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NLRP3-mediated inflammation in cardio-oncology: sterile yet harmful

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Abstract

Despite significant advances and the continuous development of novel, effective therapies to treat a variety of malignancies, cancer therapy-induced cardiotoxicity has been identified as a prominent cause of morbidity and mortality, closely competing with secondary malignancies. This unfortunate limitation has prompted the inception of the field of cardio-oncology with its purpose to provide the necessary knowledge and key information on mechanisms that support the use of the most efficacious cancer therapy with minimal or no interruption while paying close attention to preventing cardiovascular related morbidity and mortality. Several mechanisms that contribute to cancer therapy-induced cardiotoxicity have been proposed and studied. These mainly involve mitochondrial dysfunction and reactive oxygen species-induced oxidative stress, lysosomal damage, impaired autophagy, cell senescence, DNA damage, and sterile inflammation with the formation and activation of the NLRP3 inflammasome. In this review, we focus on describing the principal mechanisms for different classes of cancer therapies that lead to

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cardiotoxicity involving the NLRP3 inflammasome. We also summarize current evidence of cardio-protection with inflammasome inhibitors in the context of heart disease in general, and further highlight the potential application of this evidence for clinical translation in at risk patients for the purpose of preventing cancer therapy associated cardiovascular morbidity and mortality. (Translational Research 2022; 000:1-19)

INTRODUCTION

Cancer remains a prominent cause of mortality worldwide, and the incidence of various cancers, including breast, liver, and myeloma among others, continues to increase.[1] The oncology field has always strived to advance research and develop new anticancer therapies that combined with early screening and lifestyle intervention (ie, smoking cessation), have significantly extended longevity and improved prognosis and quality of life for many cancer survivors.[1] Although cancer management has improved dramatically over the last few decades, serious side effects of cancer therapy have been reported, including the risk of cardiotoxicity.[2] Cardiotoxicity secondary to chemotherapy is the most significant adverse reaction of many cancer treatments, with a devastating impact on overall morbidity and mortality for cancer survivors.[3] Additionally, pre-existing cardiovascular risk, specific antineoplastic agent usage, or the combination of different antineoplastic therapies, can ultimately increase the probability for cancer patients to experience cardiac-related side effects.[3,4]

Anti-cancer therapies have been developed and tailored for the treatment of diverse types of cancer, targeting distinct pathways or having different effects on the target cells.[4] However, cell injury, including that of tumor cells, can promote the activation of cellular pathways linked to damage response and healing. One such pathway is the NACHT, leucine-rich repeat (LRR), and pyrin domain (PYD) domains-containing protein 3 (Nod-like receptor protein 3), NLRP3 inflammasome, a stereotyped, gene-coded, response to cell and tissue damage, which can promote unintended cell dysfunction and perpetuate myocellular injury (Fig 1).[5,6] The NLRP3 pathway activation has been observed in several pre-clinical and clinical settings as a potential driver of cardiotoxicity. This review focuses on the NLRP3 inflammasome biology, its role in the development of cardiovascular disease, and the experimental evidence that links the mechanism of action of anticancer therapies to the activation of the NLRP3 inflammasome in the myocardium.

DEFINITION OF CHEMOTHERAPY-INDUCED CARDIOTOXICITY

The manifestations of cardiotoxicity related to antineoplastic agents vary from asymptomatic myocardial injury, revealed by a moderate increase in plasmatic levels of cardiac damage biomarkers (ie, cardiac troponin and brain natriuretic peptide),[7] to a more severe decline in left ventricular ejection fraction (LVEF).[8–10] While the asymptomatic form may usually predict a benign progression after treatment discontinuation, critical LVEF decline is often characterized by progressive and irreversible structural myocardial impairment over time.[8,11]

Cardiotoxicity signs vary considerably. Acute symptoms include epicardial coronary arterial related syndromes, myopericarditis, and disturbances in the heart conduction system leading

to both atrial and conduction defects and ventricular arrhythmias.[2,8] In contrast, long-term cancer survivors may remain asymptomatic for lengthy periods of time and experience left or right ventricular systolic and/or diastolic dysfunction long after the remission phase.[4] This observation, unfortunately, supports the premise regarding the possible progression to a more severe phenotype of cardiotoxicity manifesting in congestive heart failure (CHF) [4].

NLRP3 INFLAMMASOME, STERILE INFLAMMATION, AND CARDIAC INJURY

The inflammasomes are a large family of macromolecular complexes that form upon the activation of intra-and extracellular receptors designated to recognize a host of dangerous stimuli.[12] The inflammasomes are conserved among different species and involve highly regulated pathways.[13] They are part of the innate immunity and link the sensing of both extracellular and intracellular danger stimuli associated with pathogen infection or tissue damage with the inflammatory response.[14] The danger signals identified by the inflammasome include microbic-and viral-associated molecules, intracellular proteins, nucleic acids, lipids, mitochondrial content, and organic and inorganic compounds. The recognition of danger- or pathogen-associated molecular patterns (DAMPs or PAMPs) is initiated by specific extracellular receptors,[12,15] as well as the engagement of the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), the retinoic acid-inducible gene (RIG-) I-like receptors (RLRs),[15] and the AIM2-like receptor (ALR), which take part in the inflammasome formation.[15,16]

NLRP3, is a pattern recognition receptor (PRR) recognizing bacterial and viral PAMPs, but also numerous DAMPs involved in tissue and cell injury. To date, NLRP3 is the most studied and well-characterized inflammasome.[15,17,18] The involvement of NLRP3 in response to the disruption of cell homeostasis makes this protein a crucial contributor to the inflammatory response to tissue damage.[15] (Fig 1)

Upon activation, the NLRP3 oligomerizes and binds (through a PYD-PYD interlinkage) with the adaptor protein apoptosis-associated speck-like protein containing a carboxy-terminal caspase recruitment domain (CARD), or simply ASC.[15,19] ASC subsequently polymerizes into insoluble filamentous structures that constitute the scaffold required to recruit the effector enzyme, pro-caspase-1, into the NLRP3 inflammasome through a CARD-CARD interaction.[15,16] This induces a proteolytical activation of zymogen pro-caspase-1 into caspase-1, which in turn mediates the release of pro-inflammatory Interleukin-1β (IL-1β) and Interleukin-18 (IL-18).[15,16,20] Caspase-1 is also responsible for a controlled form of cell death known as pyroptosis.[21] Pyroptotic cell death features a plasma-membrane disruption with the release of intracellular content, which serves as a pro-inflammatory mediator, propagating the signaling to bystander cells.[21]

As part of the innate immune response, every cell type constituting the heart can induce the expression of NLRP3. Eventually, however, each cell type produces a different response. In endothelial cells, leukocyte and fibroblast activation of NLRP3 induce the processing of IL-1β.[22–24] In cardiomyocytes, the IL-1β production may be scarce, favoring a pyroptotic cell death. Pyroptosis is often the culprit behind cardiomyocyte loss following the activation of the NLRP3 pathway in the heart.[5,25,26] It becomes evident that a sustained inflammatory

risk can diminish the cardiomyocyte number over time, limiting the contractile capacity of the heart.

Priming and triggering of NLRP3 inflammasome.

As stated above, the inflammasome pathway is highly regulated.[13] The priming and triggering of the NLRP3 inflammasome are the two distinct yet essential steps orchestrating the activation of the NLRP3 inflammasome (Fig 1).[6,15] The priming is mediated by the presence of DAMPs and alarmins signaling through toll-like receptors (TLR) and NOD2.[6] Additionally, the activation of the receptor for advanced glycation end-products (RAGE) or the release of other pro-inflammatory cytokines can ultimately constitute a priming signal.[6,15,27] The intracellular signaling cascade following activation of the above-mentioned receptors culminates with the release of the inducing nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB)[28–30]. NF-kB is responsible for the transcription of hundreds of pro-inflammatory genes, including those required to synthesize all NLRP3 inflammasome components.[6,15] Following successful priming, the cell needs an additional signal to complete the NLRP3 inflammasome assembly.[6,26,31] This second signal, named triggering, functions as a safety mechanism to prevent excessive activation of the NLRP3 inflammatory process. The triggering phase culminates with the activation of caspase-1, which proteolytically cleaves IL-1β and IL-18 and mediates their release by inducing the formation of pores on the cytoplasmic membrane generated by the oligomerization of the N-terminal domain of the cell-membrane-pore-forming protein gasdermin D (GSDMD).[5,32,33]

The activation of the purinergic receptor channel P2 × 7 is one of the signals leading to NLRP3 triggering. Upon binding with extracellular ATP, the opening of the channel mediates the extracellular release of potassium (K^+). The efflux of K^+ ions activates the mitotic serine and/or threonine kinase NEK7, a member of the NIMA-related kinases proteins (NEK), that binds NLRP3 and mediates its activation by inducing oligomerization and consequent interaction with the other inflammasome components.[34,35]

In addition to K^+ efflux, the mobilization of calcium (Ca^{2+}) from the endoplasmic reticulum (ER) into the cytoplasm (or leaks within the interstitial space) has been proven to be a trigger signal for the NLRP3 inflammasome.[36] Furthermore, lysosomal damage, and interrupted autophagic processes that may occur during cellular injury or stress can activate the inflammasome as well. The first process depicts the pathogenesis of gouty arthritis, in which uric acid precipitates in the joints due to the destabilization of lysosomes in pro-inflammatory cells upon clearing.[37] The phagocytosis of tiny crystals such as monosodium urate or calcium phosphate crystals and silicates, in general, can induce a lysosomal engulfment and consequent leak of lysosomal enzymes into the cytoplasm.[38] Cell homeostasis relies on autophagy, a lysosome-dependent regulated mechanism, to degrade and recycle many cellular components, including cytoplasmic organelles such as mitochondria.[39] Experimental inhibition of several components in the autophagic process has been linked with triggering the NLRP3 inflammasome.[15,26] Conversely, in cardiac cells, the experimental induction of autophagy through the administration of an activator, such as rapamycin or cell starvation, can reduce the NLRP3 response once already activated.[40]

Mitochondria are the primary energy source of the cells and cardiomyocytes, due to their high metabolic demands, contain a significantly higher number of mitochondria compared to any other cell type.[41] Following myocardial damage, mitochondria can contribute to increase the oxidative stress.[42] The altered mitochondrial metabolism has been experimentally proven to trigger the signaling cascade of many pro-inflammatory pathways, including the NLRP3.[36] Mitochondrial dysfunction and electron chain transport impairment are the primary determinants in producing reactive oxygen species (ROS) in cells,[43,44] although ROS may be generated through other non-mitochondrial sources.[45] ROS generation and mitochondrial DNA (mtDNA), cardiolipin, and thioredoxin-interacting protein (TXNIP) can all activate a robust NLRP3-mediated response.[46,47] This is particularly important in the context of cardiotoxicity or any other cardiac injury given that mitochondria occupy ~ 30% by volume of the cardiomyocyte.[48]

ROLE OF NLRP3 INFLAMMASOME IN CARDIOVASCULAR DISEASE

In recent years, overwhelming scientific evidence has established the important role of the NLRP3 inflammasome in the pathogenesis of several cardiovascular disorders, including those with ischemic and non-ischemic etiologies.[5,49,50]

Atherosclerosis, acute myocardial infarction and hypertrophic cardiomyopathy.

Atherosclerosis is a chronic condition that can affect many significant arteries in the human body.[51,52] Atherosclerotic plaques occur as a consequence of cholesterol lipid accumulation in the intima layer of the arteries.[51] In the attempt to clear the lesion, macrophages become foam cells, a lipid-laden cell capable to trigger a detrimental pro-inflammatory reaction mediated by NLRP3.[53,54] In the context of the coronary arteries, the destabilization of the atherosclerotic plaque and its consequent rupture is the culprit of the pathogenesis of acute myocardial infarction (AMI).[52] To confirm the contributions of the NLRP3 inflammasome and its related signals in exacerbating atherogenesis, several animal mechanistic studies have been performed. Low-density lipoprotein receptor (LDLR) knock-out mice transplanted with bone marrow cells derived from mice with genetic deletion of NLRP3, ASC, and IL-1β, displayed lower atherogenesis following a high-cholesterol diet.[55]

In addition to atherosclerosis, NLRP3 activity is detrimental for cardiomyocytes as well. Following an AMI, activation of NLRP3 in cardiomyocytes induces pyroptotic cell death, which, in addition to the ischemia-reperfusion-mediated injury, contributes significantly to the extent of the infarcted area secondary to AMI.[14] A genetic deletion strategy or pharmacological inhibition of NLRP3 and its products has been beneficial in reperfused and non-reperfused myocardial infarction models.[26] Inhibiting NLRP3 has been demonstrated (in pre-clinical settings) to help lower the extent of infarct and prevent cardiac dysfunction following AMI.[15,26,14] A genetic deletion strategy or pharmacological inhibition of NLRP3 and its products has been beneficial in reperfused and non-reperfused myocardial infarction models.[26] Inhibiting NLRP3 has been demonstrated (in pre-clinical settings) to help lower the extent of infarct and prevent cardiac dysfunction following AMI.[14,15,26]

NLRP3 activity has also been linked to hypertrophic cardiomyopathy.[56] In several models of induced volume overload, possibly in response to the activity of Ca^{2+}/calmodulin-dependent

protein kinase II δ (CaMKIIδ), the genetic deletion or pharmacological inhibition of NLRP3 lowered the inflammatory risk and the consequent fibrotic response.[56] NLRP3 inhibition was able to prevent cardiac remodeling and heart failure onset following hypertrophic/hypertensive cardiomyopathy.[56]

Metabolic syndrome.

