Interleukin-1 and Inflammation in Cardiovascular Disease

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Abstract

Interleukin 1 (IL-1) is a pro-inflammatory cytokine with important roles in innate immunity and tissue homeostasis. Inflammation is crucial as it protects the host by reacting against pathogens and repairing tissues however, improper use of the inflammatory cascade results in pathogenesis of several acute and chronic diseases. IL-1 together with the NLR family pyrin domain containing 3 (NLRP3) inflammasome are key players in inflammation and modulate cardiac function as well. Literature concerning the role of IL-1 and the inflammasome is reviewed, together with a concise narrative overview pathways affected during signaling. Specific examples of the role of IL-1 in pathogenic outcomes in cardiovascular disease (CVD) are also reviewed.

Key words: Interleukin-1, cardiovascular diseases, inflammation, atherosclerosis, myocardial infarction, arrythmias,

Introduction

Interleukin-1 (IL-1) is a pro-inflammatory cytokine assembled by the innate immune system. It acts on innate immune cells as well as on lymphocytes during adaptive immune responses, for instance, naïve T-helper cells can be differentiated and maintained with the help of IL-1 (1).

IL-1 was initially referred to as an endogenous pyrogen since it increases body temperature, resulting in pyrexia which is the hallmark of inflammation. The IL-1 family consists of 11 members and 10 receptors, of which IL-1α and IL-1β are the most commonly studied. IL-1 receptor antagonist (IL-1RA) regulates their activity since it binds to the IL-1 receptor instead of IL-1α and IL-1β (2). The IL-1 receptor is a heterodimer made up of IL-1Ra and IL-1R accessory protein (IL-1RacP) sub-units. IL-1α or IL-1β binding with the IL-1 receptor induce the synthesis acute phase and pro-inflammatory proteins a via a signal transduction cascade, contributing to the inflammatory response.

Most of the IL-1 family members act indirectly on immune processes. Activation of nuclear factor kappa light chain enhancer of activated B cells NF-κB, IL-1β directs transcription and gene expression of cyclooxygenase type 2 (COX-2), type 2 phospholipase A and inducible nitric oxide synthase (iNOS), resulting in the production of prostaglandin-E2 (PGE2), platelet

activating factor (PAF) and nitric oxide (NO). Thus, the biological effects of IL-1, mediated through the aforementioned signal transduction products include: pyrexia, diminished pain threshold, vasodilatation and lowered blood pressure. NO and PGE2 also significantly affect immune responses, such that PGE2 non-specific T-cell suppression is highly prevalent (4). Moreover, IL-1 signalling modulates reparative processes through regulation of gene expression in fibroblasts and smooth muscle cells, achieved by altering the Matrix Metalloproteinase/Tissue Inhibitor of Metalloproteinases ratio (5).

IL-1β signalling induces release of secondary pro-inflammatory cytokines and chemokines including IL-6, tumour necrosis factor α (TNFα) , and granulocyte colony stimulating factor (G-CSF), which provide for the transient development of the inflammatory disease (6). IL-1β is a powerful pro-inflammatory cytokine which is activated via two stages: IL-1β precursor is synthesised consequent Toll-like Receptors (TLRs) activation. Then, pro-IL-1β is transformed to mature IL-1β with the aid of caspase-1 which activates pro-IL-1β by cleaving it. IL-1β causes vasodilation, recruitment of leukocytes through IL-8 and activation of neutrophils, leading to phagocytosis, degranulation and oxidative burst activity to occur (3).

Interleukin-1 in Atherosclerosis

Patients who have elevated inflammatory markers such as C-reactive protein (CRP), are at more risk of suffering from cardiovascular disease (CVD) even if otherwise healthy (7). In patients with a history of CVD, decreased C-reactive protein (CRP) levels result in a similar decrease in the incidence of CVD when compared to decreased LDL-cholesterol levels (8). In the past decades, atherosclerosis has been defined as a type of inflammatory disease. Pro-inflammatory lipoproteins running in the circulation increase the permeability of endothelial cells thus, more lipids and inflammatory macrophages (or foam cells) subside in the tunica intima of the blood vessels. Cholesterol plaque develops, which consists of a necrotic core and a fibrous cap (9). Over time, this deposition induces the production of cytokines including IL-1α, NLR family pyrin domain containing 3 (NLRP3) inflammasome activation, IL-1β and IL-18 (Figure 1). This deposition of fats and cholesterol clogs the vessels causing disruption in blood flow and is partly attributed to elevated expression of IL-1β and IL-1R in plaques and the more they are expressed, the more severe is the disease (10). IL-1 has various effects on cells involved in atherogenesis, mainly the endothelial cells, smooth muscle cells and macrophages.

