. Dong Q & Wright JR Expression of C-reactive protein by alveolar macrophages. J. Immunol 156, 4815–4820 (1996). [PubMed: 8648129]
95. Yasojima K, Schwab C, McGeer EG & McGeer PL Generation of C-reactive protein and complement components in atherosclerotic plaques. Am. J. Pathol 158, 1039–1051 (2001). [PubMed: 11238052]
96. Aviles RJ et al. Inflammation as a risk factor for atrial fibrillation. Circulation 108, 3006–3010 (2003). [PubMed: 14623805]
97. 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). [PubMed: 20832129]
98. Ishii Y et al. Inflammation of atrium after cardiac surgery is associated with inhomogeneity of atrial conduction and atrial fibrillation. Circulation 111, 2881–2888 (2005). [PubMed: 15927979]
99. Dernellis J & Panaretou M Relationship between C-reactive protein concentrations during glucocorticoid therapy and recurrent atrial fibrillation. Eur. Heart J 25, 1100–1107 (2004). [PubMed: 15231367]
100. Ho KM & Tan JA Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: a dose-response meta-analysis. Circulation 119, 1853–1866 (2009). [PubMed: 19332460]
101. Jabati S et al. Biomarkers of inflammation, thrombogenesis, and collagen turnover in patients with atrial fibrillation. Clin. Appl. Thromb 24, 718–723 (2018).
102. Hijazi Z et al. Biomarkers of inflammation and risk of cardiovascular events in anticoagulated patients with atrial fibrillation. Heart 102, 508–517 (2016). [PubMed: 26839066]
103. 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). [PubMed: 24656480]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

104. Kistler PM et al. Atrial electrical and structural abnormalities in an ovine model of chronic blood pressure elevation after prenatal corticosteroid exposure: implications for development of atrial fibrillation. Eur. Heart J 27, 3045–3056 (2006). [PubMed: 17098760]
105. 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). [PubMed: 24763464]
106. Friedman PL, Stewart JR & Wit AL Spontaneous and induced cardiac arrhythmias in subendocardial Purkinje fibers surviving extensive myocardial infarction in dogs. Circ. Res 33, 612–626 (1973). [PubMed: 4752860]
107. Nuss HB, Kääb S, Kass DA, Tomaselli GF & Marbán E Cellular basis of ventricular arrhythmias and abnormal automaticity in heart failure. Am. J. Physiol 277, H80–H91 (1999). [PubMed: 10409185]
108. Morita N, Mandel WJ, Kobayashi Y & Karagueuzian HS Cardiac fibrosis as a determinant of ventricular tachyarrhythmias. J. Arrhythmia 30, 389–394 (2014).
109. Anderson RD et al. Focal ventricular tachycardias in structural heart disease: prevalence, characteristics, and clinical outcomes after catheter ablation. JACC Clin. Electrophysiol 6, 56–69 (2020). [PubMed: 31971907]
110. Ayoub KF, Pothineni NVK, Rutland J, Ding Z & Mehta JL Immunity, inflammation, and oxidative stress in heart failure: emerging molecular targets. Cardiovasc. Drugs Ther 31, 593–608 (2017). [PubMed: 28956198]
111. Singer M et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315, 801–810 (2016). [PubMed: 26903338]
112. Angus DC & van der Poll T Severe sepsis and septic shock. N. Engl. J. Med 369, 840–851 (2013). [PubMed: 23984731]
113. [No authors listed]. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit. Care Med 20, 864–874 (1992). [PubMed: 1597042]
114. Lewis O et al. Incidence, risk factors and outcomes of new onset supraventricular arrhythmias in African American patients with severe sepsis. Ethn. Dis 26, 205–212 (2016). [PubMed: 27103771]
115. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH & Benjamin EJ Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. JAMA 306, 2248–2254 (2011). [PubMed: 22081378]
116. Meierhenrich R et al. Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. Crit. Care 14, R108 (2010). [PubMed: 20537138]
117. Christian S-A et al. Clinical characteristics and outcomes of septic patients with new-onset atrial fibrillation. J. Crit. Care 23, 532–536 (2008). [PubMed: 19056018]
118. Brathwaite D & Weissman C The new onset of atrial arrhythmias following major noncardiothoracic surgery is associated with increased mortality. Chest 114, 462–468 (1998). [PubMed: 9726731]
119. Launey Y et al. Impact of low-dose hydrocortisone on the incidence of atrial fibrillation in patients with septic shock: a propensity score-inverse probability of treatment weighting cohort study. J. Intensive Care Med 34, 238–244 (2019). [PubMed: 28292220]
120. Oppert M et al. Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. Crit. Care Med 33, 2457–2464 (2005). [PubMed: 16276166]
121. Trappe HJ et al. Prognosis of patients with ventricular tachycardia and ventricular fibrillation: role of the underlying etiology. J. Am. Coll. Cardiol 12, 166–174 (1988). [PubMed: 3379202]
122. Henkel DM et al. Ventricular arrhythmias after acute myocardial infarction: a 20-year community study. Am. Heart J 151, 806–812 (2006). [PubMed: 16569539]
123. Khairy P et al. Prognostic significance of ventricular arrhythmias post-myocardial infarction. Can. J. Cardiol 19, 1393–1404 (2003). [PubMed: 14631474]
124. Salerno F et al. Myocarditis and cardiac channelopathies: a deadly association? Int. J. Cardiol 147, 468–470 (2011). [PubMed: 21295362]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

125. Li HS, Ligons DL & Rose NR Genetic complexity of autoimmune myocarditis. Autoimmun. Rev 7, 168–173 (2008). [PubMed: 18190873]
126. Fenton FH, Cherry EM, Hastings HM & Evans SJ Multiple mechanisms of spiral wave breakup in a model of cardiac electrical activity. Chaos 12, 852–892 (2002). [PubMed: 12779613]
127. Jalife J Ventricular fibrillation: mechanisms of initiation and maintenance. Annu. Rev. Physiol 62, 25–50 (2000). [PubMed: 10845083]
128. Kurian TK & Efimov IR Mechanisms of fibrillation: neurogenic or myogenic? Reentrant or focal? Multiple or single? Still puzzling after 160 years of inquiry. J. Cardiovasc. Electrophysiol 21, 1274–1275 (2010). [PubMed: 20550608]
129. Aiba T & Tomaselli GF Electrical remodeling in the failing heart. Curr. Opin. Cardiol 25, 29–36 (2010). [PubMed: 19907317]
130. Anderson ME Multiple downstream proarrhythmic targets for calmodulin kinase II: moving beyond an ion channel-centric focus. Cardiovasc. Res 73, 657–666 (2007). [PubMed: 17254559]
131. Janse MJ Electrophysiological changes in heart failure and their relationship to arrhythmogenesis. Cardiovasc. Res 61, 208–217 (2004). [PubMed: 14736537]
132. Steinberger J, Lucas RV, Edwards JE & Titus JL Causes of sudden unexpected cardiac death in the first two decades of life. Am. J. Cardiol 77, 992–995 (1996). [PubMed: 8644651]
133. Baksi AJ, Kanaganayagam GS & Prasad SK Arrhythmias in viral myocarditis and pericarditis. Card. Electrophysiol. Clin 7, 269–281 (2015). [PubMed: 26002391]
134. Woodruff JF & Woodruff JJ Involvement of T lymphocytes in the pathogenesis of coxsackie virus B3 heart disease. J. Immunol 113, 1726–1734 (1974). [PubMed: 4610045]
135. Liu W et al. IL-21R expression on $CD8^+$ T cells promotes $CD8^+$ T cell activation in coxsackievirus B3 induced myocarditis. Exp. Mol. Pathol 92, 327–333 (2012). [PubMed: 22465422]
136. Liu W, Moussawi M, Roberts B, Boyson JE & Huber SA Cross-regulation of T regulatory-cell response after coxsackievirus B3 infection by NKT and γδ T cells in the mouse. Am. J. Pathol 183, 441–449 (2013). [PubMed: 23746656]
137. Tavora F et al. Fatal parvoviral myocarditis: a case report and review of literature. Diagn. Pathol 3, 21 (2008). [PubMed: 18447927]
138. Gaaloul I et al. Postmortem diagnosis of infectious heart diseases: a mystifying cause of sudden infant death. Forensic Sci. Int 262, 166–172 (2016). [PubMed: 27016640]
139. Peretto G et al. Ventricular arrhythmias in myocarditis: characterization and relationships with myocardial inflammation. J. Am. Coll. Cardiol 75, 1046–1057 (2020). [PubMed: 32138965]
140. Park H et al. Increased phosphorylation of Ca^{2+} handling proteins as a proarrhythmic mechanism in myocarditis. Circ. J 78, 2292–2301 (2014). [PubMed: 25056499]
141. Xu H-F et al. MicroRNA-1 represses Cx43 expression in viral myocarditis. Mol. Cell. Biochem 362, 141–148 (2012). [PubMed: 22045061]
142. Pasquié JL May fever trigger ventricular fibrillation? Indian Pacing Electrophysiol. J 5, 139–145 (2005). [PubMed: 16943953]
143. Porres JM et al. Fever unmasking the Brugada syndrome. Pacing Clin. Electrophysiol 25, 1646–1648 (2002). [PubMed: 12494626]
144. Mok N-S et al. A newly characterized SCN5A mutation underlying Brugada syndrome unmasked by hyperthermia. J. Cardiovasc. Electrophysiol 14, 407–411 (2003). [PubMed: 12741714]
145. Dinckal MH et al. Incessant monomorphic ventricular tachycardia during febrile illness in a patient with Brugada syndrome: fatal electrical storm. Europace 5, 257–261 (2003). [PubMed: 12842640]
146. Pasquié JL et al. Fever as a precipitant of idiopathic ventricular fibrillation in patients with normal hearts. J. Cardiovasc. Electrophysiol 15, 1271–1276 (2004). [PubMed: 15574177]
147. Omori K et al. Recurrent idiopathic ventricular fibrillation induced by high fever. Am. J. Emerg. Med 33, 1331.e1–1331.e3 (2015).
148. Kumar V, Patel N, Van Houzen N & Saini N Brugada-type electrocardiographic changes induced by fever. Circulation 127, 2145–2146 (2013). [PubMed: 23716383]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