A long-term diagnosis with metabolic syndrome is one of the main determinants of insulin resistance and type II diabetes, which may result in diabetic cardiomyopathy. Dysregulation of glucose metabolism and liver disease are crucial components responsible for increasing oxidative stress, which function as priming signals for an NLRP3-mediated response. Several pre-clinical investigations have connected sustained cardiac damage by NLRP3 activation to the structural cardiac abnormalities occurring secondary to diabetes.[57–60]

The presence of comorbidities at the time of cancer diagnosis, including metabolic disorders, can indeed influence cancer treatment decision due to the overall increased cardiovascular risk.[61]

Moreover, future studies are needed to better understand the metabolic interaction between cancer and cardiovascular disease and how they affect one another. Metabolic abnormalities and inflammation often coexist and negatively impact both cancer progression and cardiovascular health. As pointed out in an elegant review by Karlstaedt et al., the metabolic reprogramming in cardiovascular disease and cancer can be quite complex, especially when attempting to elucidate how cancer cells affect other organs and potentially impair their function.[62]

Atrial fibrillation.

Atrial fibrillation (AF) commonly occurs in patients with HF and is associated with the cardiotoxic effects of anti-cancer therapy.[4] IL-1ß and IL-18 are increased in patients with AF and molecular analysis shows that NLRP3 protein is increased in atrial samples of patients with AF.[63–65] To further strengthen this association, experimental studies using mice expressing an active mutant NLRP3 in cardiomyocytes demonstrated the development of spontaneous premature atrial contractions and inducible AF. Moreover, the use of AAV9-mediated silencing of NLRP3 in cardiomyocytes abolished the effects of the mutant NLRP3.[64]

Inflammatory cardiomyopathy.

The effect of NLRP3 activation has also been investigated in relation to acute myocarditis, an inflammatory disease of the myocardium characterized by devastating effects with an uncertain prognosis.[66,67] Although the etiology is not fully understood, it appears to be viral in most patients. Unfortunately, myocarditis is more often reported as a consequence of cancer therapies that target the immune system.[68]

The presence of NLRP3 increased in patients who suffer from a more severe heart failure symptomatology.[66] In the pre-clinical model of Coxsackievirus B3 (CVB3)-mediated myocarditis in mice, NLRP3 activity, as well as IL-1β expression, were found to increase

a week after the onset of the disease.[67] Interestingly, caspase-1 inhibition or IL-1 blockade both ameliorated the progression of the disease in mice following CVB3 myocarditis.[67] In a recent study, the NLRP3 inflammasome activation has also been linked to the pathogenesis of myocarditis following mRNA vaccination (mRNA-1273 COVID-19 vaccine).[69] This information will likely become more relevant with the rapid advancement of mRNA vaccines for cancer immunotherapy in the near future.[69,70]

Pericardial inflammation.

The NLRP3 has been linked with the pathogenesis of pericardial inflammation.[71] Pericarditis is an injury due to an acute inflammatory reaction to the pericardium, a mesothelial layer surrounding and protecting the heart.[71,72] The etiology of the disease is predominantly linked to viral infection, although pericarditis can arise due to cancer therapies, particularly following radiation therapy.[73] Additionally, pericarditis may occur as part of the paraneoplastic syndrome.[74] A recent study has revealed that the NLRP3 inflammasome is central in the pathogenesis of acute pericarditis.[75] NLRP3, ASC, and caspase 1 activity were measured in pericardial samples of patients with chronic pericarditis experiencing an acute flare.[75] In the same study, a murine model of pericarditis was developed by intra-pericardial instillation of zymosan A, from *Saccharomyces cerevisiae*, to elicit an inflammatory response mimicking an acute pericarditis phenotype in mice.[75] Pharmacological inhibition of NLRP3 or the blockade of IL-1α and IL-1β were able to inhibit pericardial effusion, thickening, and inflammation in mice with acute pericarditis. These findings are in agreement with a phase 3 clinical study testing rilonacept, an inhibitor of both IL-1α and IL-1β, in patients with recurrent pericarditis.[71,76] Rilonacept use was associated with a staggering 96% reduction in recurrences compared to placebo.[76] Similar results were seen in the smaller AIRTRIP trial using anakinra, a recombinant IL-1 receptor antagonist (IL-1Ra) in patients with recurrent pericarditis resistant to colchicine.[77]

NLRP3 AND CANCER THERAPY-INDUCED CARDIOTOXICITY

Anthracyclines.

Anthracyclines are a class of anticancer drugs used to treat a variety of cancers, including forms of leukemia, lymphomas, bladder cancer, breast cancer, small cell lung cancer, and other solid tumors.[78] The first anthracycline, daunorubicin, was extracted from Streptomyces peucetius in the 1960s. Doxorubicin (DOX) was later identified in a mutant strain of Streptomyces peucetius and showed higher potency. More anthracyclines (Epirubicin, Idarubicin, Mitoxantrone, and Valrubicin) and anthracycline formulations have been developed.[78,79] There are different mechanisms of action attributed to anthracyclines that prove effective against cancer cells.[80,81] One of the main mechanisms is the inhibition of topoisomerase-II, leading to increased DNA breaks, arrest of the cell cycle, and cell death. In addition, anthracyclines can intercalate within the DNA double helix and inhibit the synthesis of DNA and RNA or can react with DNA and initiate apoptosis. Furthermore, DOX induces the generation of ROS in the presence of specific enzymes (NADH dehydrogenase, xanthine oxidase, cytochrome P450 reductase).[2]

Anthracyclines display many side effects, that vary between the different types and formulations.[78] DOX is the most investigated anthracycline due to its ample use and the frequent development of adverse side effects, the most common of which is anthracycline-induced cardiomyopathy (AICM).[82] The administration protocols and dosages of anthracyclines have been adjusted to lower the occurrence and the severity of these side effects.[82] However, AICM remains a serious complication of anthracycline-based anti-cancer treatment that may occur acutely (a few days after administration) or late (a month to several years) and is refractory to common therapies used to treat cardiovascular disease.[83] Common side effects are myopericarditis, tachycardia, electrocardiographic changes (eg, nonspecific ST-T alterations), premature atrial and ventricular beats, and left ventricular (LV) dysfunction and failure in the most severe cases.[82,84,85]

Cardiomyocytes are terminally differentiated cells, therefore the mechanism of damage to the cardiomyocytes may differ from the mechanism that damages cancer cells. Several mechanisms of action have been identified in the search for the cause of AICM.[86] One emerging mechanism is the DOX-induced NLRP3 inflammasome pathway activation, leading to the new paradigm that the NLRP3 inflammasome inhibition may reduce AICM. Initial experimental studies showed that DOX induces elevation of circulating IL-1β in mice, and treatment of mice with IL-1Ra reduced the mortality, cardiac fibrosis, dysfunction, and cardiomyocyte apoptosis following DOX treatment.[87] These were evidence of the potential involvement of the NLRP3 pathway after DOX treatment. However, the proof that DOX led to the NLRP3 inflammasome activation came from the study by Sauter et al., which showed that bone marrow-derived macrophages (BMDMs) production of IL-1β, following DOX treatment, was inhibited in BMDMs from ASC$^{-/-}$, Caspase$^{-/-}$, and NLRP3$^{-/-}$ mice.[88] Furthermore, NLRP3$^{-/-}$ mice failed to promote pro-caspase-1 and pro-IL-1β cleavage, further indicating the necessity of NLRP3 protein to promote inflammasome activation in these cells. Moreover, ROS inhibitors could reduce the release of IL-1β in BMDMs treated with DOX. These data were replicated a few years after in wild type and NLRP3$^{-/-}$ BMDMs.[89] It has been reported that the specific NLRP3 inhibitor 16673-34-0, given 30 minutes before DOX, and then once a day for 10 days, reduced DOX induced cardiac dysfunction in wild-type mice.[90] The effects of DOX on the inflammasome activation became evident also in cardiomyocytes. DOX induces NLRP3-dependent cell death in cultured H9c2 cardiomyocytes.[91]. In a different study, Caspase-1$^{-/-}$, and NLRP3$^{-/-}$ mice displayed preserved function and remodeling, and no activation of the inflammasome pathway, when treated with DOX, further proving the detrimental effects of NLRP3 activation on cardiac structure and function following DOX treatment.[88] Recently, it has been demonstrated that ROS scavenging reduces ROS generation and NLRP3 inflammasome activation in primary cardiomyocytes.[92] Despite this compelling evidence suggesting a cardioprotective effect of NLRP3 inflammasome inhibition in DOX-treated mice, an inflammasome-independent NLRP3 activity may also be responsible for protective effects against DOX. Kobayashi et al. have shown that 15 mg/kg cumulative dose of DOX did not induce cardiac dysfunction in wild type mice, but NLRP3 deletion caused a drop in LV fractional shortening. This protective effect of NLRP3 was linked to a NLRP3-dependent IL-10 production from macrophages.[93] This discrepancy is difficult to reconcile because similar animal strain and dose of DOX used (15mg/kg) were previously reported in other

studies. However, in this study, the effect of DOX on cardiac function in wild type mice was negligible, which needs further exploration. Other protective inflammasome effects have been reported in the past. [94]

Other anti-inflammatory drugs linked to NLRP3 activity have been investigated. One example is resveratrol, a polyphenolic compound naturally produced by plants, which was shown to reduce DOX cardiomyopathy in mice with late-onset of hypertension-induced cardiomyopathy.[95] Resveratrol, like many other drugs linked to NLRP3 activity is not a direct inhibitor of NLRP3.[96] However, it was found capable of inhibiting the activation step of the NLRP3 inflammasome by suppressing mitochondrial damage.[97]

Radiation Therapy.

Radiation therapy (RT) directed to the chest is part of the treatment of several tumors (Hodgkin's Lymphoma, breast, neck, and lung cancer), that can result in irradiation of the heart as an involuntary target. High doses of radiation, from single or fractionated doses, can lead to a complexity of cardiovascular events as arrhythmia, atherosclerosis, pericarditis, constrictive cardiomyopathies, and valvular abnormalities.[4] Recent improvements in RT aimed to reduce radiation dose and injury to healthy tissues mitigated but did not eliminate the occurrence of asymptomatic cardiovascular abnormalities that are difficult to detect. Low dose radiation exposure has been associated with an increased risk of developing heart failure with preserved ejection fraction (HFpEF) in older women after breast cancer therapy,[98] and contribute to impair peak oxygen consumption (VO_2 peak), reduced diastolic functional reserve index and elevation in NTproBNP in patients receiving thoracic radiation for lung and breast cancer.[99,100]

Radiation drives oxidative stress leading to DNA damage that can accelerate senescence and cell death in tumor cells. However, the specific mechanisms by which radiation can impact healthy tissues (directly or indirectly) have not been completely elucidated yet. Several signals induced by radiation can lead to mitochondrial instability with ROS production leading to NLRP3 inflammasome activation.[101] Radiation therapy has been reported to induce local and systemic inflammatory increased levels of IL-1β and IL-18 have in animal models.[102] Human arteries with chronic radiation injury expressed high levels of IL-1α, IL-1β, caspase-1 and NLRP3.[103] Gamma radiation induces death of microvascular endothelial cells associated with the activation of inflammasome signaling.[104] The successful use of IL-1β blockers supports the idea that the NLRP3 inflammasome can be involved in radiation-induced cardiovascular injury. In mice receiving chest radiation, anakinra treatment was able to prevent the decrease in cardiac contractile reserve observed in control irradiated mice.[105] Interleukin-1 receptor type I (IL-1RI) deletion reproduces similar data and improved survival of mice six months after irradiation.[105] Furthermore, the use of anakinra in irradiated $ApoE^{-/-}$ mice was able to attenuate radiation-induced arterial inflammation.[103] Even though cardiomyocytes have been shown to be quite resistant to direct damage from radiation,[106] other cardiac cell types can contribute to the complexity of the cardiovascular inflammation and damage, leaving this broad field to be further explored.