When IL-1β acts on endothelial cells it enhances the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (11). IL-1β also activates chemokines such as monocyte chemoattractant protein-1 (MCP-1). This attracts phagocytes which are active mediators in CVDs. IL-1β further acts on smooth muscle cells by directing the production of platelet-derived growth factor which can direct smooth muscle cell proliferation (12). IL-1β also stimulates further plaque growth and rupture, which together factors contribute to atherosclerosis that may result in the formation atherothrombosis (13).. Necrosis and apoptosis are frequent events which occur in atherosclerotic lesions and these can activate IL-1α and IL-1β as well (14). IL-1 also induces activation and liberation of another noteworthy cytokine; IL-6. IL-6 stimulates hepatocytes which in turn increase the synthesis of fibrinogen which boosts

thrombosis and plasminogen activator inhibitor (PAI) which in turn restricts fibrinolysis.

IL-6 also directs hepatocytes to boost synthesis of C-reactive protein (CRP). Thus IL-1 amplifies the inflammatory response due to a single IL-1 molecule inducing multiple IL-6 molecules which further activate the expression of several pro-inflammatory mediators, further promoting atherogenesis and the development of several other CVDs (12).

It is essential to highlight the importance of the balance which needs to present between IL-1 and IL-1Ra. Nicklin *et al.* (2000) utilised a IL-1^{++}/IL-$1Ra^{--}$mouse model to investigate the effects of an imbalanced IL-1 and IL1-Ra ratio. Through this model, IL-1 was unopposed and as a consequence, the mice developed severe vascular inflammation together with the occurrence of several inflammatory cells across the wall of the arteries. The vessel walls were observed stenosed and collapsed leading to infarction (15). Other *in-vivo* rodent outline the atherogenic properties of both IL-1α and IL-1β. The first strain consisted of mice deficient in apolipoprotein E (ApoE). When the bone marrow of the first strain of mice was replaced by an IL-1α or IL-1β deficient one, these mice presented with reduced atheromas when compared to the control mice which received the wild type bone marrow (17). Notably, in this study, IL-1α deficient mice presented with greater protection against atheroma formation rather than when mice where deficient in both IL-1α and IL-1β. Thus, compound deficiency of both IL-1α and IL-1β, does not give additional protection in atherosclerotic lesion formation (18). The second strain consisted of mice lacking in low-density lipoprotein receptor (LDL-R) with overexpression of IL-1Ra. The mice in this strain presented with significant reduction in atheroma formation. ApoE deficient mice deficient in IL-1Ra, presented with reduced plaque formation in the root of the aorta but not in the brachiocephalic artery. Deficiency of IL-1Ra also resulted in differences in the structural remodelling of the endothelium and collagen resulting in the maintenance of the atheroma's fibrous cap (18). This may thus demonstrate IL-1Ra's role in protecting against atheromatous plaque rupture (19).

High cholesterol levels induce the IL-1β precursor to be cleaved to active IL-1β. This