149. Jabbari R et al. Incidence and risk factors of ventricular fibrillation before primary angioplasty in patients with first ST-elevation myocardial infarction: a nationwide study in Denmark. J. Am. Heart Assoc 4, e001399 (2015). [PubMed: 25559012]

150. Karam N et al. Identifying patients at risk for prehospital sudden cardiac arrest at the early phase of myocardial infarction: the e-MUST study (Evaluation en Médecine d'Urgence des Stratégies Thérapeutiques des infarctus du myocarde). Circulation 134, 2074–2083 (2016). [PubMed: 27793995]

151. Bhar-Amato J, Davies W & Agarwal S Ventricular arrhythmia after acute myocardial infarction: 'the perfect storm'. Arrhythmia Electrophysiol. Rev 6, 134–139 (2017).

152. Mehta RH et al. Incidence of and outcomes associated with ventricular tachycardia or fibrillation in patients undergoing primary percutaneous coronary intervention. JAMA 301, 1779–1789 (2009).

153. Piccini JP, Berger JS & Brown DL Early sustained ventricular arrhythmias complicating acute myocardial infarction. Am. J. Med 121, 797–804 (2008). [PubMed: 18724970]

154. Nahrendorf M et al. The healing myocardium sequentially mobilizes two monocyte subsets with divergent and complementary functions. J. Exp. Med 204, 3037–3047 (2007). [PubMed: 18025128]

155. Dan GA The dynamic nature of ventricular tachycardia initiation. Drugs Today 46, 777–783 (2010).

156. Walker NL, Burton FL, Kettlewell S, Smith GL & Cobbe SM Mapping of epicardial activation in a rabbit model of chronic myocardial infarction: response to atrial, endocardial and epicardial pacing. J. Cardiovasc. Electrophysiol 18, 862–868 (2007). [PubMed: 17537208]

157. Marchlinski FE, Waxman HL, Buxton AE & Josephson ME Sustained ventricular tachyarrhythmias during the early postinfarction period: electrophysiologic findings and prognosis for survival. J. Am. Coll. Cardiol 2, 240–250 (1983). [PubMed: 6863760]

158. Verma A et al. Relationship between successful ablation sites and the scar border zone defined by substrate mapping for ventricular tachycardia post-myocardial infarction. J. Cardiovasc. Electrophysiol 16, 465–471 (2005). [PubMed: 15877614]

159. Mont L et al. Predisposing factors and prognostic value of sustained monomorphic ventricular tachycardia in the early phase of acute myocardial infarction. J. Am. Coll. Cardiol 28, 1670–1676 (1996). [PubMed: 8962550]

160. Gwechenberger M et al. Cardiac myocytes produce interleukin-6 in culture and in viable border zone of reperfused infarctions. Circulation 99, 546–551 (1999). [PubMed: 9927402]

161. Frangogiannis NG et al. Critical role of monocyte chemoattractant protein-1/CC chemokine ligand 2 in the pathogenesis of ischemic cardiomyopathy. Circulation 115, 584–592 (2007). [PubMed: 17283277]

162. Frangogiannis NG Chemokines in the ischemic myocardium: from inflammation to fibrosis. Inflamm. Res 53, 585–595 (2004). [PubMed: 15693606]

163. Anzai A et al. The infarcted myocardium solicits GM-CSF for the detrimental oversupply of inflammatory leukocytes. J. Exp. Med 214, 3293–3310 (2017).

164. Bloch Thomsen PE et al. Long-term recording of cardiac arrhythmias with an implantable cardiac monitor in patients with reduced ejection fraction after acute myocardial infarction: the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study. Circulation 122, 1258–1264 (2010). [PubMed: 20837897]

165. O'Gara PT et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. J. Am. Coll. Cardiol 61, e78–e140 (2013). [PubMed: 23256914]

166. Myerburg RJ, Mitrani R, Interian A & Castellanos A Interpretation of outcomes of antiarrhythmic clinical trials: design features and population impact. Circulation 97, 1514–1521 (1998). [PubMed: 9576433]

167. Tung R, Zimetbaum P & Josephson ME A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death. J. Am. Coll. Cardiol 52, 1111–1121 (2008). [PubMed: 18804736]

168. Wang C et al. Changes of interleukin-1beta and tumor necrosis factor-alpha of right atrial appendages in patients with rheumatic valvular disease complicated with chronic atrial

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

fibrillation [Chinese]. Zhonghua Xin Xue Guan Bing Za Zhi 33, 522–525 (2005). [PubMed: 16053785]

169. Chen X et al. Downregulation of peroxisome proliferator-activated receptor-γ expression in hypertensive atrial fibrillation. Clin. Cardiol 32, 337–345 (2009). [PubMed: 19569080]
170. Leftheriotis DI et al. The predictive value of inflammatory and oxidative markers following the successful cardioversion of persistent lone atrial fibrillation. Int. J. Cardiol 135, 361–369 (2009). [PubMed: 18640731]
171. Marcus GM et al. Interleukin-6 and atrial fibrillation in patients with coronary artery disease: data from the Heart and Soul Study. Am. Heart J 155, 303–309 (2008). [PubMed: 18215601]
172. Henningsen KMA et al. Prognostic impact of hs-CRP and IL-6 in patients with persistent atrial fibrillation treated with electrical cardioversion. Scand. J. Clin. Lab. Invest 69, 425–432 (2009). [PubMed: 19204850]
173. Li J et al. Role of inflammation and oxidative stress in atrial fibrillation. Heart Rhythm 7, 438–444 (2010). [PubMed: 20153266]
174. Wu N et al. Elevated plasma levels of Th17-related cytokines are associated with increased risk of atrial fibrillation. Sci. Rep 6, 26543 (2016). [PubMed: 27198976]
175. 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). [PubMed: 25955429]
176. Nikoo MH et al. Increased IL-17A in atrial fibrillation correlates with neutrophil to lymphocyte ratio. Iran. J. Immunol 11, 246–258 (2014). [PubMed: 25549592]
177. Pinto A et al. Immuno-inflammatory predictors of stroke at follow-up in patients with chronic non-valvular atrial fibrillation (NVAF). Clin. Sci 116, 781–789 (2009).
178. Sun Z et al. Cross-talk between macrophages and atrial myocytes in atrial fibrillation. Basic Res. Cardiol 111, 63 (2016). [PubMed: 27660282]
179. Monnerat G et al. Macrophage-dependent IL-1β production induces cardiac arrhythmias in diabetic mice. Nat. Commun 7, 13344 (2016). [PubMed: 27882934]
180. El Khoury N, Mathieu S & Fiset C Interleukin-1β reduces L-type Ca^{2+} current through protein kinase Cϵ activation in mouse heart. J. Biol. Chem 289, 21896–21908 (2014). [PubMed: 24936064]
181. De Jesus NM et al. Antiarrhythmic effects of interleukin 1 inhibition after myocardial infarction. Heart Rhythm 14, 727–736 (2017). [PubMed: 28111350]
182. Ridker PM et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N. Engl. J. Med 377, 1119–1131 (2017). [PubMed: 28845751]
183. Vasireddi S, Sattayaprasert P & Laurita K Inflammatory cytokine interleukin-6 has a larger impact on calcium-mediated arrhythmia substrates compared to interleukin-1β [abstract]. J. Am. Coll. Cardiol 71, A412 (2018).
184. Lazzerini PE 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). [PubMed: 31423933]
185. Aromolaran AS et al. Interleukin-6 inhibition of hERG underlies risk for acquired long QT in cardiac and systemic inflammation. PLoS ONE 13, e0208321 (2018). [PubMed: 30521586]
186. Lazzerini PE et al. Antiarrhythmic potential of anticytokine therapy in rheumatoid arthritis: tocilizumab reduces corrected QT interval by controlling systemic inflammation. Arthritis Care Res 67, 332–339 (2015).
187. Hsiao Y-W et al. Rhodiola crenulata reduces ventricular arrhythmia through mitigating the activation of IL-17 and inhibiting the MAPK signaling pathway. Cardiovasc. Drugs Ther 10.1007/s10557-020-07072-z (2020).
188. Liew R et al. Role of tumor necrosis factor-α in the pathogenesis of atrial fibrosis and development of an arrhythmogenic substrate. Circ. J 77, 1171–1179 (2013). [PubMed: 23370453]
189. Sawaya SE 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). [PubMed: 17122196]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