Tyrosine kinase inhibitors.

Genetic alterations of tyrosine kinases (TK) are often responsible for tumor development and progression.[107] TKs are pivotal proteins in regulating cellular functions, including cell proliferation, differentiation, and migration, making these specific proteins highly critical in the progression of mutagenesis toward a carcinogenic cell phenotype.[108,109]

The activation of TK signaling involves the triggering of the mitogen-activated protein kinase (MAPK) cascade, which activates Ras, a small G protein.[109] Ras resides inactive on the inner layer of the plasma membrane and binds to a molecule of guanosine diphosphate. (GDP).[109] When active, the guanosine triphosphate bounded Ras phosphorylates the first serine-threonine kinase in the MAP kinase cascade, leading to the phosphorylation cascade downstream that MAP kinases which culminates with the activation of a targeted transcriptional factor involved in the transcription of a particular set of genes.[107,110] Tyrosine kinases are classified explicitly by their specificity for their own receptors and ligands. Extracellular domain receptor tyrosine kinases (RTKs) consist of epidermal-grow factor receptor (EGFR), platelet-derived grow factor receptor (PDGFR), fibroblast grow factor receptor (FGFR), and vascular endothelial growth factor (VEGFR), while intracellular proteins with regulatory activities include the SRC, ABL, FAK, and Janus, a member of the family of non-receptor tyrosine kinase (NRTK).[111]

Pharmacological tyrosine kinase inhibitors (TKI) are molecules that bind and block the ATP site, resulting in irreversible inhibition of its activity. Alternatively, monoclonal antibodies, are human chimeric or bispecific antibodies directed against the extracellular domain of the RTKs.[112]

More than 50 pharmacologic TKIs have been authorized by the Food and Drug Administration (FDA), and the majority are utilized as cancer treatments.[113] Unfortunately, small molecule TKIs and inhibiting antibodies frequently carry side effects, including an increased risk of cardiac toxicity, which can significantly impact the quality of life of cancer survivors.[114]

The mechanism of TKI cardiotoxicity is not yet fully elucidated; however, mitochondrial dysfunction and consequent oxidative stress seem to have a critical role in damaging cardiac cells.[44,107,115] Metastatic renal cell carcinoma and gastrointestinal stromal tumors are often treated with sunitinib and nilotinib, TKIs approved by US and European Commission regulatory agencies. Sunitinib and nilotinib have been associated with increased cardiac dysfunction in treated cancer patients. Pre-clinical evidence has also uncovered a link between the administration of sunitinib to cultured H9c2 cardiomyocytes and mitochondrial dysfunction and ROS production, which ultimately lead to an impairment of the mitochondrial electron transport chain and cardiomyocyte death.[116] Both ROS production and ER stress are known activating stimuli for NLRP3. In fact, elevated signaling of the NLRP3 pathway was seen in both AC-16 and H9C2 cell lines following treatment with sunitinib. NLRP3 expression and IL-1β and IL-18 production were reduced by pharmacological inhibition of the oxidative stress following the exposure to sunitinib. [117] Sunitinib was also able to increase autophagic flux in treated H9c2 cells. Pharmacological assessment with autophagy inhibitors (3-Methyladenine, Bafilomycin A1, and Chloroquine

diphosphate) confirmed that geldanamycin, a heat shock protein-90 inhibitor, attenuated the cytotoxicity of sunitinib by limiting the activity of the autophagic pathway.[118,119] Nilotinib, a Bcr-Abl kinase inhibitor, in H9c2 cells, increased ER stress markers such as ATF4 and CHOP and mediated cytotoxicity in cultured cardiomyocytes.[118,119] Other TKIs, including imatinib and masitinib, activated NLRP3 inflammasome by causing lysosomal swelling and damage in BMDMs.[120] Lysosomal destabilization following TKI leads to cathepsin-mediated destabilization of myeloid cell membranes and K^+ efflux, which triggers the NLRP3 activity.[120] Although there is no strong correlation between the use of TKIs and NLRP3, these results argue in favor of an association between TKIs and NLRP3 inflammasome activity as a conceivable explanation for the cardiotoxicity of this modality of cancer therapy. Further studies using either pharmacologic inhibition or genetic deletion of NLRP3 components are needed to shed more light on this plausible association.

Immune Checkpoint inhibitor-associated cardiotoxicities.

Although rare, the adverse cardiac manifestations following immune checkpoint inhibitor (ICI) therapy can be life-threatening.[121] Approximately 70% to 90% of cancer patients treated with ICI suffer side effects following treatment. These side effects can range from encephalitis and hepatitis to a devastating episode of myocarditis.[9,122] Typically, these side effects occur within 12 weeks from therapy initiation, with 15% of the patients experiencing severe manifestation.[9] Myocarditis is the most severe side effect; pathologically, myocarditis is distinguished by the presence of myocyte necrosis and mononuclear infiltrates. These infiltrates are mainly CD3, CD4 and CD8 positive lymphocytes, including CD68 positive macrophages.[121,123]

The higher risk of myocarditis was correlated with anti-CTLA4 and anti-PD-1 antibodies.[9,124] Unfortunately, ICI administration has been linked to other cardiovascular manifestations; including heart failure up to 2%, and ventricular arrhythmias in up to 1% of the total patients.[125] Pericarditis and pericardial effusions were reported as well, with 0.38% in patients with pericardial effusion needing surgical pericardiocentesis to relieve symptoms.[9,126]

The evidence of an NLRP3 involvement in the ICI-induced cardiotoxicity is still limited. As already mentioned before, NLRP3 plays a key role in the pathogenesis of myocarditis and pericarditis,[66,75] which are the two most life-threatening manifestations of ICI-related side effects.[68,122,127,128] In pre-clinical studies, the activity of NLRP3, MyD88, and p65/NF-kB was assessed in mice treated with Ipilimumab and Nivolumab, a CTLA-4, and PD-1 blocking agents.[129] Mice treated with Ipilimumab showed a significant decrease in cardiac function compared to untreated mice (−11% of the fractional shortening). Although no pathological investigation of myocardial inflammation was performed, the myocardial expression of NLRP3, MyD88, and several interleukins were measured.[129] Additional data linking NLRP3 and myocardial inflammation following ICI therapy were generated in a model of myocardial injury achieved by immunizing BALB/c mice with murine cardiac troponin I (cTnI) peptide concomitant with administration of PD-1 antibody.[130] Despite the limitations, these findings provide a signal of NLRP3 involvement in the pathogenesis of ICI cardiomyopathy. More studies are needed to test the effects of specific NLRP3 inhibitors

and also measuring exclusive readouts of NLRP3 activity (ie, ASC aggregation and/or caspase-1 activity).

Trastuzumab-mediated cardiotoxicity.

Trastuzumab is a humanized monoclonal antibody specifically developed to inhibit the Human epidermal growth factor receptor 2 (HER2) signaling.[131] HER2 activation is implicated in the activation of mitogenic and pro-survival pathways that alter neo-transformed cell proliferation.[131] HER2 signaling is indeed altered in almost 30% of breast cancers and up to 34% of gastric neoplasia.[131] The efficacy in inhibiting HER2 signaling makes trastuzumab the first-line treatment option for many cancers; however, incidents of cardiotoxic effects have been reported, including QT-prolongation and myocardial dysfunction.[131,132] Cardiotoxicity induced by trastuzumab administration exhibits, in most cases, a benign prognosis. Indeed, the most common cardiac manifestations tend to resolve on their own after the discontinuation of treatment.[131] Nonetheless, a few clinical reports have pointed to long-term cardiac consequences following trastuzumab treatment, including deteriorated cardiac health when co-administered with anthracyclines.[133] The mechanism behind trastuzumab cardiac toxicity is still not fully identified; however, oxidative stress and autophagy seem again to be implicated. HER2 signaling is necessary for the routine upkeep of cellular function in any cell type, including cardiomyocytes. The activity of MAPK, Phosphoinositide 3 Kinase (PI3K), and Protein kinase B (AKT) is also initiated by the signaling of HER2. These pathways are essential for promoting energy production and ROS scavenging in cardiomyocytes.[133] Thus, the inhibitory effect of trastuzumab, which is beneficial to combat cancer, becomes detrimental to the survival of cardiomyocytes, which in turn become more prone to oxidative stress.[134] Pre-clinical murine and rat models have shown that trastuzumab increases nitrosative and oxidative stress in treated animals causing myocardial ultrastructural changes while compromising cardiomyocyte survival.[135–137]

An additional mechanism proposed to explain the trastuzumab-induced cardiotoxicity is the impairment of the autophagic flux in cardiomyocytes. Alteration of HER2 signaling has been detrimental by lowering LC3 I/II expression and increasing p62 levels while impairing autophagosome-associated effector peptides including Atg 5–12, Atg 7, Atg 14, and Beclin 1 in mouse cardiomyocytes treated with trastuzumab.[134] Ultimately, the impairment of autophagy leads to increased ROS production, altering the overall oxidative stress status in cardiomyocytes. [138]

Preliminary evidence linking the oxidative stress induced by trastuzumab to the activity of NLRP3 inflammasome was obtained in immortalized rat atrial HL-1 cardiomyocytes exposed to a subclinical concentration of DOX and Trastuzumab.[139] Although this study is reported in abstract format, it constitutes one of the first reports on the potential role of NLRP3 and trastuzumab-mediated cardiotoxicity. Trastuzumab mediated an increase in transcriptional levels of NLRP3 and TLR4/MyD88, as well as p65/NF-κB in treated HL-1 cells. The authors also measured the secretion of pro-inflammatory cytokines, including IL-1β, a primary product of NLRP3 activity.[139] These pieces of information are indeed partial and will benefit from additional future investigations in which targeted genetic

deletion of NLRP3, or the use of specific pharmacological inhibitors will be investigated employing a more comprehensive in vivo model of trastuzumab-induced cardiotoxicity.

Sodium-glucose Cotransporter-2 (SGLT-2) inhibitors have been linked with anti-inflammatory activity against NLRP3 in diabetic cardiomyopathy in mice.[140] Recently, SGLT-2 inhibitors have been investigated as potential cardioprotective agents against cardiotoxicity in HL-1 cells with DOX and trastuzumab (100 nM) and treated with 50 nM dapagliflozin. Dapagliflozin improved Ca^{2+} homeostasis and inhibited the pro-inflammatory "NLRP3-NF-*k*B–cytokines" pathways. [141] Although SGLT-2 inhibitors present anti-inflammatory properties, these classes of molecules are not direct inhibitors of the NLRP3 inflammasome. Indeed, recent evidence suggests an inhibitory activity on the MyD88 and NF-kb pathway which drives the priming of the NLRP3 inflammasome.[142]

Pharmacologic inhibitory strategies against NLRP3 activation.