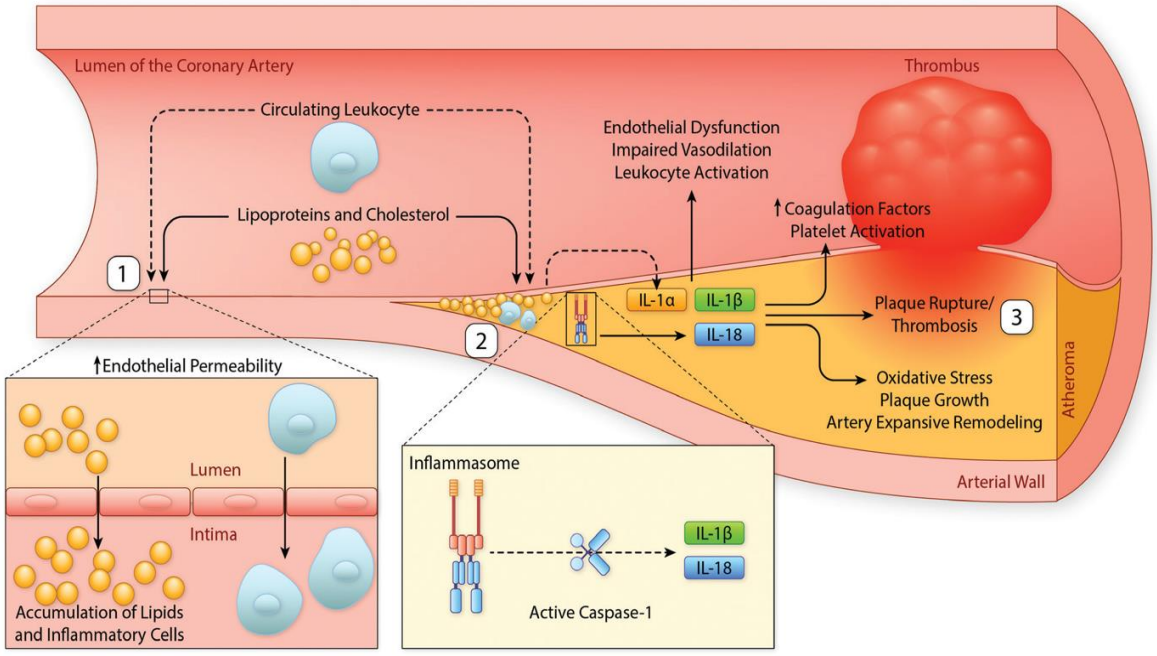

Figure 1: A visual representation of the role of IL-1 in the process of atherosclerosis. Retrieved from Abbate *et al.*, 2020.

occurs due to the deposition of cholesterol crystals in plaque which direct the activation of the NLRP3 inflammasome by activating cathepsin B in the cytoplasm (20). Indeed, experiments performed on LDL-R deficient mice with NLRP3, apoptosis-associated speck-like protein containing a CARD domain (ASC), IL-1α or IL-1β deficiency fed a high fat diet, resulted in a significant reduction of atherosclerotic lesions when compared to the mice with wild type bone marrow (21). Mice with an irregularly functioning inflammasome and caspase-1 deficiency coupled with reduced ApoE or LDL-R, were considered to be protected against inflammatory reactions when compared to mice that are ApoE or LDL-R deficient but have a functional caspase-1 (22). This demonstrated the crucial role of caspase-1 as a mediator in activating pro-IL-1β to IL-1β and further progression of inflammation. The extent to which NLRP3 inflammasome is expressed in plaque has been shown to correlate with the severity of the CVD (23). Another study however shows that ApoE mice with a dysfunctional NLRP3 inflammasome, does not decrease the severity or the incidence of atherogenesis (24). The reason for which these studies produced opposite results with regard to the role of the NLRP3 inflammasome in atherosclerosis still remains indefinite thus, further studies need to be implemented to rule out the proper role of the inflammasome.

Interleukin-1 in Myocardial Infarction

When the ventricular cardiomyocyte undergoes necrosis following an infarct, an inflammatory cascade occurs which functions to clear away the damaged tissue and replace it with fibrous tissue resulting in with scarring. Contents within the dying myocardial cells are released and an inflammatory response initiates via activation of the innate immune system. Receptors at the cell surface sense the released ligands as danger signals and activate cytokines and chemokine pathways (25). The NF-κB system is activated which causes endothelial cells to upregulate the expression of adhesion molecules. Chemokines bind to their receptors on circulating leukocytes and these infiltrating leukocytes remove the infarct composed of necrotic cells and debris (26). Consequently, cytokines and growth factors are induced which adjust extracellular matrix metabolism and activate fibroblasts and endothelial cells causing healing to shift from the inflammatory to the proliferative phase (27). Then leukocytes undergo apoptosis and are removed from the area whilst myocardial fibroblasts at the area of infarction differentiate into myofibroblasts which produce a vast amount of extracellular matrix proteins (28). New vessels start to form surrounded by a muscular coat whilst uncoated vessels start to regress. Inflammatory cells, fibroblasts and vascular cells undergo apoptosis resulting in mature scar formation made up of collagen (28). As healing is taking place, ventricular remodelling occurs. This includes the remodelling of both necrotic zone and non-infarcted zone of the ventricle. This may result in ventricular hypertrophy resulting in a deterioration of cardiac function (5). IL-1 family members are highly expressed in myocardial infarction and a clinical analysis confirms that serum IL-1β levels increased in patients with acute myocardial infarction (AMI) soon after chest pain sets in. However other studies did not record increased serum IL-1β levels in patients with AMI. The discrepancy in these aforementioned studies may have occurred since IL-1β may bind to large proteins such as α2 macroglobulin or to the IL-1R2 receptor. As a result, serum IL-1β levels could be harder to detect (5). IL-1Ra levels were also significant in AMI patients.