190. 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). [PubMed: 15923312]
191. 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). [PubMed: 17383682]
192. Kao Y-H et al. Tumor necrosis factor-α decreases sarcoplasmic reticulum Ca2+-ATPase expressions via the promoter methylation in cardiomyocytes. Crit. Care Med 38, 217–222 (2010). [PubMed: 19730253]
193. Haudek SB, Taffet GE, Schneider MD & Mann DL TNF provokes cardiomyocyte apoptosis and cardiac remodeling through activation of multiple cell death pathways. J. Clin. Invest 117, 2692–2701 (2007). [PubMed: 17694177]
194. Baeuerle PA & Henkel T Function and activation of NF-kappaB in the immune system. Annu. Rev. Immunol 12, 141–179 (1994). [PubMed: 8011280]
195. Chow JC, Young DW, Golenbock DT, Christ WJ & Gusovsky F Toll-like receptor-4 mediates lipopolysaccharide-induced signal transduction. J. Biol. Chem 274, 10689–10692 (1999). [PubMed: 10196138]
196. Karki R & Igwe OJ Toll-like receptor 4-mediated nuclear factor kappa B activation is essential for sensing exogenous oxidants to propagate and maintain oxidative/nitrosative cellular stress. PLoS ONE 8, e73840 (2013). [PubMed: 24058497]
197. Xu Q et al. High mobility group Box 1 was associated with thrombosis in patients with atrial fibrillation. Medicine 97, e0132 (2018). [PubMed: 29595637]
198. Monnerat-Cahli G et al. Toll-like receptor 4 activation promotes cardiac arrhythmias by decreasing the transient outward potassium current (Ito) through an IRF3-dependent and MyD88-independent pathway. J. Mol. Cell. Cardiol 76, 116–125 (2014). [PubMed: 25169970]
199. Liu M et al. Mitochondrial dysfunction causing cardiac sodium channel downregulation in cardiomyopathy. J. Mol. Cell. Cardiol 54, 25–34 (2013). [PubMed: 23123323]
200. Yao C et al. Enhanced cardiomyocyte NLRP3 inflammasome signaling promotes atrial fibrillation. Circulation 138, 2227–2242 (2018). [PubMed: 29802206]
201. Van Wagoner DR & Chung MK Inflammation, inflammasome activation, and atrial fibrillation. Circulation 138, 2243–2246 (2018). [PubMed: 30571523]
202. Chen G, Chelu MG, Dobrev D & Li N Cardiomyocyte inflammasome signaling in cardiomyopathies and atrial fibrillation: mechanisms and potential therapeutic implications. Front. Physiol 9, 1115 (2018). [PubMed: 30150941]
203. Heijman J et al. Atrial myocyte NLRP3/CaMKII nexus forms a substrate for postoperative atrial fibrillation. Circ. Res 127, 1036–1055 (2020). [PubMed: 32762493]
204. Temple IP, Inada S, Dobrzynski H & Boyett MR Connexins and the atrioventricular node. Heart Rhythm 10, 297–304 (2013). [PubMed: 23085482]
205. De Jesus NM et al. Atherosclerosis exacerbates arrhythmia following myocardial infarction: role of myocardial inflammation. Heart Rhythm 12, 169–178 (2015). [PubMed: 25304682]
206. Goshima K & Tonomura Y Synchronized beating of embryonic mouse myocardial cells mediated by FL cells in monolayer culture. Exp. Cell Res 56, 387–392 (1969). [PubMed: 5387911]
207. Gaudesius G, Miragoli M, Thomas SP & Rohr S Coupling of cardiac electrical activity over extended distances by fibroblasts of cardiac origin. Circ. Res 93, 421–428 (2003). [PubMed: 12893743]
208. Camelliti P, Green CR, LeGrice I & Kohl P Fibroblast network in rabbit sinoatrial node: structural and functional identification of homogeneous and heterogeneous cell coupling. Circ. Res 94, 828–835 (2004). [PubMed: 14976125]
209. Quinn TA et al. Electrotonic coupling of excitable and nonexcitable cells in the heart revealed by optogenetics. Proc. Natl Acad. Sci. USA 113, 14852–14857 (2016). [PubMed: 27930302]
210. Rubart M et al. Electrical coupling between ventricular myocytes and myofibroblasts in the infarcted mouse heart. Cardiovasc. Res 114, 389–400 (2018). [PubMed: 29016731]
211. Fontes MSC, van Veen TAB, de Bakker JMT & van Rijen HVM Functional consequences of abnormal Cx43 expression in the heart. Biochim. Biophys. Acta 1818, 2020–2029 (2012). [PubMed: 21839722]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

212. Leuschner F et al. Rapid monocyte kinetics in acute myocardial infarction are sustained by extramedullary monocytopoiesis. J. Exp. Med 209, 123–137 (2012). [PubMed: 22213805]
213. Fei Y-D et al. Macrophages facilitate post myocardial infarction arrhythmias: roles of gap junction and KCa3.1. Theranostics 9, 6396–6411 (2019). [PubMed: 31588225]
214. Kohl P & Noble D Mechanosensitive connective tissue: potential influence on heart rhythm. Cardiovasc. Res 32, 62–68 (1996). [PubMed: 8776404]
215. Kohl P, Kamkin AG, Kiseleva IS & Noble D Mechanosensitive fibroblasts in the sino-atrial node region of rat heart: interaction with cardiomyocytes and possible role. Exp. Physiol 79, 943–956 (1994). [PubMed: 7873162]
216. Roell W et al. Overexpression of Cx43 in cells of the myocardial scar: correction of post-infarct arrhythmias through heterotypic cell-cell coupling. Sci. Rep 8, 7145 (2018). [PubMed: 29739982]
217. Li K et al. Differential macrophage polarization in male and female BALB/c mice infected with coxsackievirus B3 defines susceptibility to viral myocarditis. Circ. Res 105, 353–364 (2009). [PubMed: 19608981]
218. Hoyer FF et al. Tissue-specific macrophage responses to remote injury impact the outcome of subsequent local immune challenge. Immunity 51, 899–914.e7 (2019). [PubMed: 31732166]
219. Vilahur G et al. Molecular and cellular mechanisms involved in cardiac remodeling after acute myocardial infarction. J. Mol. Cell. Cardiol 50, 522–533 (2011). [PubMed: 21219908]
220. Chen B & Frangogiannis NG The role of macrophages in nonischemic heart failure. JACC Basic Transl. Sci 3, 245–248 (2018). [PubMed: 30062210]
221. Rosenkranz S TGF-β1 and angiotensin networking in cardiac remodeling. Cardiovasc. Res 63, 423–432 (2004). [PubMed: 15276467]
222. Kuwahara F et al. Hypertensive myocardial fibrosis and diastolic dysfunction: another model of inflammation? Hypertension 43, 739–745 (2004). [PubMed: 14967845]
223. Ren J et al. Proinflammatory protein CARD9 is essential for infiltration of monocytic fibroblast precursors and cardiac fibrosis caused by angiotensin II infusion. Am. J. Hypertens 24, 701–707 (2011). [PubMed: 21436792]
224. Kagitani S et al. Tranilast attenuates myocardial fibrosis in association with suppression of monocyte/macrophage infiltration in DOCA/salt hypertensive rats. J. Hypertens 22, 1007–1015 (2004).
225. Frangogiannis NG et al. Evidence for an active inflammatory process in the hibernating human myocardium. Am. J. Pathol 160, 1425–1433 (2002). [PubMed: 11943726]
226. Frangogiannis NG et al. MCSF expression is induced in healing myocardial infarcts and may regulate monocyte and endothelial cell phenotype. Am. J. Physiol. Heart Circ. Physiol 285, H483–H492 (2003). [PubMed: 12689859]
227. Frangogiannis N Transforming growth factor-β in tissue fibrosis. J. Exp. Med 217, e20190103 (2020). [PubMed: 32997468]
228. Verma SK et al. Interleukin-10 inhibits bone marrow fibroblast progenitor cell-mediated cardiac fibrosis in pressure-overloaded myocardium. Circulation 136, 940–953 (2017). [PubMed: 28667100]
229. Simões FC et al. Macrophages directly contribute collagen to scar formation during zebrafish heart regeneration and mouse heart repair. Nat. Commun 11, 600 (2020). [PubMed: 32001677]
230. Vasquez C et al. Enhanced fibroblast-myocyte interactions in response to cardiac injury. Circ. Res 107, 1011–1020 (2010). [PubMed: 20705922]
231. Rudolph V et al. Myeloperoxidase acts as a profibrotic mediator of atrial fibrillation. Nat. Med 16, 470–474 (2010). [PubMed: 20305660]
232. Fu X, Kassim SY, Parks WC & Heinecke JW Hypochlorous acid generated by myeloperoxidase modifies adjacent tryptophan and glycine residues in the catalytic domain of matrix metalloproteinase-7 (matrilysin): an oxidative mechanism for restraining proteolytic activity during inflammation. J. Biol. Chem 278, 28403–28409 (2003). [PubMed: 12759346]
233. Holzwirth E et al. Myeloperoxidase in atrial fibrillation: association with progression, origin and influence of renin-angiotensin system antagonists. Clin. Res. Cardiol 109, 324–330 (2020). [PubMed: 31236695]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

234. Li S et al. Myeloperoxidase and risk of recurrence of atrial fibrillation after catheter ablation. J. Investig. Med 61, 722–727 (2013).