Pharmacologic inhibition of the NLRP3 inflammasome has been tested in pre-clinical studies of cardiotoxicity induced by cancer therapies, mainly following anthracycline administration (Table I). A sulfonylurea compound named glyburide, used for the treatment of type-II diabetes, was found to inhibit NLRP3 inflammasome at high concentrations in vitro.[143,144] A derivative of this compound, named 16673-34-0, lacking the cyclohexylurea moiety responsible for lowering blood glucose levels, was tested in both ischemic and non-ischemic cardiomyopathies in mice, including an anthracycline model of cardiotoxicity. Marchetti and colleagues induced cardiac dysfunction with a single dose injection of 10mg/kg of DOX.[90] Mice were then treated with the 16673-34-0 NLRP3 inflammasome inhibitor at 100 mg/kg given 30 minutes before DOX, and then once a day for 10 days.[90] Mice treated with NLRP3 inhibitor displayed a less severe reduction in cardiac contractility, measured as LVEF, and reduced LV interstitial fibrosis deposition.[90] 16673-34-0 was found to reduce the activity of NLRP3 and caspase-1 and to consequently reduce infarct size expansion in mice.[90,145] 16673-34-0 was also protective in the setting of a non-reperfused MI, which emphasized the beneficial role of NLRP3 inhibition independently from infarct size reduction.[90]

MCC950 is a small molecule that inhibits NLRP3 ATPase activity.[146–151] The use of MCC950 in several models of myocardial infarction, including pig and murine models, reduced infarct size, cardiac dysfunction, and IL-1β expression.[152,153] MCC950 also reduced myocardial fibrosis and IL-1β production in a hypertensive murine model induced by angiotensin II infusion.[154] MCC950 reduced hypertrophic remodeling preserving cardiac function in a model of post-menopausal heart disease.[155] Furthermore, the use of MCC950 (20 mg/kg/daily) for 15 weeks improved autophagy flux while reducing myocardial cell death.[156]Importangtly, MCC950 has been tested successfully following DOX administration. Meng and colleagues have induced cardiac dysfunction in rats by administering 3 mg/kg of DOX every two days for 2 weeks, for a total cumulative dose of 21mg/kg. MCC950 at the dosage of 10 mg/kg was injected intraperitoneally 30 minutes before DOX treatment and once a day for the duration of DOX treatment.[157] MCC950 co-administered with DOX prevented the decline of LV contractility and reduced NLRP3 and IL-1β expression in the heart while reducing myocardial apoptotic cell death.[157]

Corroborating results were obtained using in vitro H9c2 cardiomyocytes pretreated with the NLRP3 inhibitor MCC950 at a concentration of 10 μM for 1 hour prior to incubation with 1 μM Dox for 48 hour. MCC950 reduced the cardiomyocyte death and reduced the protein levels of NLRP3, caspase-1, and IL-1β.[158]

Endogenous hydrogen sulfide (H_2S) is a colorless and odorless gas that is produced endogenously by the human body and exerts essential physiological functions.[159] Administration of H_2S has been shown to be protective against several cardiovascular diseases.[160] Sodium sulfide (Na_2S), an H_2S donor, reduced the NLRP3- dependent caspase-1 activation and pyroptotic cell death in treated primary cardiomyocytes following a canonical activation of NLRP3. Na_2S additionally reduced caspase-1 activity, and infarct size in mice subjected to experimental AMI.[161] H_2S appears to reduce both the priming and triggering signals activating the NLRP3 inflammasome.[162] Notably, H_2S has also been tested in reducing DOX-induced cardiomyopathy. In vitro, H9c2 cells were treated with 5 μM DOX to model the anthracycline-induced cardiotoxicity; 30 minute prior to DOX administration, a group of cells received 400 μmol/l of the H_2S donor, sodium hydrosulfide (NaHS).[163] Exogenous H_2S attenuated DOX-induced cytotoxicity in H9c2 cells by reducing phosphorylation of p38 MAPK. NaHS preserved cell viability, reduced apoptotic cell death, and reduced ROS production.[163] Similar results were obtained by another group using a similar in vitro model of cardiotoxicity. H_2S protected H9c2 cells against DOX administration through inhibition of ER stress. DOX was administered in a range from 2 to 10 mmol/l for 24 hour.[163] NaHS was then administered for 30 minute before exposure to DOX at the concentration of 400 mmol/l. NaHS preserved cardiomyocyte death while reducing the oxidative stress following DOX administration.[163]An orally active, slow-releasing H_2S-donor, SG1002, was tested in mice following DOX administration. Mice were randomized to either regular chow or SG1002 enriched chow a week prior to the DOX regimen (5 weekly doses of Doxorubicin hydrochloride at 5 mg/kg). SG1002 prevented early decline in cardiac function following DOX measured by global longitudinal strain and contractile reserve assessment following isoproterenol challenge.[164]

Although never tested to date in chemotherapy-induced cardiotoxicity, other pharmacological NLRP3 inhibitors are available. These molecules have been well documented, with promising results, in pre-clinical studies focused on several cardiovascular diseases.[5]

Colchicine is one of the oldest drugs in use today and was first described in Egyptian medical text. The clinical use of colchicine is not only limited to treating gout, but also for familial Mediterranean fever as well as acute and recurrent pericarditis; all diseases in which the pathogenesis is mediated by NLRP3 activity.[75,165,166] Colchicine is also under clinical investigation in several randomized trials enrolling patients with acute and chronic coronary artery disease. Colchicine treatment has been consistently found to be effective in reducing cardiovascular risk in acute settings.[167–173]

An additional small synthetic inhibitor for kappa B kinase β (IKKβ) inhibitor, Bay 11-7082, was shown to inhibit the NLRP3 ATPase independently from its IKKβ inhibitory activity. This characteristic makes Bay 11-7082 capable of blocking the priming signaling by

preventing NF-kB nuclear translocation while precluding the oligomerization of the NLRP3 components.[174]

OLT1177 is a beta-sulfonyl nitrile molecule that also inhibits the ATPase activity of the NLRP3 inflammasome.[175,176] OLT1177 was able to inhibit NLRP3 activity in monocytes isolated from patients with the cryopyrin-associated periodic syndrome (CAPS); therefore, with constitutively activated NLRP3.[176] Phase 2 Clinical trials have been conducted to assess the safety of OLT1177 in patients with gout and with heart failure with reduced ejection fraction (HFrEF).[177]

PERSPECTIVES AND CONCLUSION

The progress of new cancer treatments and the development of improved approaches to manage patients have dramatically increased life expectancy following a cancer diagnosis. Consequently, cardiotoxicity secondary to cancer therapy has become the non-tumor related prominent leading cause of morbidity and mortality among cancer survivors.

Although with limited success, several strategies to limit cancer therapy-related cardiotoxicity have been explored. Through improved understanding the variety of established and novel cancer therapies, opportunities exist to improve understanding of the pathophysiology of cancer treatment-induced cardiotoxicity. Refining these therapeutic strategies will meet an urgent clinical need for better cardioprotective interventions that could improve outcomes for cancer survivors.

Increasing evidence suggests that the activity of the NLRP3 inflammasome is central in the pathogenesis of several cardiovascular diseases. The most characterized mechanisms responsible for the activation of NLRP3 are mainly linked to mitochondrial dysfunction, the release of ROS, and impaired autophagy, which can foster NLRP3-mediated cell death. All the studies summarized here have explored the role of NLRP3, mostly through indirect measures. Considering the nature of this convoluted pathway and the tight regulations, it is essential to suggest the use of more complex genetically-modified animal models in order to illustrate the involvement of the NLRP3-dependent pyroptotic cell death as a mechanism of cardiac damage following cancer therapy.

The similarities shared by the involvement of NLRP3 inflammasome across many cancer treatments with existing disease processes such as atherosclerosis, acute myocardial infarction, heart failure, and myopericardial inflammatory disorders suggest the relationship between NLRP3, and cancer therapy-associated cardiotoxicity is plausible and merits additional study. Nevertheless, comorbid conditions, including atherosclerosis, hypertension and metabolic syndromes, can worsen cardiac health by triggering NLRP3 activity even before a cancer diagnosis is made and the administration of cancer therapy with potential cardiotoxic effects is initiated.

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Abbreviation:

AF	Atrial fibrillation
AICM	Anthracycline-induced cardiomyopathy
AKT	Protein kinase B
ALR	AIM2-like receptor
AMI	Acute myocardial infarction
ASC	Apoptosis-associated speck-like protein containing a CARD domain
BMDM	Bone marrow-derived macrophages
Ca^{2+}	Calcium
CaMKIIδ	Ca^{2+}/calmodulin-dependent protein kinase II δ
CAPS	Cryopyrin-associated periodic syndrome
CARD	Carboxy-terminal caspase recruitment domain
CHF	Congestive heart failure
CVB3	Coxsackievirus B3
DAMPS	Danger-associated molecular patterns
DOX	Doxorubicin
EGFR	Epidermal-grow factor receptor
ER	Endoplasmic reticulum
FDA	Food and Drug Administration
FGFR	Fibroblast grow factor receptor
GDP	Guanosine diphosphate
GSDMD	Gasdermin D
H_2S	Hydrogen sulphide
HER2	Human epidermal growth factor receptor 2
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICI	Immune checkpoint inhibitor

IKKβ	Inhibitor for kappa B kinase β
IL-18	Interleukin-18
IL-1Ra	Recombinant IL-1 receptor antagonist
IL-1RI	Interleukin-1 receptor type I
IL-1β	Interleukin-1β
K^+	Potassium
LDLR	Low-density lipoprotein receptor
LRR	Leucine-rich repeats
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
mtDNA	Mitochondrial DNA
Na_2S	Sodium sulphide
NaHS	Sodium hydrosulfide
NEK	NIMA-related kinases proteins
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLR	(NOD)-like receptors
NLRP3	Nod-like receptor protein 3
NOD	Nucleotide-binding and oligomerization domain
NRTK	Non-receptor tyrosine kinase
NTproBNP	N-terminal-pro hormone B-type natriuretic peptide
PAMPS	Pathogen-associated molecular patterns
PDGFR	Platelet-derived grow factor receptor
PI3K	Phosphoinositide 3 Kinase
PRR	Pattern recognition receptor
PYD	Pyrin domain
RAGE	Receptor for advanced glycation end-products
ROS	Reactive oxygen species
RT	Radiation therapy

RTK	Receptor tyrosine kinases
SGLT2	Sodium-glucose Cotransporter-2
TK	Tyrosine kinases
TKI	Tyrosine kinase inhibitors
TLR	Toll-like receptors
TXNIP	Thioredoxin-interacting protein
VEGFR	Vascular endothelial growth factor
VO_2	against medical advice

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: A Can J Clin 2019;69:7–34. 10.3322/caac.21551.
2. Mondal P, Jain D, Aronow WS, Frishman WH. Cardiotoxicity of Cancer Therapies. Cardiol in Rev 2019;27:230–5. 10.1097/CRD.0000000000000239. [PubMed: 30433897]
3. Cadeddu C, Mercurio V, Spallarossa P, et al. Preventing anti-blastic drug-related cardiomyopathy: Old and new therapeutic strategies. J Cardiovasc Med 2016;17:S64–75. 10.2459/JCM.0000000000000382.
4. Herrmann J Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. Nature Rev Cardiol 2020;17:474–502. 10.1038/s41569-020-0348-1. [PubMed: 32231332]
5. Toldo S, Mezzaroma E, Buckley LF, et al. Targeting the NLRP3 inflammasome in cardiovascular diseases. Pharmacol and Therap 2022;236:108053. 10.1016/j.pharmthera.2021.108053. [PubMed: 34906598]
6. Toldo S, Mezzaroma E, McGeough MD, et al. Independent roles of the priming and the triggering of the NLRP3 inflammasome in the heart. Cardiovasc Res 2015;105:203–12. 10.1093/cvr/cvu259. [PubMed: 25524927]
7. Lyon AR, Dent S, Stanway S, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. Eur J Heart Fail 2020;22:1945–60. 10.1002/EJHF.1920. [PubMed: 32463967]
8. Koutsoukis A, Ntalianis A, Repasos E, Kastritis E, Dimopoulos MA, Paraskevaidis I. Cardio-oncology: A focus on cardiotoxicity. Euro Cardiol Rev 2018;13:64–9. 10.15420/ecr.2017:17:2.
9. Zhang L, Reynolds KL, Lyon AR, Palaskas N, Neilan TG. The Evolving Immunotherapy Landscape and the Epidemiology, Diagnosis, and Management of Cardiotoxicity: JACC: CardioOncology Primer. JACC: CardioOncology 2021;3:35–47. 10.1016/j.jaccao.2020.11.012. [PubMed: 33842895]
10. Ananthan K, Lyon AR. The Role of Biomarkers in Cardio-Oncology. J Cardiovasc Translational Res 2020;13:431–50. 10.1007/s12265-020-10042-3.
11. Herrmann J, Lerman A, Sandhu NP, Villarraga HR, Mulvagh SL, Kohli M. Evaluation and management of patients with heart disease and cancer: Cardio-oncology. Mayo Clin Proceedings 2014;89:1287–306. 10.1016/j.mayocp.2014.05.013.
12. Bianchi ME. DAMPs. PAMPs and alarmins: all we need to know about danger. J Leukocyte Biol 2006;81:1–5. 10.1189/jlb.0306164. [PubMed: 17032697]
13. Broz P, Dixit VM. Inflammasomes: Mechanism of assembly, regulation and signaling. Nature Rev Immunol 2016;16:407–20. 10.1038/NRI.2016.58. [PubMed: 27291964]