Indeed, IL-1Ra levels were significantly elevated in patients with AMI and IL-1Ra expression occurred ahead of release of necrosis markers. Such levels of IL-1Ra correspond with the degree of cardiomyocyte loss (29). IL-1α acts as a warning biomarker early on in the onset of AMI, and it activates IL-1β activity via activation of the NLRP3 inflammasome (30).

IL-1 signalling also induces the inflammatory response after infarction takes place. In IL-1Ra null mice, decreased neutrophil recruitment was observed together with enhanced neutrophil apoptosis. This was suggested to occur since because IL-1 has the ability to prolong neutrophil survival by preventing their apoptosis (31). IL-1 pro-inflammatory effects may intensify injury via several pathways. For instance, enhanced neutrophil levels may result in direct cardiomyocyte death and IL-1 signalling, which may activate matrix degradation thus enhanced matrix remodelling of the ventricle takes place. Thus, evidence in IL-1Ra deficient mice shows that IL-1 may contribute to injury, but it does not aggravate it (31).

IL-1 produces several effects on the myocardium: it induces apoptosis alone or alongside other cytokines such as interferon γ (IFN γ) and TNFα (5). This further promotes cardiac muscle injury. IL-1 causes cardiomyocyte hypertrophy by elevating expression of atrial natriuretic factor and repressing Ca^{2+} regulatory genes (32). IL-1β represses cardiac function as well via NO-dependent and NO-independent pathways and also via inhibiting c-adrenergic agonist which elevates cardiac contractility and cAMP accumulation. Apart from IL-1 leaving its effects directly on cardiomyocytes, it also influences gene expression of several cells which aid in infarct healing (Figure 2). IL-1 activates both endothelial cells and leukocytes. These induce adhesion molecule production and integrin expression respectively. Moreover, IL-1 also induces macrophages and endothelial cells to produce chemokines. These attract leukocytes to site of injury via chemotaxis. Fibroblasts are also affected by action of IL-1 and are involved in the reparative process. In IL-1Ra null mice, fibrosis following inafrct was significantly reduced (5); demonstrating the crucial effect IL-1 has on fibroblast activation and migration to the site of injury. Additionally,

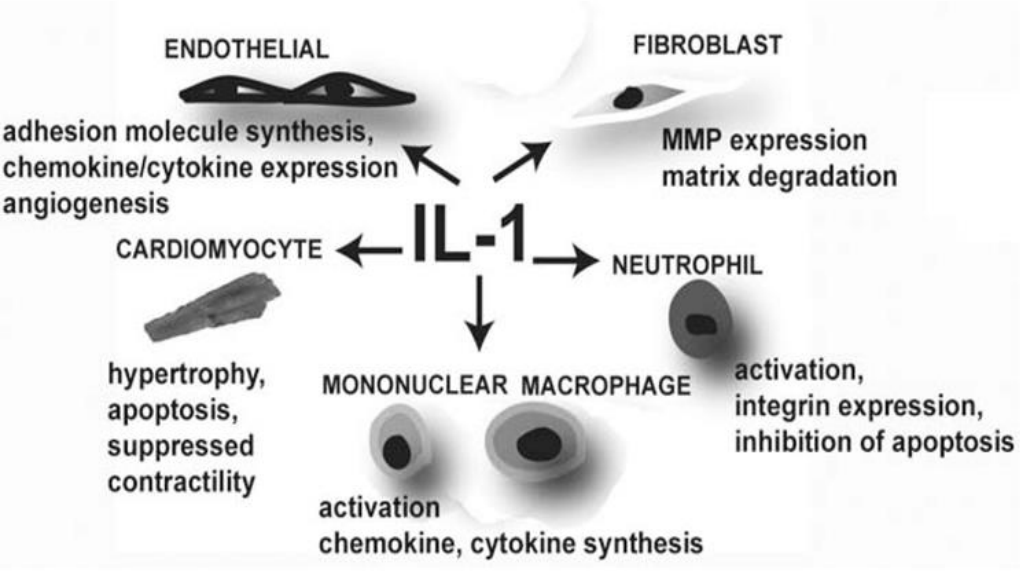

Figure 2: The effects of IL-1 on mediators of infarction and healing. Retrieved from Bujak and Frangogiannis *et al.*, 2009.

IL-1β enhances expression of angiotensin II type 2 receptors on cardiac fibroblasts, thus allowing for fibrous tissue build up (33). Transforming growth factor- β (TGF- β) is a pro-fibrotic mediator which was also reduced in infarcts conducted in IL-1Ra null mice, causing less collagen to be deposited in the healing scar and the area around the infarct (34).