235. Friedrichs K et al. Induction of atrial fibrillation by neutrophils critically depends on CD11b/CD18 integrins. PLoS ONE 9, e89307 (2014). [PubMed: 24558493]

236. Abe I et al. Association of fibrotic remodeling and cytokines/chemokines content in epicardial adipose tissue with atrial myocardial fibrosis in patients with atrial fibrillation. Heart Rhythm 15, 1717–1727 (2018). [PubMed: 29908372]

237. Iacobellis G et al. Influence of excess fat on cardiac morphology and function: study in uncomplicated obesity. Obes. Res 10, 767–773 (2002). [PubMed: 12181385]

238. Thanassoulis G et al. Pericardial fat is associated with prevalent atrial fibrillation: the Framingham heart study. Circ. Arrhythm. Electrophysiol 3, 345–350 (2010). [PubMed: 20558845]

239. Lee CG et al. Interleukin-13 induces tissue fibrosis by selectively stimulating and activating transforming growth factor β1. J. Exp. Med 194, 809–821 (2001). [PubMed: 11560996]

240. Okuma T et al. C-C chemokine receptor 2 (CCR2) deficiency improves bleomycin-induced pulmonary fibrosis by attenuation of both macrophage infiltration and production of macrophage-derived matrix metalloproteinases. J. Pathol 204, 594–604 (2004). [PubMed: 15538737]

241. Johnson JL et al. Relationship of MMP-14 and TIMP-3 expression with macrophage activation and human atherosclerotic plaque vulnerability. Mediators Inflamm 2014, 276457 (2014). [PubMed: 25301980]

242. Fallowfield JA et al. Scar-associated macrophages are a major source of hepatic matrix metalloproteinase-13 and facilitate the resolution of murine hepatic fibrosis. J. Immunol 178, 5288–5295 (2007). [PubMed: 17404313]

243. Abe H et al. Macrophage hypoxia signaling regulates cardiac fibrosis via Oncostatin M. Nat. Commun 10, 2824 (2019). [PubMed: 31249305]

244. Haro H et al. Matrix metalloproteinase-7-dependent release of tumor necrosis factor-α in a model of herniated disc resorption. J. Clin. Invest 105, 143–150 (2000). [PubMed: 10642592]

245. Boixel C et al. Fibrosis of the left atria during progression of heart failure is associated with increased matrix metalloproteinases in the rat. J. Am. Coll. Cardiol 42, 336–344 (2003). [PubMed: 12875773]

246. Lindsey ML et al. Matrix metalloproteinase-7 affects connexin-43 levels, electrical conduction, and survival after myocardial infarction. Circulation 113, 2919–2928 (2006). [PubMed: 16769909]

247. Al-Khatib SM et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation 138, e272–e391 (2018). [PubMed: 29084731]

248. Lehnart SE et al. Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. Circulation 116, 2325–2345 (2007). [PubMed: 17998470]

249. Li H et al. A peptidomimetic inhibitor suppresses the inducibility of β1-adrenergic autoantibody-mediated cardiac arrhythmias in the rabbit. J. Interv. Card. Electrophysiol 44, 205–212 (2015). [PubMed: 26446828]

250. Lazzerini PE, Capecchi PL, Laghi-Pasini F & Boutjdir M Autoimmune channelopathies as a novel mechanism in cardiac arrhythmias. Nat. Rev. Cardiol 14, 521–535 (2017). [PubMed: 28470179]

251. Drew BJ et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. J. Am. Coll. Cardiol 55, 934–947 (2010). [PubMed: 20185054]

252. Priori SG et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 10, 1932–1963 (2013). [PubMed: 24011539]

253. Kallergis EM, Goudis CA, Simantirakis EN, Kochiadakis GE & Vardas PE Mechanisms, risk factors, and management of acquired long QT syndrome: a comprehensive review. ScientificWorldJournal 2012, 212178 (2012). [PubMed: 22593664]
254. Nakamura K et al. Anti-KCNH2 antibody-induced long QT syndrome: novel acquired form of long QT syndrome. J. Am. Coll. Cardiol 50, 1808–1809 (2007). [PubMed: 17964047]
255. Suzuki S et al. Novel autoantibodies to a voltagegated potassium channel Kv1.4 in a severe form of myasthenia gravis. J. Neuroimmunol 170, 141–149 (2005). [PubMed: 16182377]
256. Fabris F et al. Induction of autoimmune response to the extracellular loop of the HERG channel pore induces QTc prolongation in guinea-pigs. J. Physiol 594, 6175–6187 (2016). [PubMed: 27296897]
257. Li J et al. Anti-KCNQ1 K^+ channel autoantibodies increase IKs current and are associated with QT interval shortening in dilated cardiomyopathy. Cardiovasc. Res 98, 496–503 (2013). [PubMed: 23447643]
258. Li J et al. Induced KCNQ1 autoimmunity accelerates cardiac repolarization in rabbits: potential significance in arrhythmogenesis and antiarrhythmic therapy. Heart Rhythm 11, 2092–2100 (2014). [PubMed: 25087487]
259. Eftekhari P et al. Anti-SSA/Ro52 autoantibodies blocking the cardiac 5-HT4 serotoninergic receptor could explain neonatal lupus congenital heart block. Eur. J. Immunol 30, 2782–2790 (2000). [PubMed: 11069058]
260. Fritsch C et al. 52-kDa Ro/SSA epitopes preferentially recognized by antibodies from mothers of children with neonatal lupus and congenital heart block. Arthritis Res. Ther 8, R4 (2006). [PubMed: 16356190]
261. Lazzerini PE et al. Arrhythmogenicity of anti-Ro/SSA antibodies in patients with torsades de pointes. Circ. Arrhythm. Electrophysiol 9, e003419 (2016). [PubMed: 27030700]
262. Hull D, Binns BA & Joyce D Congenital heart block and widespread fibrosis due to maternal lupus erythematosus. Arch. Dis. Child 41, 688–690 (1966). [PubMed: 5927926]
263. Chameides L et al. Association of maternal systemic lupus erythematosus with congenital complete heart block. N. Engl. J. Med 297, 1204–1207 (1977).
264. Brucato A, Cimaz R, Caporali R, Ramoni V & Buyon J Pregnancy outcomes in patients with autoimmune diseases and anti-Ro/SSA antibodies. Clin. Rev. Allergy Immunol 40, 27–41 (2011). [PubMed: 20012231]
265. Hayashi T et al. Outcome of prenatally diagnosed isolated congenital complete atrioventricular block treated with transplacental betamethasone or ritodrine therapy. Pediatr. Cardiol 30, 35–40 (2009). [PubMed: 18661167]
266. Jaeggi ET et al. Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. Circulation 110, 1542–1548 (2004). [PubMed: 15353508]
267. Seisenberger C et al. Functional embryonic cardiomyocytes after disruption of the L-type α1C (Cav1.2) calcium channel gene in the mouse. J. Biol. Chem 275, 39193–39199 (2000). [PubMed: 10973973]
268. Karnabi E et al. Congenital heart block: identification of autoantibody binding site on the extracellular loop (domain I, S5-S6) of α1D L-type Ca channel. J. Autoimmun 34, 80–86 (2010). [PubMed: 19640679]
269. Ruffatti A et al. Plasmapheresis, intravenous immunoglobulins and bethametasone – a combined protocol to treat autoimmune congenital heart block: a prospective cohort study. Clin. Exp. Rheumatol 34, 706–713 (2016). [PubMed: 27385463]
270. Korkmaz S et al. Provocation of an autoimmune response to cardiac voltage-gated sodium channel $Na_V1.5$ induces cardiac conduction defects in rats. J. Am. Coll. Cardiol 62, 340–349 (2013). [PubMed: 23684688]
271. Maguy A, Tardif J-C, Busseuil D, Ribi C & Li J Autoantibody signature in cardiac arrest. Circulation 141, 1764–1774 (2020). [PubMed: 32312099]