14. Mauro AG, Bonaventura A, Mezzaroma E, Quader M, Toldo S. NLRP3 Inflammasome in Acute Myocardial Infarction. J Cardiovasc Pharmacol 2019;74:175–87. 10.1097/FJC.0000000000000717. [PubMed: 31356555]
15. Toldo S, Mezzaroma E, Mauro AG, Salloum F, Van Tassell BW, Abbate A. The Inflammasome in Myocardial Injury and Cardiac Remodeling. Antioxidants & Redox Sign 2015;22:1146–61. 10.1089/ars.2014.5989.
16. Sutterwala FS, Haasken S, Cassel SL. Mechanism of NLRP3 inflammasome activation. Ann N Y Acad Sci 2014;1319:82–95. 10.1111/nyas.12458. [PubMed: 24840700]
17. Mezzaroma E, Toldo S, Abbate A. Role of NLRP3 (cryopyrin) in acute myocardial infarction. Cardiovasc Res 2013;99:225–6. 10.1093/cvr/cvt123. [PubMed: 23695832]
18. de Torre-Minguela C, del Castillo PM, Pelegrın P. The NLRP3 and pyrin inflammasomes: Implications in the pathophysiology of autoinflammatory diseases. Frontiers in Immunol 2017;8:43. 10.3389/fimmu.2017.00043.
19. Rock KL, Latz E, Ontiveros F, Kono H. The Sterile Inflammatory Response. Ann Rev of Immunol 2010;28:321–42. 10.1146/annurev-immunol-030409-101311. [PubMed: 20307211]
20. Fantuzzi G, Dinarello CA. Interleukin-18 and interleukin-1β: Two cytokine substrates for ICE (caspase-1). J Clin Immunol 1999;19:1–11. 10.1023/A:1020506300324. [PubMed: 10080100]
21. Bergsbaken T, Fink SL, Cookson BT. Pyroptosis: Host cell death and inflammation. Nature Rev Microbiol 2009;7:99–109. 10.1038/nrmicro2070. [PubMed: 19148178]
22. Takahashi M NLRP3 Inflammasome as a Novel Player in Myocardial Infarction. Intern Heart J 2014;55:101–5. 10.1536/ihj.13-388.
23. Takahashi Masafumi. Cell-specific signaling of NLRP3 in acute myocardial infarction. J Cardiovasc Pharmacol. Published online 2019.
24. Mezzaroma E, Marchetti C, Toldo S. Mezzaroma Letter by, et al. regarding article, “NLRP3 inflammasome as a therapeutic target in myocardial infarction.”. Int Heart J 2014;55:379. 10.1536/IHJ.14-140. [PubMed: 24942779]
25. Zhaolin Z, Guohua L, Shiyuan W, Zuo W. Role of pyroptosis in cardiovascular disease. Cell Proliferation 2019;52:e12563. 10.1111/CPR.12563. [PubMed: 30525268]
26. Toldo S, Abbate A. The NLRP3 inflammasome in acute myocardial infarction. Nature Rev Cardiol 2018;15:203–14. 10.1038/nrcardio.2017.161. [PubMed: 29143812]
27. Frangogiannis NG. Pathophysiology of myocardial infarction. Compr Physiol 2015;5:1841–75. 10.1002/cphy.c150006. [PubMed: 26426469]
28. Bertheloot D, Latz E. HMGB1, IL-1α, IL-33 and S100 proteins: Dual-function alarmins. Cellular and Molecular Immunol 2017;14:43–64. 10.1038/cmi.2016.34.
29. Dumitriu IE, Baruah P, Valentinis B, et al. Release of High Mobility Group Box 1 by Dendritic Cells Controls T Cell Activation via the Receptor for Advanced Glycation End Products. The J Immunol 2005;174:7506–15. 10.4049/jimmunol.174.12.7506. [PubMed: 15944249]
30. Lawrence T The nuclear factor NF-kappaB pathway in inflammation. Cold Spring Harb Perspect Biol 2009;1:a001651. 10.1101/cshperspect.a001651. [PubMed: 20457564]
31. Lu A, Magupalli VG, Ruan J, et al. Unified polymerization mechanism for the assembly of asc-dependent inflammasomes. Cell 2014;156:1193–206. 10.1016/j.cell.2014.02.008. [PubMed: 24630722]
32. Liu X, Zhang Z, Ruan J, et al. Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. Nature 2016;535:153–8,. 10.1038/nature18629 2016 535:7610. [PubMed: 27383986]
33. Rathinam VAK, Vanaja SK, Fitzgerald KA. Regulation of inflammasome signaling. Nature Immunol 2012;13:333–42. 10.1038/NI.2237. [PubMed: 22430786]
34. Mariathasan S, Weiss DS, Newton K, et al. Cryopyrin activates the inflammasome in response to toxins and ATP. Nature 2006;440:228–32. 10.1038/NATURE04515. [PubMed: 16407890]
35. He Y, Zeng MY, Yang D, Motro B, Núñez G. NEK7 is an essential mediator of NLRP3 activation downstream of potassium efflux. Nature 2016;530:354–7. 10.1038/NATURE16959. [PubMed: 26814970]

36. Murakami T, Ockinger J, Yu J, et al. Critical role for calcium mobilization in activation of the NLRP3 inflammasome. Proc Natl Acad Sci U S A 2012;109:11282–7. 10.1073/PNAS.1117765109. [PubMed: 22733741]
37. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006;440:237–41. 10.1038/nature04516. [PubMed: 16407889]
38. Lima H, Jacobson LS, Goldberg MF, et al. Role of lysosome rupture in controlling Nlrp3 signaling and necrotic cell death. Cell Cycle 2013;12:1868–78. 10.4161/CC.24903. [PubMed: 23708522]
39. Klionsky DJ, Petroni G, Amaravadi RK, et al. Autophagy in major human diseases. The EMBO Journal 2021;40:e108863. 10.15252/embj.2021108863. [PubMed: 34459017]
40. Sun Q, Fan J. Inflammasome and Autophagy Regulation: A Two-way Street. Molecular Med 2017;23:1. 10.2119/molmed.2017.00077.
41. Li A, Gao M, Jiang W, Qin Y, Gong G. Mitochondrial Dynamics in Adult Cardiomyocytes and Heart Diseases. Frontiers in Cell and Developmental Biol 2020;8:1555. 10.3389/FCELL.2020.584800/BIBTEX.
42. Heid ME, Keyel PA, Kamga C, Shiva S, Watkins SC, Salter RD. Mitochondrial reactive oxygen species induces NLRP3-dependent lysosomal damage and inflammasome activation. The J Immunol 2013;191:5230–8. 10.4049/jimmunol.1301490. [PubMed: 24089192]
43. Lesnefsky EJ, Chen Q, Tandler B, Hoppel CL. Mitochondrial dysfunction and myocardial ischemia-reperfusion: implications for novel therapies. Ann Rev Pharmacol and Toxicol 2017;57:535–65. 10.1146/annurev-pharmtox-010715-103335. [PubMed: 27860548]
44. Chen Q, Vazquez EJ, Moghaddas S, Hoppel CL, Lesnefsky EJ. Production of reactive oxygen species by mitochondria: Central role of complex III. J Biological Chemistry 2003;278:36027–31. 10.1074/jbc.M304854200.
45. Davidson SM, Adameová A, Barile L, et al. Mitochondrial and mitochondrial-independent pathways of myocardial cell death during ischaemia and reperfusion injury. J Cellular and Molecular Med 2020;24:3795–806. 10.1111/JCMM.15127.
46. Alhawiti NM, Al Mahri S, Aziz MA, Malik SS, Mohammad S. TXNIP in metabolic regulation: physiological role and therapeutic outlook. Curr Drug Targets 2017;18. 10.2174/1389450118666170130145514.
47. Iyer SS, He Q, Janczy JR, et al. Mitochondrial cardiolipin is required for Nlrp3 inflammasome activation. Immunity 2013;39:311–23. 10.1016/j.immuni.2013.08.001. [PubMed: 23954133]
48. Huang J, Li R, Wang C. The role of mitochondrial quality control in cardiac ischemia/reperfusion injury. Oxidative Medicine and Cellul Longevity 2021:2021. 10.1155/2021/5543452.
49. Wang Y, Liu X, Shi H, et al. NLRP3 inflammasome, an immune-inflammatory target in pathogenesis and treatment of cardiovascular diseases. Clin Transl Med 2020;10:91–106. 10.1002/CTM2.13. [PubMed: 32508013]
50. An N, Gao Y, Si Z, et al. Regulatory Mechanisms of the NLRP3 Inflammasome, a Novel Immune-Inflammatory Marker in Cardiovascular Diseases. Front Immunol 2019;10. 10.3389/FIMMU.2019.01592.
51. Hansson GK, Robertson AKL. Söderberg-Nauclér C. Inflammation and atherosclerosis. Ann Rev Pathol 2006;1:297–329. 10.1146/ANNUREV.PATHOL.1.110304.100100. [PubMed: 18039117]
52. Anderson JL, Morrow DA. Acute Myocardial Infarction. Campion EW. New Eng J Med 2017;376:2053–64. 10.1056/NEJMra1606915.
53. Grebe A, Hoss F, Latz E. NLRP3 Inflammasome and the IL-1 Pathway in Atherosclerosis. Circ Res 2018;122:1722–40. 10.1161/CIRCRESAHA.118.311362. [PubMed: 29880500]
54. Jin Y, Fu J. Novel Insights Into the NLRP 3 Inflammasome in Atherosclerosis. J Am Heart Assoc 2019;8. 10.1161/JAHA.119.012219.
55. Duewell P, Kono H, Rayner KJ, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 2010;464:1357–61. 10.1038/nature08938. [PubMed: 20428172]
56. Suetomi T, Willeford A, Brand CS, et al. Inflammation and NLRP3 Inflammasome Activation Initiated in Response to Pressure Overload by Ca2+/Calmodulin-Dependent Protein Kinase II δ Signaling in Cardiomyocytes Are Essential for Adverse Cardiac Remodeling. Circulation 2018;138:2530–44. 10.1161/CIRCULATIONAHA.118.034621. [PubMed: 30571348]