IL-1 upregulates matrix metalloproteinase (MMP) synthesis, resulting in reduced collagen deposition and consequent matrix degradation (35). Suppression of the inflammatory response may be advantageous due to it reducing the extent of fibrosis of the infarcted ventricle. Collagen deposition and MMP expression are downregulated in IL-1Ra null infarcts thus interstitial remodelling is decreased (36). Finally, IL-1 enhances angiogenesis but the mechanism through which this is carried out is still unknown. This is shown by a study which involved three rat models that had undergone IL-1 inhibition in which new vessel formation was suppressed (37).

Interleukin-1 in Arrhythmias

Several studies performed on guinea pigs show that IL-1 is able to lengthen cardiomyocyte action potential (AP) via modifications in Ca^{2+} channels function (38). A recent study highlights the role of IL-1α in prolonging the action potential whereas IL-1β mediation resulted in extra-systolic patterns in rat atrial cardiomyocytes (39). Another model of diabetic mice outlines IL-1β acting in a similar fashion to IL-1α in lengthening the action potential and IL-1β also diminishes the K^{+} current and upregulates Ca^{2+} entry in cardiomyocytes. These IL-1β induced modifications are responsible for arrhythmia generation. These arrhythmias can be successfully eliminated by treatment with IL-1 receptor antagonist or by inhibiting the NLRP3 inflammasome (40). IL-1β is reported to inhibit L-type Ca^{2+} channels and inhibits expression of sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) and phospholamban (41). IL-1β also leaves its effect on connexin 43 (Cx43), which is a crucial protein present in gap junctions of cardiomyocytes and is a main contributor to the unity of the cardiomyocytes allowing them to beat in synchrony as a single unit (42). Thus cardiomyocytes may be disconnected from one another as a result of IL-1β Cx43 downregulation.

Interestingly, IL-1β is upregulated during atherosclerosis and AMI. Similarly, models of atherosclerotic mice post infarction showed a threefold elevation in IL-1β levels expressed, together with a twofold decrease in Cx43 thus resulting in a corresponding elevation in ventricular arrhythmias (43). In a case-controlled study in which 122 patients had atrial fibrillation and 63 patients acted as controls, it was noted that IL-1 levels were remarkably higher in atrial fibrillation (AF) patients thus showing the great role IL-1 plays in progression of arrhythmias and atrial fibrillation amongst other cardiovascular diseases previously mentioned (44).

Conclusion

The recognition of the part IL-1 plays in inflammation together with the discovery of specific external signals which trigger the inflammatory cascade, are crucial providers for the proper apprehension of the aetiology of several human diseases. This field of study is of increasing interest within the in the medical community . The biology of IL-1 has is polarised since it provides both beneficial and destructive contributions to patients' response to infection and injury. The IL-1 cytokine family together with the NLPR3 inflammasome are vital in responding to injury and are the key contributors to the

CVDs. Pre-clinical and clinical studies of IL-1β blockade have been demonstrated to be a promising approach in in the treatment of CVDs. Thus, IL-1β inhibition presents us with promising occasions where we can combat inflammatory diseases. Patients with risk of recurrent inflammation present with elevated CRP levels and benefit immensely from IL-1 blockade. Notably, the advancements made in this area of study were immense throughout the years, but numerous questions remain unanswered, and more studies need to be implemented. For instance, whether specific inhibition of exclusive cytokines or common receptors (e.g. IL-1Ra by anakinra which blocks both IL-1α and IL-1β) represent suitable therapies in CVD has yet to be confirmed. Nonetheless, we have entered an exciting era in which the clinical benefits from decades of research done to outline the role of immune and inflammatory pathways in CVDs can be consolidated.

Declarations

Conflict of interest: N.A.

Ethical statement: N.A.