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272. Maguy A et al. KCNQ1 antibodies for immunotherapy of long QT syndrome type 2. J. Am. Coll. Cardiol 75, 2140–2152 (2020). [PubMed: 32354382]
273. Ahmed MS et al. A supramolecular nanocarrier for delivery of amiodarone anti-arrhythmic therapy to the heart. Bioconjug. Chem 30, 733–740 (2019). [PubMed: 30615425]
274. Leuschner F et al. Silencing of CCR2 in myocarditis. Eur. Heart J 36, 1478–1488 (2015). [PubMed: 24950695]
275. Aghajanian H et al. Targeting cardiac fibrosis with engineered T cells. Nature 573, 430–433 (2019). [PubMed: 31511695]
276. Behling J, Kaes J, Münzel T, Grabbe S & Loquai C New-onset third-degree atrioventricular block because of autoimmune-induced myositis under treatment with anti-programmed cell death-1 (nivolumab) for metastatic melanoma. Melanoma Res 27, 155–158 (2017). [PubMed: 27977496]
277. Heinzerling L et al. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. J. Immunother. Cancer 4, 50 (2016). [PubMed: 27532025]
278. Peretto G et al. Arrhythmias in myocarditis: state of the art. Heart Rhythm 16, 793–801 (2019). [PubMed: 30476544]
279. Mehta D, Ravindran K & Kuebler WM Novel regulators of endothelial barrier function. Am. J. Physiol. Lung Cell. Mol. Physiol 307, L924–L935 (2014). [PubMed: 25381026]
280. Wang TJ et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham heart study. Circulation 107, 2920–2925 (2003). [PubMed: 12771006]
281. Mahoney P, Kimmel S, DeNofrio D, Wahl P & Loh E Prognostic significance of atrial fibrillation in patients at a tertiary medical center referred for heart transplantation because of severe heart failure. Am. J. Cardiol 83, 1544–1547 (1999). [PubMed: 10363868]
282. Carson PE et al. The influence of atrial fibrillation on prognosis in mild to moderate heart failure. The V-HeFT Studies. The V-HeFT VA Cooperative Studies Group. Circulation 87, VI102–VI110 (1993). [PubMed: 8500233]
283. Middlekauff HR, Stevenson WG & Stevenson LW Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. Circulation 84, 40–48 (1991). [PubMed: 2060110]
284. Kusumoto FM et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society. Circulation 140, e382–e482 (2019). [PubMed: 30586772]
285. Cheema O et al. Patterns of myocardial fibrosis by CMR in patients with conduction abnormalities [abstract]. J. Cardiovasc. Magn. Reson 14, P213 (2012).
286. Kottkamp H Fibrotic atrial cardiomyopathy: a specific disease/syndrome supplying substrates for atrial fibrillation, atrial tachycardia, sinus node disease, AV node disease, and thromboembolic complications. J. Cardiovasc. Electrophysiol 23, 797–799 (2012). [PubMed: 22554187]
287. January CT et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. Circulation 140, e125–e151 (2019). [PubMed: 30686041]
288. January CT et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 130, 2071–2104 (2014). [PubMed: 24682348]
289. Ericson J et al. ImmGen microarray gene expression data: data generation and quality control pipeline. ImmGen https://www.immgen.org/Protocols/ImmGenDataGenerationAndQCDocumentation.pdf (2012).
290. Silvestre-Roig C, Hidalgo A & Soehnlein O Neutrophil heterogeneity: implications for homeostasis and pathogenesis. Blood 127, 2173–2181 (2016).
291. Nicolás-Ávila JÁ, Adrover JM & Hidalgo A Neutrophils in homeostasis, immunity, and cancer. Immunity 46, 15–28 (2017). [PubMed: 28099862]

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292. Ramos GC et al. Myocardial aging as a T-cell-mediated phenomenon. Proc. Natl Acad. Sci. USA 114, E2420–E2429 (2017). [PubMed: 28255084]
293. Liu K et al. In vivo analysis of dendritic cell development and homeostasis. Science 324, 392–397 (2009). [PubMed: 19286519]
294. Choi J-H et al. Identification of antigen-presenting dendritic cells in mouse aorta and cardiac valves. J. Exp. Med 206, 497–505 (2009). [PubMed: 19221394]
295. Clemente-Casares X et al. A $CD103^+$ conventional dendritic cell surveillance system prevents development of overt heart failure during subclinical viral myocarditis. Immunity 47, 974–989.e8 (2017). [PubMed: 29166591]
296. Adamo L et al. Modulation of subsets of cardiac B lymphocytes improves cardiac function after acute injury. JCI Insight 3, e120137 (2018).
297. Bönner F, Borg N, Burghoff S & Schrader J Resident cardiac immune cells and expression of the ectonucleotidase enzymes CD39 and CD73 after ischemic injury. PLoS ONE 7, e34730 (2012). [PubMed: 22514659]
298. Adamo L et al. Myocardial B cells are a subset of circulating lymphocytes with delayed transit through the heart. JCI Insight 5, e134700 (2020). [PubMed: 31945014]
299. Ingason AB, Mechmet F, Atacho DAM, Steingrímsson E & Petersen PH Distribution of mast cells within the mouse heart and its dependency on Mitf. Mol. Immunol 105, 9–15 (2019). [PubMed: 30471646]
300. Patella V et al. Human heart mast cells. Isolation, purification, ultrastructure, and immunologic characterization. J. Immunol 154, 2855–2865 (1995). [PubMed: 7533185]
301. Mackins CJ et al. Cardiac mast cell-derived renin promotes local angiotensin formation, norepinephrine release, and arrhythmias in ischemia/reperfusion. J. Clin. Invest 116, 1063–1070 (2006). [PubMed: 16585966]
302. Liao C et al. Cardiac mast cells cause atrial fibrillation through PDGF-A-mediated fibrosis in pressure-overloaded mouse hearts. J. Clin. Invest 120, 242–253 (2010). [PubMed: 20038802]
303. Deisseroth K Optogenetics. Nat. Methods 8, 26–29 (2011). [PubMed: 21191368]
304. Miesenböck G The optogenetic catechism. Science 326, 395–399 (2009). [PubMed: 19833960]
305. Boyden ES, Zhang F, Bamberg E, Nagel G & Deisseroth K Millisecond-timescale, genetically targeted optical control of neural activity. Nat. Neurosci 8, 1263–1268 (2005). [PubMed: 16116447]
306. Li X et al. Fast noninvasive activation and inhibition of neural and network activity by vertebrate rhodopsin and green algae channelrhodopsin. Proc. Natl Acad. Sci. USA 102, 17816–17821 (2005). [PubMed: 16306259]
307. Nagel G et al. Channelrhodopsin-2, a directly light-gated cation-selective membrane channel. Proc. Natl Acad. Sci. USA 100, 13940–13945 (2003). [PubMed: 14615590]
308. Lundby A, Mutoh H, Dimitrov D, Akemann W & Knöpfel T Engineering of a genetically encodable fluorescent voltage sensor exploiting fast Ci-VSP voltage-sensing movements. PLoS ONE 3, e2514 (2008). [PubMed: 18575613]
309. Nakai J, Ohkura M & Imoto K A high signal-to-noise Ca^{2+} probe composed of a single green fluorescent protein. Nat. Biotechnol 19, 137–141 (2001). [PubMed: 11175727]
310. Bruegmann T et al. Optogenetic control of heart muscle in vitro and in vivo. Nat. Methods 7, 897–900 (2010). [PubMed: 20881965]
311. Arrenberg AB, Stainier DYR, Baier H & Huisken J Optogenetic control of cardiac function. Science 330, 971–974 (2010). [PubMed: 21071670]
312. Wang Y et al. Optogenetic control of heart rhythm by selective stimulation of cardiomyocytes derived from $Pnmt^+$ cells in murine heart. Sci. Rep 7, 40687 (2017). [PubMed: 28084430]
313. Bruegmann T et al. Optogenetic defibrillation terminates ventricular arrhythmia in mouse hearts and human simulations. J. Clin. Invest 126, 3894–3904 (2016). [PubMed: 27617859]
314. Bruegmann T, Beiert T, Vogt CC, Schrickel JW & Sasse P Optogenetic termination of atrial fibrillation in mice. Cardiovasc. Res 114, 713–723 (2018). [PubMed: 29293898]

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315. Nyns ECA et al. Optogenetic termination of ventricular arrhythmias in the whole heart: towards biological cardiac rhythm management. Eur. Heart J 38, 2132–2136 (2017). [PubMed: 28011703]

316. Lee S et al. Real-time in vivo imaging of the beating mouse heart at microscopic resolution. Nat. Commun 3, 1054 (2012). [PubMed: 22968700]

317. Aguirre AD, Vinegoni C, Sebas M & Weissleder R Intravital imaging of cardiac function at the single-cell level. Proc. Natl Acad. Sci. USA 111, 11257–11262 (2014). [PubMed: 25053815]

318. Jones JS, Small DM & Nishimura N In vivo calcium imaging of cardiomyocytes in the beating mouse heart with multiphoton microscopy. Front. Physiol 9, 969 (2018). [PubMed: 30108510]

319. Kavanagh DPJ, Lokman AB, Neag G, Colley A & Kalia N Imaging the injured beating heart intravitally and the vasculoprotection afforded by haematopoietic stem cells. Cardiovasc. Res 115, 1918–1932 (2019). [PubMed: 31062860]

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Box 1 | Leukocytes and their subsets in heart homeostasis

Macrophages comprise 75% of total cardiac leukocytes, and their subsets and functions in cardiac health are described in the main text, but how other leukocytes present in the heart contribute to heart homeostasis and conduction in steady state is mostly unknown.

Neutrophils

Neutrophils are polymorphonuclear, phagocytic leukocytes that act as the first line of host defence against pathogens but also mediate inflammation-induced injury. Rarely found in the healthy myocardium, neutrophils are terminally differentiated cells with phenotypic heterogeneity and functional versatility[290,291]. The granulocyte population in the heart increases with age[292]. Myeloperoxidase, which is a haem enzyme abundantly expressed by neutrophils, promotes atrial fibrosis, leading to an increased vulnerability to atrial fibrillation[231].

Dendritic cells

Dendritic cells, which are the major antigen-presenting cells, have an essential role in adaptive immunity and are an important link between the innate and adaptive immune systems[293]. The healthy heart contains resident cardiac dendritic cells, abundant in the aortic valve and sinus, that constitute about 1% of total cardiac leukocytes. These dendritic cells comprise $CD103^+CD11b^-$ and $CD103^-CD11b^+$ subsets[26,294]; $CD103^+$ cardiac dendritic cells proliferate more than $CD11b^+$ cardiac dendritic cells[295]. CD26 expression is higher in cardiac dendritic cells than in cardiac macrophages[295]. Resident dendritic cells isolated from the aorta and valves present antigens to $CD8^+$ T cells in vitro and in vivo[294].