57. Camell CD, Günther P, Lee A, et al. Aging Induces an Nlrp3 Inflammasome-Dependent Expansion of Adipose B Cells That Impairs Metabolic Homeostasis. Cell Metabolism 2019;30:1024–39,. 10.1016/J.CMET.2019.10.006 e6. [PubMed: 31735593]
58. Gao J, Xie Q, Wei T, Huang C, Zhou W, Shen W. Nebivolol improves obesity-induced vascular remodelling by suppressing NLRP3 activation. J Cardiovasc Pharmacol 2019;73:326–33. 10.1097/FJC.0000000000000667. [PubMed: 31082961]
59. Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. Nature Rev Endocrinol 2017;13:633–43. 10.1038/NRENDO.2017.90. [PubMed: 28799554]
60. Vandanmagsar B, Youm YH, Ravussin A, et al. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nature Med 2011;17:179–88,. 10.1038/nm.2279 2011 17:2. [PubMed: 21217695]
61. Subramaniam S, Kong YC, Zaharah H, et al. Baseline cardiovascular comorbidities, and the influence on cancer treatment decision-making in women with breast cancer. Ecancermedicalscience 2021:15. 10.3332/ECANCER.2021.1293.
62. Karlstaedt A, Moslehi J, de Boer RA. Cardio-onco-metabolism: metabolic remodeling in cardiovascular disease and cancer. Nature Rev Cardiol 2022;19:414–25,. 10.1038/S41569-022-00698-62022 19:6. [PubMed: 35440740]
63. Fowler ED, Wang N, Hancox JC, et al. The Role of IL-1β on Atrial Fibrillation Physiopathology. Biophysical J 2020; 118:569a–70a. 10.1016/J.BPJ.2019.11.3100.
64. Yao C, Veleva T, Scott L, et al. Enhanced Cardiomyocyte NLRP3 Inflammasome Signaling Promotes Atrial Fibrillation. Circulation 2018;138:2227–42. 10.1161/CIRCULATIONAHA.118.035202. [PubMed: 29802206]
65. Luan Y, Guo Y, Li S, et al. Interleukin-18 among atrial fibrillation patients in the absence of structural heart disease. EP Europace 2010;12:1713–8. 10.1093/EUROPACE/EUQ321.
66. Toldo S, Kannan H, Bussani R, et al. Formation of the inflammasome in acute myocarditis. Internat J Cardiol 2014;171: e119–21. 10.1016/j.ijcard.2013.12.137.
67. Wang Y, Gao B, Xiong S. Involvement of NLRP3 inflammasome in CVB3-induced viral myocarditis. Am J Physiol - Heart and Circulatory Physiol 2014;307:H1438–47. 10.1152/AJPHEART.00441.2014/ASSET/IMAGES/LARGE/ZH40221413250007.JPEG.
68. Eftekhar SP, Yazdanpanah N, Rezaei N. Immune checkpoint inhibitors and cardiotoxicity: possible mechanisms, manifestations, diagnosis and management. Expert Rev Anticancer Ther 2021;21:1211–28. 10.1080/14737140.2021.1979396. [PubMed: 34511008]
69. Won T, Gilotra NA, Wood MK, et al. Increased Interleukin 18-Dependent Immune Responses Are Associated With Myopericarditis After COVID-19 mRNA Vaccination. Front Immunol 2022;13. 10.3389/FIMMU.2022.851620.
70. Miao L, Zhang Y, Huang L. mRNA vaccine for cancer immunotherapy. Molecular Cancer 2021;20. 10.1186/S12943-021-01335-5. [PubMed: 33485358]
71. Bonaventura A, Vecchie A, Mauro AG, Brucato AL, Imazio M, Abbate A. An update on the pathophysiology of acute and recurrent pericarditis. Panminerva Med 2021;63:249–60. 10.23736/S0031-0808.20.04205-6. [PubMed: 33337127]
72. Doctor NS, Shah AB, Coplan N, Kronzon I. Acute Pericarditis. Solomon CG, ed. Progress in Cardiovasc Diseases 2017;59:349–59. 10.1016/j.pcad.2016.12.001.
73. Totterman KJ, Pesonen E, Siltanen P. Radiation-related chronic heart disease. Chest 1983;83:875–8. 10.1378/chest.83.6.875. [PubMed: 6851689]
74. Higgins AY, O'Halloran TD, Chang JD. Chemotherapy-induced cardiomyopathy. Heart Failure Rev 2015;20:721–30. 10.1007/s10741-015-9502-y.
75. Mauro AG, Bonaventura A, Vecchié A, et al. The Role of NLRP3 Inflammasome in Pericarditis: Potential for Therapeutic Approaches. JACC Basic Transl Sci 2021;6:137–50. 10.1016/J.JACBTS.2020.11.016. [PubMed: 33665514]
76. Klein AL, Imazio M, Cremer P, et al. Phase 3 Trial of Interleukin-1 Trap Rilonacept in Recurrent Pericarditis. New Eng J Med 2021;384:31–41. 10.1056/NEJMOA2027892. [PubMed: 33200890]
77. Brucato A, Imazio M, Gattorno M, et al. Effect of anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence: The AIRTRIP randomized clinical trial. JAMA - J Am Med Ass 2016;316:1906–12. 10.1001/JAMA.2016.15826.

78. Rayner DM, Cutts SM. Anthracyclines. Side Effects of Drugs Annl 2022;36:683–94. 10.1016/B978-0-444-63407-8.00045-9.

79. Bernstein D Anthracycline Cardiotoxicity. Circulation Res 2018;122:188–90. 10.1161/CIRCRESAHA.117.312395. [PubMed: 29348242]

80. Rayner DM, Cutts SM. Anthracyclines. Side Effects of Drugs Annual 2022;36:683–94. 10.1016/B978-0-444-63407-8.00045-9.

81. Zhang S, Liu X, Bawa-Khalfe T, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med 2012;18:1639–42. 10.1038/NM.2919. [PubMed: 23104132]

82. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of Anthracyclines. Frontiers in Cardiovasc Med 2020;7. 10.3389/fcvm.2020.00026.

83. Takemura G, Fujiwara H. Doxorubicin-induced cardiomyopathy from the cardiotoxic mechanisms to management. Prog Cardiovasc Dis 2007;49:330–52. 10.1016/J.PCAD.2006.10.002. [PubMed: 17329180]

84. Henriksen PA. Anthracycline cardiotoxicity: An update on mechanisms, monitoring and prevention. Heart 2018;104:971–7. 10.1136/heartjnl-2017-312103. [PubMed: 29217634]

85. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015;131:1981–8. 10.1161/CIRCULATIONAHA.114.013777. [PubMed: 25948538]

86. Schirone L, Toldo S, Cianflone E, Sala V, Greco E. The role of anthracyclines in cardio-oncology: oxidative stress, inflammation, and autophagy. Oxid Med Cell Longev 2022;2022:1–3. 10.1155/2022/9862524.

87. Zhu J, Zhang J, Xiang D, et al. Recombinant human interleukin-1 receptor antagonist protects mice against acute doxorubicin-induced cardiotoxicity. Eur J Pharmacol 2010;643:247–53. 10.1016/J.EJPHAR.2010.06.024. [PubMed: 20599921]

88. Sauter KAD, Wood LJ, Wong J, Iordanov M, Magun BE. Doxorubicin and daunorubicin induce processing and release of interleukin-1β through activation of the NLRP3 inflammasome. Cancer Biol and Therapy 2011;11:1008–16. 10.4161/cbt.11.12.15540.

89. Wong J, Tran LT, Magun EA, Magun BE, Wood LJ. Production of IL-1β by bone marrow-derived macrophages in response to chemotherapeutic drugs: Synergistic effects of doxorubicin and vincristine. Cancer Biol and Therapy 2014;15:1395–403. 10.4161/cbt.29922.

90. Marchetti C, Toldo S, Chojnacki J, et al. Pharmacologic Inhibition of the NLRP3 Inflammasome Preserves Cardiac Function after Ischemic and Nonischemic Injury in the Mouse. J Cardiovasc Pharmacol 2015;66:1–8. 10.1097/FJC.0000000000000247. [PubMed: 25915511]

91. Meng L, Lin H, Zhang J, et al. Doxorubicin induces cardiomyocyte pyroptosis via the TINCR-mediated posttranscriptional stabilization of NLR family pyrin domain containing 3. J Molecular and Cellular Cardiol 2019;136:15–26. 10.1016/j.yjmcc.2019.08.009.

92. Yan Y, Xiang C, Yang Z, Miao D, Zhang D. Rho Kinase Inhibition by Fasudil Attenuates Adriamycin-Induced Chronic Heart Injury. Cardiovasc Toxicol 2020;20:351–60. 10.1007/S12012-019-09561-6. [PubMed: 31894538]

93. Kobayashi M, Usui F, Karasawa T, et al. NLRP3 Deficiency Reduces Macrophage Interleukin-10 Production and Enhances the Susceptibility to Doxorubicin-induced Cardiotoxicity. Scientific Reports 2016;6:1–11. 10.1038/srep26489. [PubMed: 28442746]

94. Zuurbier CJ. NLRP3 Inflammasome in Cardioprotective Signaling. J Cardiovasc Pharmacol 2019;74:271–5. 10.1097/FJC.0000000000000696. [PubMed: 31356546]

95. Maayah ZH, Alam AS, Takahara S, et al. Resveratrol reduces cardiac NLRP3-inflammasome activation and systemic inflammation to lessen doxorubicin-induced cardiotoxicity in juvenile mice. FEBS Lett 2021;595:1681–95. 10.1002/1873-3468.14091. [PubMed: 33876420]

96. Mauro AG, Bonaventura A, Abbate A. Drugs to Inhibit the NLRP3 Inflammasome: Not Always On Target. J Cardiovasc Pharmacol 2019;74:225–7. 10.1097/FJC.0000000000000729. [PubMed: 31415453]

97. Chang YP, Ka SM, Hsu WH, et al. Resveratrol inhibits NLRP3 inflammasome activation by preserving mitochondrial integrity and augmenting autophagy. J Cellular Physiol 2015;230:1567–79. 10.1002/JCP.24903. [PubMed: 25535911]

98. Saiki H, Petersen IA, Scott CG, et al. Risk of Heart Failure with Preserved Ejection Fraction in Older Women after Contemporary Radiotherapy for Breast Cancer. Circulation 2017;135:1388–96. 10.1161/CIRCULATIONAHA.116.025434. [PubMed: 28132957]

99. Canada JM, Thomas GK, Trankle CR, et al. Increased C-reactive protein is associated with the severity of thoracic radiotherapy-induced cardiomyopathy. Cardiooncology 2020;6. 10.1186/S40959-020-0058-1.

100. Canada JM, Trankle CR, Carbone S, et al. Determinants of Cardiorespiratory Fitness Following Thoracic Radiotherapy in Lung or Breast Cancer Survivors. Am J Cardiol 2020;125:988–96. 10.1016/j.amjcard.2019.12.019. [PubMed: 31928717]

101. Huang S, Che J, Chu Q, Zhang P. The Role of NLRP3 Inflammasome in Radiation-Induced Cardiovascular Injury. Front Cell Dev Biol 2020;8. 10.3389/FCELL.2020.00140.

102. Yoshimoto Y, Suzuki Y, Mimura K, et al. Radiotherapy-Induced Anti-Tumor Immunity Contributes to the Therapeutic Efficacy of Irradiation and Can Be Augmented by CTLA-4 Blockade in a Mouse Model. PLOS ONE 2014;9:e92572. 10.1371/JOURNAL.PONE.0092572. [PubMed: 24686897]

103. Christersdottir T, Pirault J, Gistera A, et al. Prevention of radiotherapy-induced arterial inflammation by interleukin-1 blockade. European Heart J 2019;40:2495–503. 10.1093/EURHEARTJ/EHZ206. [PubMed: 31081038]

104. Smith AO, Ju W, Adzraku SY, et al. Gamma Radiation Induce Inflammasome Signaling and Pyroptosis in Microvascular Endothelial Cells. J Inflammation Res 2021;14:3277. 10.2147/JIR.S318812.

105. Mezzaroma E, Mikkelsen RB, Toldo S, et al. Role of Interleukin-1 in Radiation-Induced Cardiomyopathy. Molecular Med 2015;21:210–8. 10.2119/molmed.2014.00243.

106. Saiki H, Moulay G, Guenzel AJ, et al. Experimental cardiac radiation exposure induces ventricular diastolic dysfunction with preserved ejection fraction. Am J Physiol Heart Circ Physiol 2017;313:H392–407. 10.1152/AJPHEART.00124.2017. [PubMed: 28550173]

107. Force T, Krause DS, van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. Nature Reviews Can 2007;7:332–44. 10.1038/nrc2106.

108. Erickson RP. Somatic gene mutation and human disease other than cancer: An update. Mutation Res - Rev in Mutation Res 2010;705:96–106. 10.1016/j.mrrev.2010.04.002.

109. Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell 2010;141:1117–34. 10.1016/j.cell.2010.06.011. [PubMed: 20602996]

110. Madhusudan S, Ganesan TS. Tyrosine kinase inhibitors in cancer therapy. Clin Biochemistry 2004;37:618–35. 10.1016/j.clinbiochem.2004.05.006.

111. Zwick E, Bange J, Ullrich A. Receptor tyrosine kinases as targets for anticancer drugs. Trends in Molecular Med 2002;8:17–23. 10.1016/S1471-4914(01)02217-1.

112. Tong M, Seeliger MA. Targeting conformational plasticity of protein kinases. ACS Chemical Biol 2015;10:190–200. 10.1021/cb500870a.

113. Lamore SD, Kohnken RA, Peters MF, Kolaja KL. Cardiovascular Toxicity Induced by Kinase Inhibitors: Mechanisms and Preclinical Approaches. Chem Res in Toxicol 2020;33:125–36. 10.1021/acs.chemrestox.9b00387. [PubMed: 31840498]

114. Mauro AG, Hunter K, Salloum FN. Cardiac complications of cancer therapies. Published online April 20, 2022. doi:10.1016/BS.ACR.2022.03.006

115. Garcia-Alvarez A, Garcia-Albeniz X, Esteve J, Rovira M, Bosch X. Cardiotoxicity of Tyrosine-Kinase-Targeting Drugs. Cardiovasc & Hematological Agents in Medicinal Chem 2010;8:11–21. 10.2174/187152510790796192.

116. Bouitbir J, Alshaikhali A, Panajatovic MV, Abegg VF, PaechF, Krähenbühl S. Mitochondrial oxidative stress plays a critical role in the cardiotoxicity of sunitinib: Running title: Sunitinib and oxidative stress in hearts. Toxicology 2019:426. 10.1016/j.tox.2019.152281.

117. Quagliariello V, Berretta M, Buccolo S, et al. Polydatin Reduces Cardiotoxicity and Enhances the Anticancer Effects of Sunitinib by Decreasing Pro-Oxidative Stress, Pro-Inflammatory Cytokines, and NLRP3 Inflammasome Expression. Frontiers in Oncol 2021;11:2188. 10.3389/fonc.2021.680758.

118. Kimura T, Uesugi M, Takase K, Miyamoto N, Sawada K. Hsp90 inhibitor geldanamycin attenuates the cytotoxicity of sunitinib in cardiomyocytes via inhibition of the autophagy pathway. Toxicology and Applied Pharmacol 2017;329:282–92. 10.1016/j.taap.2017.06.015.
119. Lekes D, Szadvari I, Krizanova O, et al. Nilotinib induces ER stress and cell death in H9c2 cells. Physiological Research 2016;65(Suppl4):S505–14. 10.33549/physiolres.933504. [PubMed: 28006933]
120. Flemming S, Fischer L, Fischenich NJ, et al. Tyrosine kinase inhibitors trigger lysosomal damage-associated cell lysis to activate the NLRP3 inflammasome. bioRxiv 2022:1–45,. 10.1101/2022.02.19.480941 Published online February 19.
121. Stein-Merlob AF, Rothberg MV, Ribas A, Yang EH. Cardiotoxicities of novel cancer immunotherapies. Heart 2021;0:1–10. 10.1136/heartjnl-2020-318083.
122. Mahmood SS, Fradley MG, Cohen J v, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol 2018;71:1755–64. 10.1016/j.jacc.2018.02.037. [PubMed: 29567210]
123. Jain V, Mohebtash M, Rodrigo ME, Ruiz G, Atkins MB, Barac A. Autoimmune Myocarditis Caused by Immune Checkpoint Inhibitors Treated with Antithymocyte Globulin. J Immunotherapy 2018;41:332–5. 10.1097/CJI.0000000000000239.
124. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nature Reviews Immunol 2020;20:651–68. 10.1038/s41577-020-0306-5.
125. Hu YB, Zhang Q, Li HJ, et al. Evaluation of rare but severe immune related adverse effects in PD-1 and PD-L1 inhibitors in non-small cell lung cancer: a meta-analysis. Translational Lung Cancer Res 2017;6(S1):S8–S20. 10.21037/tlcr.2017.12.10.
126. Palaskas N, Morgan J, Daigle T, et al. Targeted Cancer Therapies With Pericardial Effusions Requiring Pericardiocentesis Focusing on Immune Checkpoint Inhibitors. Am J Cardiol 2019;123:1351–7. 10.1016/j.amjcard.2019.01.013. [PubMed: 30765065]
127. Lyon AR, Yousaf N, Battisti NML, et al. Immune checkpoint inhibitors and cardiovascular toxicity. 2018;19:e447–e458. doi:10.1016/S1470-2045(18)30457-1
128. Johnson DB, Balko JM, Compton ML, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. New Eng J Med 2016;375:1749–55. 10.1056/nejmoa1609214. [PubMed: 27806233]
129. Quagliariello V, Passariello M, Rea D, et al. Evidences of CTLA-4 and PD-1 blocking agents-induced cardiotoxicity in cellular and preclinical models. J Personalized Medicine 2020;10:1–19. 10.3390/jpm10040179.
130. Zhang H, Lin J, Shen Y, Pan J, Wang C, Cheng L. Protective Effect of Crocin on Immune Checkpoint Inhibitors-Related Myocarditis Through Inhibiting NLRP3 Mediated Pyroptosis in Cardiomyocytes via NF-kB Pathway. J Inflammation Res 2022;15:1653–66. 10.2147/JIR.S348464.
131. Nemeth BT, Varga Zv, Wu WJ, Pacher P. Trastuzumab cardiotoxicity: from clinical trials to experimental studies. British J Pharmacol 2017;174:3727–48. 10.1111/bph.13643.
132. Dirican A, Levent F, Alacacioglu A, et al. Acute cardiotoxic effects of adjuvant trastuzumab treatment and its relation to oxidative stress. Angiology 2014;65:944–9. 10.1177/0003319714523112. [PubMed: 24576982]
133. Dokmanovic M, King KE, Mohan N, Endo Y, Wu WJ. Cardiotoxicity of ErbB2-targeted therapies and its impact on drug development, a spotlight on trastuzumab. Expert Opinion on Drug Metabolism and Toxicol 2017;13:755–66. 10.1080/17425255.2017.1337746.
134. Mohan N, Jiang J, Wu WJ. Implications of Autophagy and Oxidative Stress in Trastuzumab-Mediated Cardiac Toxicities. Austin Pharmacol Pharm. 2017;2. Accessed May 16, 2022. Available at: http://www.ncbi.nlm.nih.gov/pubmed/30288503%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC6168002
135. Gordon LI, Burke MA, Singh ATK, et al. Blockade of the erbB2 receptor induces cardiomyocyte death through mitochondrial and reactive oxygen species-dependent pathways. J Biological Chemistry 2009;284:2080–7. 10.1074/jbc.M804570200.

136. ElZarrad MK, Mukhopadhyay P, Mohan N, et al. Trastuzumab alters the expression of genes essential for cardiac function and induces ultrastructural changes of cardiomyocytes in mice. PLoS ONE 2013;8:79543. 10.1371/journal.pone.0079543.

137. Zeglinski M, Ludke A, Jassal DS, Singal PK. Trastuzumab-induced cardiac dysfunction: A "dual-hit.". Experimental and Clin Cardiol 2011;16:70–4.

138. Mohan N, Shen Y, Endo Y, ElZarrad MK, Wu WJ. Trastuzumab, but not pertuzumab, dysregulates HER2 signaling to mediate inhibition of autophagy and increase in reactive oxygen species production in human cardiomyocytes. Molecular Can Therapeutics 2016;15:1321–31. 10.1158/1535-7163.MCT-15-0741.

139. Maurea N, Quagliariello V, Iaffaioli RV, De Laurentiis M, Botti G. the Sodium-Glucose Cotransporter-2 Inhibitor Dapagliflozin Exerts Cardioprotective Effects Against Doxorubicin and Trastuzumab Toxicity Through Tlr4/Myd88/Nf-Kb Signaling and Nlrp3 Inflammasome Pathway. J Am Coll Cardiol 2020;75:1192. 10.1016/s0735-1097(20)31819-2.

140. Ye Y, Bajaj M, Yang HC, Perez-Polo JR, Birnbaum Y. SGLT-2 Inhibition with Dapagliflozin Reduces the Activation of the Nlrp3/ASC Inflammasome and Attenuates the Development of Diabetic Cardiomyopathy in Mice with Type 2 Diabetes. Further Augmentation of the Effects with Saxagliptin, a DPP4 Inhibitor. Cardiovasc Drugs and Therapy 2017;31:119–32. 10.1007/S10557-017-6725-2.

141. Maurea N, Quagliariello V, de Laurentiis M, et al. The SGLT-2 inhibitor dapagliflozin reduces cell death and apoptosis in cardiomyocytes exposed to trastuzumab and doxorubicin through NLRP3-mediated pathways. 2021;39(15_suppl):e15041–e15041. doi:10.1200/JCO.2021.39.15_SUPPL.E15041

142. Maurea N, Quagliariello V, Iaffaioli RV, de Laurentiis M, Botti G. the Sodium-Glucose Cotransporter-2 Inhibitor Dapagliflozin Exerts Cardioprotective Effects Against Doxorubicin and Trastuzumab Toxicity Through Tlr4/Myd88/Nf-Kb Signaling and Nlrp3 Inflammasome Pathway. J Am Coll Cardiol 2020;75:1192. 10.1016/s0735-1097(20)31819-2.

143. Luzi L, Pozza G. Glibenclamide: an old drug with a novel mechanism of action? Acta Diabetol 1997;34:239–44. 10.1007/S005920050081. [PubMed: 9451465]

144. Lamkanfi M, Mueller JL, Vitari AC, et al. Glyburide inhibits the Cryopyrin/Nalp3 inflammasome. J Cell Biol 2009;187:61–70. 10.1083/jcb.200903124. [PubMed: 19805629]

145. Marchetti C, Chojnacki J, Toldo S, et al. A novel pharmacologic inhibitor of the NLRP3 inflammasome limits myocardial injury after ischemia-reperfusion in the mouse. J Cardiovasc Pharmacol 2014;63:316–22. 10.1097/FJC.0000000000000053. [PubMed: 24336017]

146. Coll RC, Hill JR, Day CJ, et al. MCC950 directly targets the NLRP3 ATP-hydrolysis motif for inflammasome inhibition. 2019;15:556–559.

147. Coll RC, Robertson AAB, Chae JJ, et al. A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. Nature Med 2015;21:248–55. 10.1038/nm.3806. [PubMed: 25686105]

148. Daniels MJD, Rivers-Auty J;, Schilling T;, et al. Fenamate NSAIDs inhibit the NLRP3 inflammasome and protect against Alzheimer's disease in rodent models. Nature Commun 2016;7:1–10. 10.1038/ncomms12504.

149. Dempsey C, Rubio Araiz A, Bryson KJ, et al. Inhibiting the NLRP3 inflammasome with MCC950 promotes non-phlogistic clearance of amyloid-β and cognitive function in APP/PS1 mice. Brain, Behavior, and Immunity 2017;61:306–16. 10.1016/j.bbi.2016.12.014. [PubMed: 28003153]

150. Van Der Heijden T, Kritikou E, Venema W, et al. NLRP3 Inflammasome Inhibition by MCC950 Reduces Atherosclerotic Lesion Development in Apolipoprotein E-Deficient Mice-Brief Report. Arterioscler Thromb Vasc Biol 2017;37:1457–61. 10.1161/ATVBAHA.117.309575. [PubMed: 28596375]

151. Vande Walle L, Stowe IB, Šácha P, et al. MCC950/CRID3 potently targets the NACHT domain of wild-type NLRP3 but not disease-associated mutants for inflammasome inhibition. PLOS Biol 2019;17:e3000354. 10.1371/JOURNAL.PBIO.3000354. [PubMed: 31525186]