B lymphocytes

B lymphocytes produce antibodies, present antigens and secrete factors involved in immune regulation. Prevalent in the healthy murine heart, B lymphocytes make up about 9% of cardiac leukocytes[23,296,297]. Myocardial B cells can be grouped into three subpopulations: $CD19^+CD11b^-$, $CD19^+CD11b^+IgM^+CD5^+$ and $CD19^+CD11b^+IgM^+CD5^-$ (REF.[296]). Most myocardial B cells reside in the microvasculature and patrol along the endothelium, whereas some cross the endothelium into myocardial tissue[298]. B cell-deficient mice have fewer myocardial $Ly6C^+$ monocytes and more myocardial $CD4^+$ and $CD8^+$ T cells[298], suggesting that B cells modulate the composition of the myocardial leukocyte pool.

T lymphocytes

T lymphocytes elicit cell-mediated immunity and are divided into T helper cells, cytotoxic T cells and regulatory T cells. In the healthy heart, T lymphocytes comprise about 3% of total cardiac leukocytes[23,297]. Aged hearts have more $CD8^+$ lymphocytes; CD4 to CD8 ratios decrease with age, but the functional implications of this change are unclear[292]. After myocardial infarction, activated $CD4^+$ T lymphocytes are found in the heart-draining lymph nodes. Elderly MHC class II-deficient mice have preserved left ventricular fractional shortening and end-diastolic dimension[292]. Heart samples from

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CD4-deficient or MHC class II-deficient mice showed reduced expression levels of pro-inflammatory cytokines compared with heart samples from wild-type mice[292]. These data indicate that $CD4^+$ T lymphocytes mediate inflammation and mild dysfunction in aged hearts.

Mast cells

Mast cells are well known as primary effector cells of allergic and anaphylactic reactions. Mouse[28,299] and human[24,300] hearts contain a fairly low number of mast cells. Most of the heart's mast cells are located in the myocardium and in the epicardium[28]. Mast cell-derived renin cleaved angiotensin I and promoted local angiotensin II formation and arrhythmias in guinea-pig isolated hearts subjected to ischaemia[301]. In addition, cardiac mast cells accumulated in the left and right atria of mice with pressure overload, where they promoted atrial fibrosis through the secretion of platelet-derived growth factor A[302].

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Box 2 | Technological developments

Optogenetics

Optogenetics combines genetic and optical methods to cause or inhibit precisely defined events in specific cells of living tissue and animals[303]. There are two classes of optogenetic devices: actuators and light-emitting sensors[304]. Actuators, such as channelrhodopsin 2 (ChR2), transduce optical signals into physiological signals. Light exposure at a certain wavelength elicits action potentials in ChR2-expressing cells, such as neurons[305,306]. ChR2 opens after absorption of a photon to generate a large permeability for cations, leading to depolarization[307]. Sensor proteins, such as voltage-sensitive fluorescent protein[308] or green Ca^{2+} indicator protein (GCaMP)[309], produce fluorescent signals in response to changes in membrane potential, intracellular Ca^{2+} concentration or synaptic transmission, which make such activity detectable. The first cardiac optogenetics studies used light to pace the hearts of transgenic mice[310] and to modulate pacemaker activity in the hearts of zebrafish[311]. Optogenetics can be used to alter the function of both cardiomyocytes[312] and non-cardiomyocytes[37]. Moreover, optogenetics can be used to terminate arrhythmias in rodent hearts[313–315].

Intravital microscopy

Intravital microscopy provides the ability to visualize and quantify events in the native tissue environment. Subcellular spatial and millisecond temporal resolution in the mouse heart in vivo were achieved by combining tissue stabilization, cardiac gating and image-processing algorithms to suppress motion artefacts[316,317]. Fluorescent imaging probes can be used to assay physiology and cell–cell interaction in the heart by staining for specific cells, including leukocytes[75]. Imaging of the genetically encoded, highly sensitive Ca^{2+} indicator GCaMP6 (REF.[76]) in the beating heart resolves Ca^{2+} dynamics in single cardiomyocytes[318]. In the future, cardiac intravital microscopy will be used quantitatively to measure not only cardiomyocyte contraction[317] but also membrane potential changes, Ca^{2+} signalling at the cellular level[318] and leukocyte trafficking[319].

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Key points

- Immune cells express various ion channels that influence their phenotypes and functions.
- Numerous leukocytes reside in the normal myocardium; their numbers, phenotypes and electrophysiological properties change in pathologies that give rise to arrhythmia, including acute myocardial infarction, sepsis, heart failure and myocarditis.
- Macrophages are the most abundant leukocytes in the heart and electrotonically couple to cardiomyocytes via connexin 43-containing gap junctions; this sink–source relationship leads to rhythmic macrophage depolarization and modulates the resting membrane potential and action potential of cardiomyocytes.
- Leukocytes might contribute to rhythm disorders either directly through altered coupling or indirectly by influencing cardiomyocytes and their environment.
- Indirect pro-arrhythmic leukocyte actions include production of cytokines and antibodies, which act on cardiomyocytes and change tissue properties by instigating fibrosis.
- Immunotherapy is an emerging option for the treatment of rhythm disorders such as atrial fibrillation.

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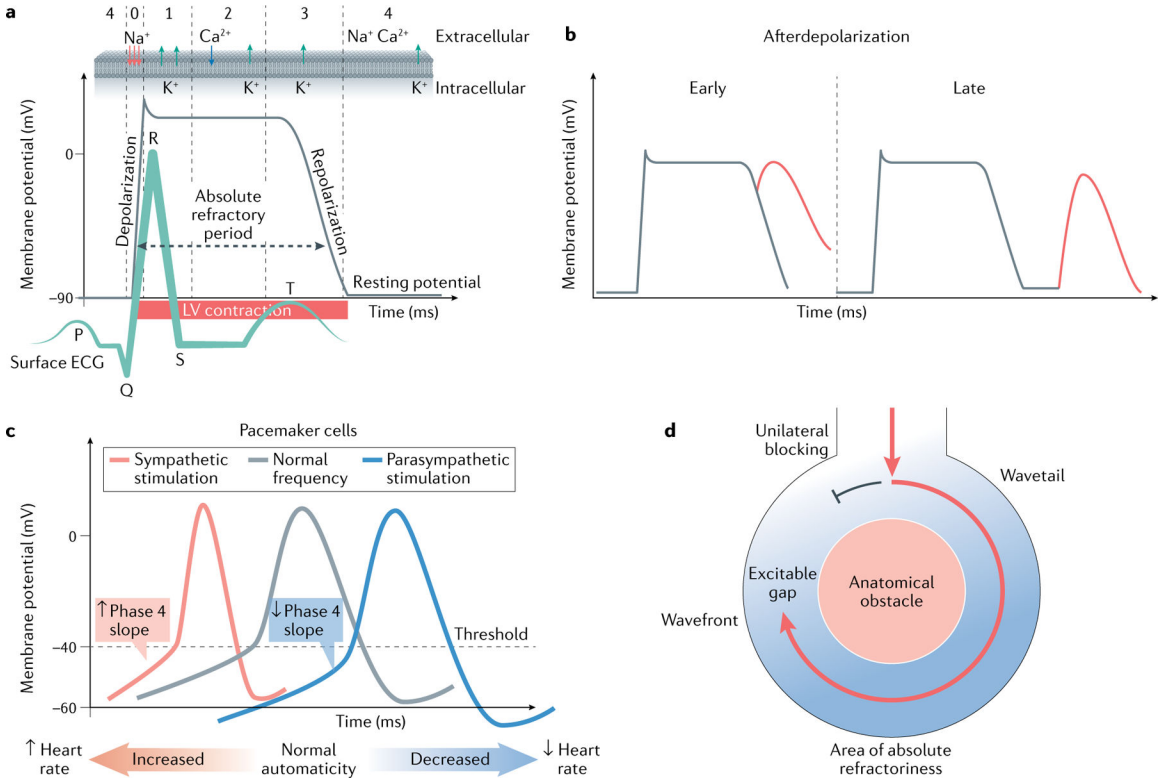

Fig. 1 |. Electrophysiological concepts of conduction and arrhythmogenesis.

a | The physiological cardiac action potential can be divided into different phases. Depolarization due to rapid Na^+ influx (phase 0). Transient K^+ channels open and cause K^+ efflux (phase 1). The plateau phase is facilitated by Ca^{2+} influx and counterbalanced by K^+ efflux (phase 2). Closing of the Ca^{2+} channels causes rapid repolarization, but K^+ channels remain open until the membrane potential returns to −90 mV (phase 3). Resting membrane potential, with Na^+ and Ca^{2+} channels closed, but K^+ channels open, holding the membrane potential at −90 mV (phase 4). **b** | Triggered activity usually results from prematurely activated cardiac tissue, causing early or late afterdepolarizations. **c** | Increased automaticity from dominant pacemaker cells is usually triggered by abnormal impulse function and can lead to tachyarrhythmias by increasing the rate of action potential discharge due to sympathetic stimulation, whereas decreased pacemaker rates slow the heart rate. **d** | A depolarizing impulse (red arrow) encounters an anatomical obstacle and circles around it. The electrical impulse constantly ‘runs around’ the block, along the excitable tissue gap. If the wavefront never reaches the refractory tail, a re-entrant loop forms, causing sustained arrhythmia. ECG, electrocardiogram; LV, left ventricular.

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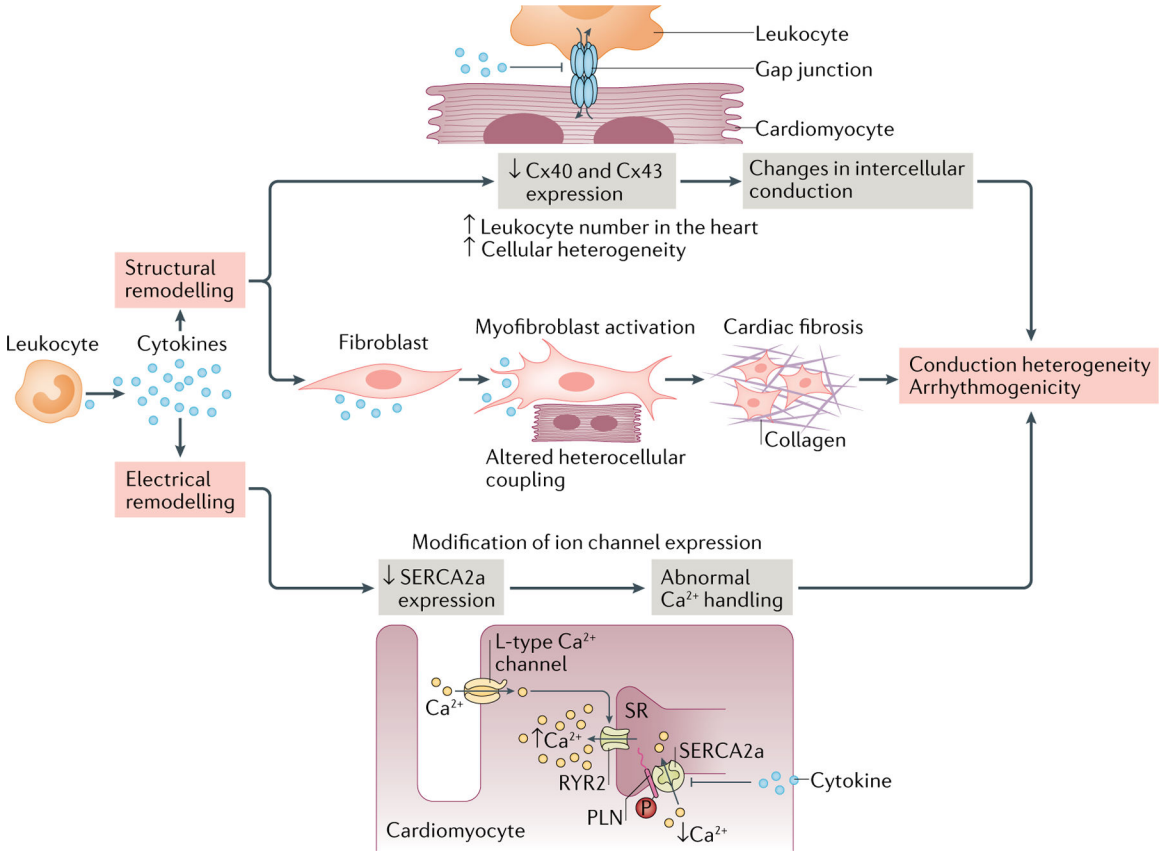

Fig. 2 |. Leukocyte-released cytokines shape the arrhythmogenic substrate.

Structural remodelling can be facilitated by leukocyte-released cytokines (such as tumour necrosis factor) by decreasing connexin (Cx) protein expression, hampering the intercellular conduction between cardiomyocytes and non-cardiomyocytes (such as leukocytes), ultimately affecting the cardiomyocyte action potential morphology, or by activating fibroblasts to become myofibroblasts, resulting in collagen deposition, shaping an arrhythmogenic substrate. Electrical remodelling by leukocyte-released cytokines usually refers to effects on ion channel expression (such as the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a (SERCA2a)), leading to abnormal Ca^{2+} handling in cardiomyocytes. Both structural and electrical remodelling increase conduction heterogeneity and arrhythmogenicity. PLN, phospholamban; RYR2, ryanodine receptor 2; SR, sarcoplasmic reticulum.

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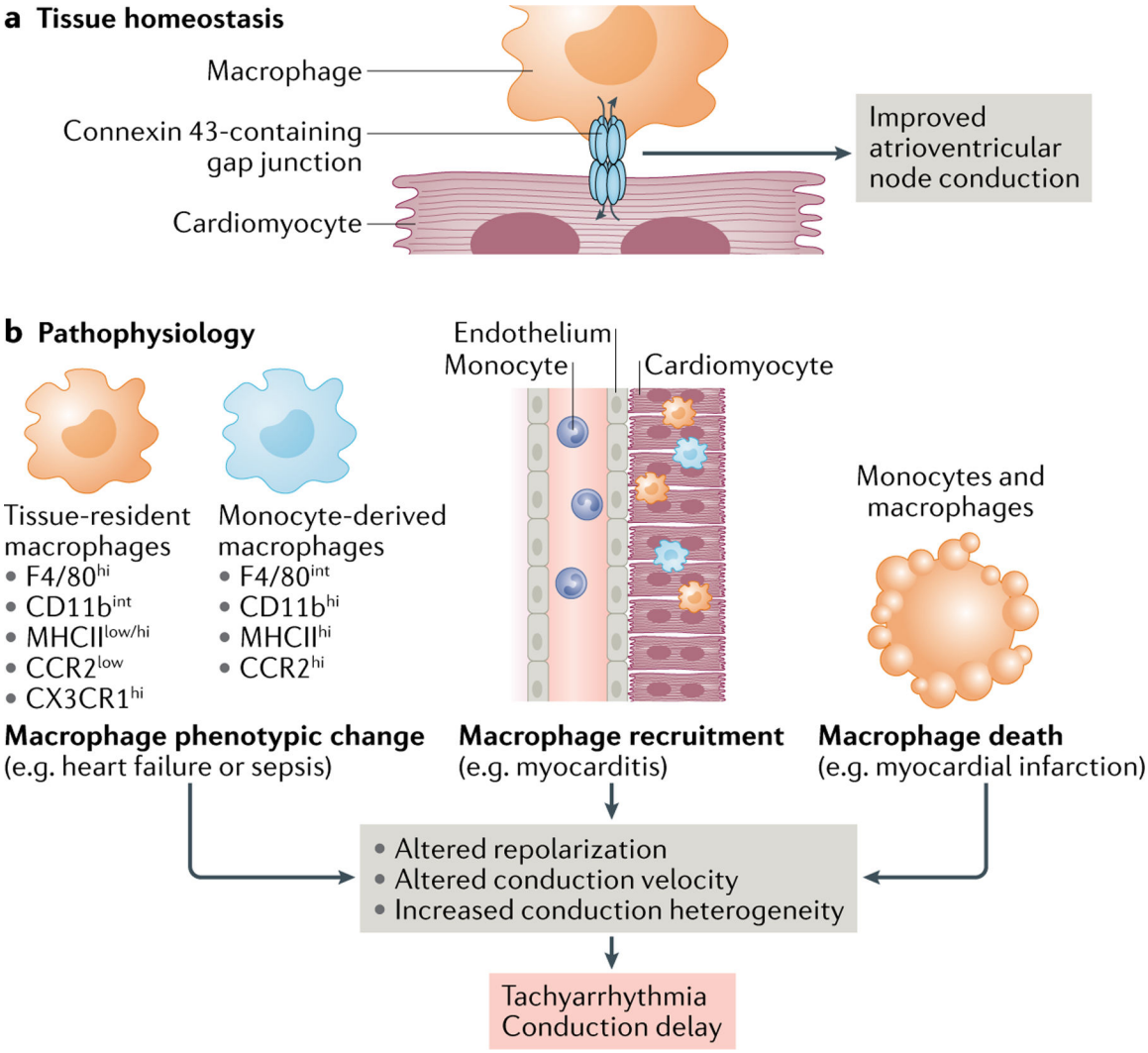

Fig. 3 |. Macrophage–cardiomyocyte interactions.

a Macrophages are coupled to cardiomyocytes via connexin 43-containing gap junctions, which allow cation exchange that contributes to the steady-state cardiomyocyte action potential and improves atrioventricular node conduction. **b** | In the diseased heart, macrophages undergo phenotypic changes (for example, tissue-resident macrophages die and are replaced by monocyte-derived macrophages, which have distinct features) and are recruited in enormous numbers to the site of injury, affecting the cardiomyocyte action potential by modulating repolarization and conduction velocity and increasing conduction heterogeneity.