152. VanHout GPJ, Bosch L, Ellenbroek GHJM, et al. The selective NLRP3-inflammasome inhibitor MCC950 reduces infarct size and preserves cardiac function in a pig model of myocardial infarction. Euro Heart J 2017;38:828–36. 10.1093/eurheartj/ehw247.
153. Cheng P, Yang G, Zhao X, et al. Precisely and Efficiently Enzyme Response Microspheres with Immune Removal Escape Loaded with MCC950 Ameliorate Cardiac Dysfunction in Acute Myocardial Infarction. J Biomed Nanotechnol 2020;16:153–65. 10.1166/JBN.2020.2885. [PubMed: 32252877]
154. Gan W, Ren J, Li T, et al. The SGK1 inhibitor EMD638683, prevents Angiotensin II–induced cardiac inflammation and fibrosis by blocking NLRP3 inflammasome activation. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 2018;1864:1–10. 10.1016/J.BBADIS.2017.10.001. [PubMed: 28986310]
155. Wang J, Sun C, Gerdes N, et al. Interleukin 18 function in atherosclerosis is mediated by the interleukin 18 receptor and the Na-Cl co-transporter. Nature Med 2015;21:820–6. 10.1038/nm.3890. [PubMed: 26099046]
156. Pavillard LE, Cañadas-Lozano D, Alcocer-Gómez E, et al. NLRP3-inflammasome inhibition prevents high fat and high sugar diets-induced heart damage through autophagy induction. Oncotarget 2017;8:99740–56. 10.18632/ONCOTARGET.20763. [PubMed: 29245937]
157. Meng L, Lin H, Zhang J, et al. Doxorubicin induces cardiomyocyte pyroptosis via the TINCR-mediated posttranscriptional stabilization of NLR family pyrin domain containing 3. J Mol Cell Cardiol 2019;136:15–26. 10.1016/J.YJMCC.2019.08.009. [PubMed: 31445005]
158. Wei S, Ma W, Li X, et al. Involvement of ROS/NLRP3 Inflammasome Signaling Pathway in Doxorubicin-Induced Cardiotoxicity. Cardiovasc Toxicol 2020;20:507–19. 10.1007/S12012-020-09576-4/FIGURES/8. [PubMed: 32607760]
159. Hosoki R, Matsuki N, Kimura H. The possible role of hydrogen sulfide as an endogenous smooth muscle relaxant in synergy with nitric oxide. Biochemical and Biophysical Res Commun 1997;237:527–31. 10.1006/bbrc.1997.6878.
160. Salloum FN. Hydrogen sulfide and cardioprotection - Mechanistic insights and clinical translatability. Pharmacol and Therapeutics 2015;152:11–7. 10.1016/j.pharmthera.2015.04.004.
161. Toldo S, Das A, Mezzaroma E, et al. Induction of microrna-21 with exogenous hydrogen sulfide attenuates myocardial ischemic and inflammatory injury in mice. Circulation: Cardiovasc Genetics 2014;7:311–20. 10.1161/CIRCGENETICS.113.000381.
162. Castelblanco M, Lugrin J, Ehirchiou D, et al. Hydrogen sulfide inhibits NLRP3 inflammasome activation and reduces cytokine production both in vitro and in a mouse model of inflammation. J Biolog Chemistry 2018;293:2546–57. 10.1074/jbc.M117.806869.
163. Wang XY, Yang CT, Zheng DD, et al. Hydrogen sulfide protects H9c2 cells against doxorubicin-induced cardiotoxicity through inhibition of endoplasmic reticulum stress. Molecular and Cellular Biochem 2012;363:419–26. 10.1007/S11010-011-1194-6/FIGURES/7.
164. Abstract 13856: Hydrogen Sulfide Donor, SG1002, Preserves Left Ventricular Global Function and Contractile Reserve in a Mouse Model of Doxorubicin Cardiotoxicity | Circulation. Accessed May 26, 2022. Available at: https://www.ahajournals.org/doi/10.1161/circ.144.suppl_1.13856
165. Leung YY, Yao Hui LL, Kraus VB. Colchicine-Update on mechanisms of action and therapeutic uses. Sem in Arthritis and Rheumatism 2015;45:341–50. 10.1016/j.semarthrit.2015.06.013.
166. Mauro AG, Thurber C, Abbate A. Colchicine in Acute Myocardial Infarction: “Teaching New Tricks to an Old Dog. Translational Medicine 2015;05. 10.4172/2161-1025.1000e133.
167. Deftereos S, Giannopoulos G, Angelidis C, et al. Anti-inflammatory treatment with colchicine in acute myocardial infarction: A pilot study. Circulation 2015;132:1395–403. 10.1161/CIRCULATIONAHA.115.017611. [PubMed: 26265659]
168. Mewton N, Roubille F, Bresson D, et al. Effect of Colchicine on Myocardial Injury in Acute Myocardial Infarction. Circulation 2021;144:859–69. 10.1161/CIRCULATIONAHA.121.056177. [PubMed: 34420373]
169. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease. J Am Coll Cardiol 2013;61:404–10. 10.1016/J.JACC.2012.10.027. [PubMed: 23265346]

170. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. New England Journal of Med 2020;383:1838–47. [PubMed: 32865380]

171. Tardif JC, Kouz S, Waters DD, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. New England Journal of Med 2019;381:2497–505. 10.1056/nejmoa1912388. [PubMed: 31733140]

172. Tong DC, Quinn S, Nasis A, et al. Colchicine in Patients With Acute Coronary Syndrome: The Australian COPS Randomized Clinical Trial. Circulation 2020;142:1890–900. 10.1161/CIRCULATIONAHA.120.050771. [PubMed: 32862667]

173. Vaidya K, Arnott C, Martínez GJ, et al. Colchicine Therapy and Plaque Stabilization in Patients With Acute Coronary Syndrome: A CT Coronary Angiography Study. JACC: Cardiovasc Imaging 2018;11:305–16. 10.1016/J.JCMG.2017.08.013. [PubMed: 29055633]

174. Juliana C, Fernandes-Alnemri T, Wu J, et al. Anti-inflammatory compounds parthenolide and bay 11-7082 are direct inhibitors of the inflammasome. J Biological Chemistry 2010;285:9792–802. 10.1074/JBC.M109.082305.

175. Lonnemann N, Hosseini S, Marchetti C, et al. The NLRP3 inflammasome inhibitor OLT1177 rescues cognitive impairment in a mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A 2020;117:32145–54. 10.1073/PNAS.2009680117. [PubMed: 33257576]

176. Marchetti C, Swartzwelter B, Gamboni F, et al. OLT1177, a β-sulfonyl nitrile compound, safe in humans, inhibits the NLRP3 inflammasome and reverses the metabolic cost of inflammation. Proceedings of the National Academy of Sci 2018;115:201716095. 10.1073/pnas.1716095115.

177. Wohlford GF, Buckley LF, Vecchié A, et al. Acute Effects of Interleukin-1 Blockade Using Anakinra in Patients with Acute Pericarditis. J Cardiovascular Pharmacol 2020;76:50–2. 10.1097/FJC.0000000000000847.

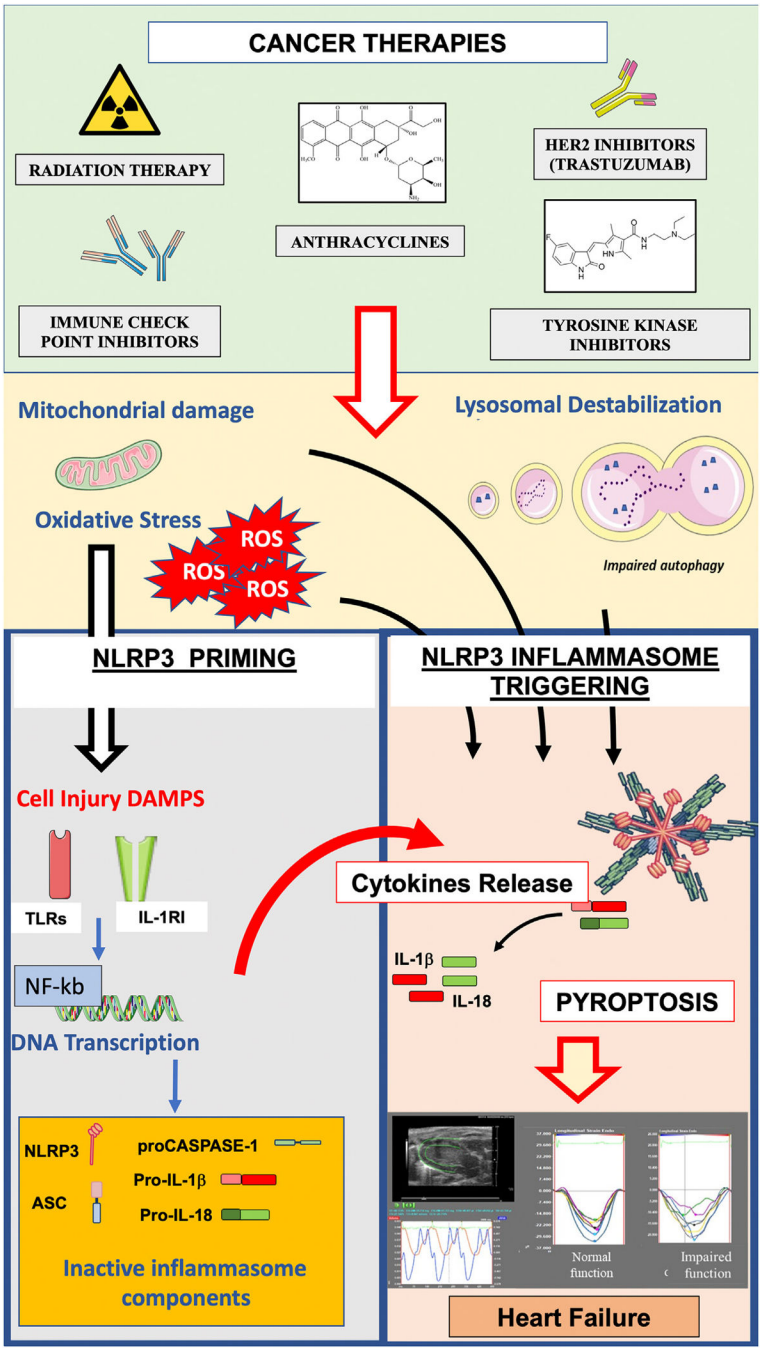

Fig 1.

Proposed mechanism of the activation of NLRP3 inflammasome following the administration of cancer therapies. Cancer treatment induces cardiomyocyte injury, which mediates the priming signaling of the NLRP3 inflammasome. NF-KB is activated, migrates to the nucleus, and begins the synthesis of the inactive NLRP3 components. Mitochondrial dysfunction in the heart consequently results in oxidative stress. Coupled with impaired autophagy, this then leads to the triggering of the NLRP3. The NLRP3 then oligomerizes and induces an auto-proteolytical activation of caspase-1. Active caspase-1 processes pro-

IL1β and pro-IL18 into their mature forms, and triggers pyroptotic myocardial cell death. This NLRP3-mediated cardiac injury can induce long-term consequences on the heart, leading to the onset of heart failure.

Table I.

Inflammasome inhibitors in cancer therapy-induced cardiotoxicity

Drug	Mechanisms of action	Model of Cardiotoxicity	Finding(s)	References
Anakinra (rhIL-1Ra)	IL-1RI antagonist	AICM	Anakinra (1 mg/Kg/day) given for 4 days after DOX injection (18 mg/kg), reduced mortality, cardiac fibrosis, cardiac dysfunction, and cardiomyocyte apoptosis at 14 days after DOX treatment.	87
16673-34-0	NLRP3 inhibitor	AICM	16673-34-0 (100 mg/kg) given 30 minutes before DOX (10 mg/kg), and then once a day for 10 days, preserved cardiac function and reduced interstitial fibrosis deposition.	90
Resveratrol	Non-specific NLRP3 inhibitor	AICM	Resveratrol added in the chow of juvenile mice treated with DOX reduced NLRP3 inflammasome activity and systemic inflammation. It also prevented the detrimental effects of Ang II in a late phase.	95
Anakinra (rhIL-1Ra)	IL-1RI antagonist	Radiation-induced cardiotoxicity	Anakinra (100 mg/kg/day for 2 weeks) in irradiated $ApoE^{-/-}$ mice was able to attenuate radiation-induced arterial inflammation.	103
Dapagliflozin (SGLT-2 Inhibitor)	Non-specific NLRP3 inflammasome inhibitor	AICM +Trastuzumab	In HL-1 cells treated with DOX and trastuzumab (100 nM) dapagliflozin (50 nM) improved Ca^{2+} homeostasis and inhibited the pro-inflammatory "NLRP3-NF-κB–cytokines" pathways.	141
Anakinra (rhIL-1Ra)	IL-1RI antagonist	Radiation-induced cardiotoxicity	Anakinra (10 mg/kg twice a day for 7 days) treatment was able to prevent the decrease in cardiac contractile reserve observed in control irradiated mice.	105
MCC950	NLRP3 ATP-ase activity inhibitor	AICM	In rats, MCC950 (10mg/kg) treatment before DOX chemotherapy prevented the decline of cardiac contractility and reduced NLRP3 and IL-1β expression in the heart while reducing myocardial apoptotic cell death.	157
MCC950	NLRP3 ATP-ase activity inhibitor	AICM	MCC950 pretreated H9c2 cardiomyocytes (10 μM) 1h prior to incubation with 1 μM DOX reduced cardiomyocyte cell death and reduced the protein levels of NLRP3, caspase-1, and IL-1β.	158
NaHS	Non-specific NLRP3 inflammasome inhibitor	AICM	In H9c2 cardiomyocytes treated with DOX (5 μM), 400 μmol/l of NaHS reduced phosphorylation of p38 MAPK kinase while preserving cell viability. NaHS administration reduced also apoptotic cell death and oxidative stress following DOX.	161
NaHS	Non-specific NLRP3 inflammasome inhibitor	AICM	H_2S protected H9c2 cells against DOX administration through inhibition of ER stress. Doxorubicin was administered in a range from 2 – 10 mmol/l for 24 h. NaHS given 30 min before exposure to DOX at the concentration of 400 mmol/l, following doxorubicin preserved cardiomyocyte death while reducing the oxidative stress.	162
SG1002 (H_2S donor)	Non-specific NLRP3 inflammasome inhibitor	AICM	In mice, oral administration of SG1002, an H_2S donor prodrug prevented early decline in cardiac function following DOX measured by global longitudinal strain and contractile reserve assessment following isoproterenol challenge.	163

AICM, anthracycline induced cardiomyopathy; DOX, Doxorubicin; IL-1Ra, Interleukin-1 receptor antagonist; IL-1RI, Interleukin-1 receptor type I; NLRP3, Nucleotide-binding and oligomerization domain, leucine-rich repeat and pyrin domain-containing protein 3