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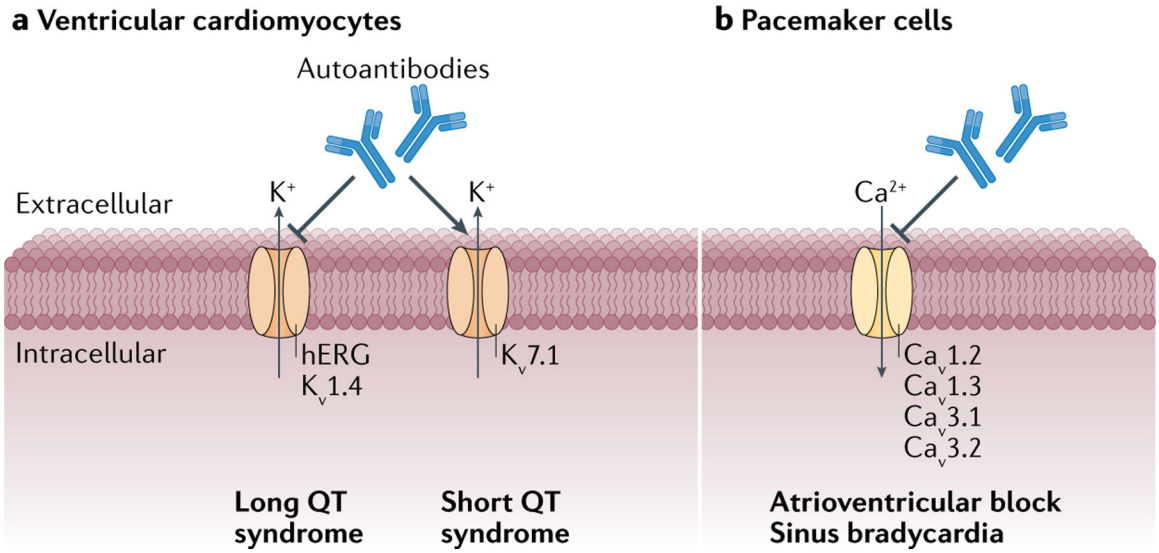

Fig. 4 |. Autoimmune channelopathies.

a | Autoantibodies released by plasma cells can either inhibit ventricular ion channels such as hERG and $K_v1.4$, producing long QT syndrome, or activate ventricular ion channels such as $K_v7.1$, producing short QT syndrome. **b** | In pacemaker cells, blockade of Ca^{2+} channel subunits by autoantibodies can generate atrioventricular block or sinus bradycardia.

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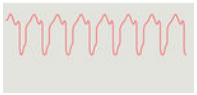
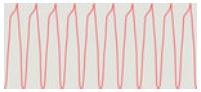
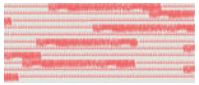
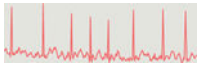
Table 1 |

Definitions of clinically important arrhythmias

Arrhythmia	Example ECg	ECg description	Underlying pathologies and their inflammatory signatures
Ventricular arrhythmias			
Ventricular tachycardia		More than three consecutive QRS complexes originating in the ventricles at a rate of >100 bpm. Regular QRS complex shape missing; subtypes include sustained (>30 s), unsustained (more than three beats, terminating spontaneously), monomorphic (symmetrical QRS morphology from beat to beat) and polymorphic (unstable and multiform QRS morphology from beat to beat)	Myocarditis: massive recruitment of macrophages and T lymphocytes[133,139,146,278] Myocardial infarction: neutrophil and monocyte recruitment, tissue-resident macrophage death and release of inflammatory cytokines and chemokines, such as CC-chemokine ligand 2, IL-1, IL-6 and tumour necrosis factor[149–151,153,157,279]
Ventricular fibrillation		Rapid and disorganized electrical activity, with pronounced variability in electrocardiographic waveform; ventricular rate usually >300 bpm; irregular shape of the QRS complex	
Ventricular flutter		Regular arrhythmia with ~300 bpm and sinusoidal, monomorphic appearance; owing to the high speed, usually no isoelectric interval between successive QRS complexes	
Ventricular tachycardia or ventricular fibrillation storm		A state of severe electrical instability defined as more than three episodes of sustained ventricular tachycardia or fibrillation within 24 h	
Sudden cardiac arrest		Sudden cessation of cardiac activity, without QRS complexes; affected patients become unresponsive, with no signs of blood circulation (such as a perceptible pulse)	
Atrial arrhythmias			
Atrial fibrillation		Absent P wave combined with an irregular ventricular rate; the isoelectric line can be characterized by either fibrillatory waves (F waves) or just minute oscillations; subtypes include paroxysmal (terminates spontaneously or with intervention within 7 days of onset), persistent (continuous atrial fibrillation that is sustained for 7 days) and longstanding persistent (continuous atrial fibrillation for >12 months)	Heart failure: recruitment of macrophages, inflammasome activation and fibrosis[280–283] Sepsis: increased blood leukocyte count, systemic release of pro-inflammatory cytokines, and changes in cardiac macrophage number and phenotype[114–117,218]
Atrial flutter		Classic sawtooth ECG sign with atria firing at a rate of 200–350 bpm; R-R intervals are regular; the ratio of P waves to QRS complexes can range from 2:1 to 4:1	
Conduction delay			
Sinus node dysfunction (sinoatrial block)		Conduction and sinus rate are usually slower than physiological sinus rhythm because the dominant pacemaker (the sinoatrial node) is disturbed; subtypes include sinus bradycardia (sinus rate <50 bpm), sinus pause (sinus node depolarizes >3 s after the last atrial depolarization) and sinus node arrest (no sinus node depolarization)	Structural abnormalities: progressive, degenerative fibrosis associated with inflammageing[284–286] Autoimmune disorders: autoantibodies against cardiac ion channels or adrenergic receptors[264–266,270]

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Arrhythmia	Example ECg	ECg description	Underlying pathologies and their inflammatory signatures
Atrioventricular block	First-degree atrioventricular block  Second-degree atrioventricular block  Third-degree atrioventricular block 	Disturbed conduction from the atria to the ventricles owing to improper function of the atrioventricular node; subtypes include first-degree atrioventricular block (P waves associated with 1:1 atrioventricular conduction, but delayed), second-degree atrioventricular block (P waves with a constant rate in which atrioventricular conduction is present but not at a ratio of 1:1) and third-degree atrioventricular block (complete heart block lacking atrioventricular conduction)	
Conduction tissue disease	Right bundle branch block  Left bundle branch block 	Complete or partial interruption of the electrical pathways in the ventricles, mostly affecting the anatomical structures in the bundle of His and Purkinje fibres; subtypes include right bundle branch block (mainly affecting the right ventricle; typical ECG signs are a wide QRS complex with large, positive, dominating R waves) and left bundle branch block (mainly affecting the left ventricle, with a broad notched or slurred R wave and a dominating S wave)	

Definitions are in accordance with clinical guidelines[3,284,287,288]. ECG, electrocardiogram.

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Table 2 |

Ion channel and connexin channel expression in leukocytes

Channel	Monocytes or macrophages	Resident macrophages	T lymphocytes	B lymphocytes	Dendritic cells
Ca^{2+} channels					
ORAI1	+	+ (m, k, a)	+	+	+
STIM1, STIM2	+	+ (m, k, a)	+	+	+
TRPM2	+	+ (m, k)	+	+	+
TRPM7	+	+ (m, k, a)	+	+	+
TRPV2	+	+ (m, k, a)	+	+	+
P2X1	+	+ (m)	+	+	−
P2X4	+	+ (m, k, a)	+	+	+
P2X7	+	+ (m, k, a)	+	+	+
$Ca_v1.3$	+	−	+	+	+
$Ca_v1.4$	+	−	+	−	+
$Ca_v2.1$	+	−	+	−	−
$Ca_v2.2$	−	−	−	+	+
$Ca_v2.3$	−	−	+	+	+
$Ca_v3.2$	−	−	+	+	+
$Ca_v3.3$	−	−	−	+	−
K^+ channels					
$K_v1.1$	−	−	+	+	−
$K_v1.2$	+	+ (m, k, a)	+	+	+
$K_v1.3$	+	+ (m, k, a)	+	+	+
$K_v2.1$	−	+ (k)	−	−	−
$K_v3.1$	−	−	+	−	−
$K_v3.4$	−	−	+	−	+
$K_v4.1$	−	+ (m)	−	−	+
$K_v7.1$	−	+ (k)	+	−	+
$K_v7.5$	−	−	+	+	−
$K_v11.1$	+	−	+	−	−

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Channel	Monocytes or macrophages	Resident macrophages	T lymphocytes	B lymphocytes	Dendritic cells
$K_{Ca}3.1$	+	+ (m, k)	+	+	+
$K_{ir}2.1$	+	+ (k)	−	−	−
$K_{ir}2.4$	−	−	+	−	+
$K_{ir}3.3$	+	−	−	−	−
$K_{ir}6.2$	+	−	+	+	+
Na^+ channels					
$Na_v1.5$	−	−	−	−	+
TRPM4	+	−	+	−	+
Gap junctions					
Cx43	+	+ (k)	+	+	+
Cx30.2	+	+ (m, k, a)	+	+	+
Cx46	+	+ (m, k, a)	+	+	+
PANX1	+	+ (m, k, a)	+	+	+
PANX2	+	+ (m, k, a)	+	+	+

Data are based on Immunological Genome Project microarray gene expression data[289]; expression was deemed to be present (+) if the robust multiarray average normalized value was >120, otherwise expression was considered to be absent (−). a, alveolar macrophages; Ca_V, voltage-gated Ca^{2+} channel; Cx, connexin; k, Kupffer cells; K_{Ca}, Ca^{2+}-activated K^+ channel; K_{ir}, inward-rectifier K^+ channel; K_V, voltage-gated K^+ channel; m, microglia; Na_V, voltage-gated Na^+ channel; PANX, pannexin; STIM, stromal interaction molecule; TRP, transient receptor potential.

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