References

1. Sims JE, Smith DE. The IL-1 family: regulators of immunity 2010;10:89–102. https://doi.org/10.1038/nri2691.
2. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases 2011;117:3720–32. https://doi.org/10.1182/blood-2010-07-273417
3. Eskan A, Benakanakere MR, Rose BG, Zhang P, Zhao J, Stathopoulou P, et al. Interleukin-1beta modulates proinflammatory cytokine production in human epithelial cells 2008;76:2080–9. https://doi.org/10.1128/IAI.01428-07.
4. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family 2009;27:519–50. https://doi.org/10.1146/annurev.immunol.021908.132612.
5. Bujak M, Frangogiannis NG. The role of Interleukin-1 in the pathogenesis of heart disease 2009;57:165–76. https://doi.org/10.1007/s00005-009-0024-y.
6. Sutton CE, Lalor SJ, Sweeney CM, Brereton CF, Lavelle EC, Mills KHG. Interleukin-1 and IL-23 induce innate IL-17 production from gammadelta T cells, amplifying Th17 responses and autoimmunity 2009;31:331–41. https://doi.org/10.1016/j.immuni.2009.08.001.
7. Hirschfield GM, Pepys MB. C-reactive protein and cardiovascular disease: new insights from an old molecule 2003;96:793–807. https://doi.org/10.1093/qjmed/hcg134.
8. Ridker, P. M., Cannon, C. P., Morrow, D., Rifai, N., Rose, L. M., McCabe, C. H., Pfeffer, M. A., & Braunwald, E. (2005). C-Reactive Protein Levels and Outcomes after Statin Therapy. New England Journal of Medicine, 352(1), 20-28. 10.1056/NEJMoa042378
9. Libby , Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis 2019;5:56. https://doi.org/10.1038/s41572-019-0106-z.
10. Galea J, Armstrong J, Gadsdon P, Holden H, Francis SE, Holt CM. Interleukin-1 beta in coronary arteries of patients with ischemic heart disease 1996;16:1000–6. https://doi.org/10.1161/01.atv.16.8.1000.
11. Libby P. Interleukin-1 Beta as a Target for Atherosclerosis Therapy: Biological Basis of CANTOS and Beyond 2017;70:2278–89. https://doi.org/10.1016/j.jacc.2017.09.028.
12. Libby P. Interleukin-1 Beta as a Target for Atherosclerosis Therapy: The Biological Basis of CANTOS and Beyond 2017;70:2278–89. https://doi.org/10.1016/j.jacc.2017.09.028.
13. Chamberlain J, Francis S, Brookes Z, Shaw G, Graham D, Alp NJ, et al. Interleukin-1 Regulates Multiple Atherogenic Mechanisms in Response to Fat Feeding 2009;4:e5073. https://doi.org/10.1371/journal.pone.0005073.
14. Clarke MCH, Talib S, Figg NL, Bennett MR. Vascular smooth muscle cell apoptosis induces interleukin-1-directed inflammation: effects of hyperlipidemia-mediated inhibition of phagocytosis 2010;106:363–72. https://doi.org/10.1161/CIRCRESAHA.109.208389.
15. Abbate A, Toldo S, Marchetti C, Kron J, Van Tassell BW, Dinarello CA. Interleukin-1 and the Inflammasome as Therapeutic Targets in Cardiovascular Disease 2020;126:1260–80. https://doi.org/10.1161/CIRCRESAHA.120.315937.
16. Nicklin MJ, Hughes DE, Barton JL, Ure JM, Duff GW. Arterial inflammation in mice lacking the interleukin 1 receptor antagonist gene 2000;191:303–12. https://doi.org/10.1084/jem.191.2.303.
17. Kamari Y, Shaish A, Shemesh S, Vax E, Grosskopf I, Dotan S, et al. Reduced atherosclerosis and inflammatory cytokines in apolipoprotein-E-deficient mice lacking bone marrow-derived interleukin-1α 2011;405:197–203. https://doi.org/10.1016/j.bbrc.2011.01.008.
18. Alexander MR, Moehle CW, Johnson JL, Yang Z, Lee JK, Jackson CL, et al. Genetic inactivation of IL-1 signaling enhances atherosclerotic plaque instability and reduces outward vessel remodeling in advanced atherosclerosis in mice 2012;122:70–9. https://doi.org/10.1172/JCI43713.
19. Gomez D, Baylis RA, Durgin BG, Newman AAC, Alencar GF, Mahan S, et al. Interleukin-1β has atheroprotective effects in advanced atherosclerotic

lesions of mice 2018;24:1418–29. https://doi.org/10.1038/s41591-018-0124-5.
20. Rajamäki K, Lappalainen J, Oörni K, Välimäki E, Matikainen S, Kovanen PT, et al. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation 2010;5:e11765. https://doi.org/10.1371/journal.pone.0011765.
21. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals that form early in disease 2010;464:1357–61. https://doi.org/10.1038/nature08938.
22. Gage J, Hasu M, Thabet M, Whitman SC. Caspase-1 deficiency decreases atherosclerosis in apolipoprotein E-null mice 2012;28:222–9. https://doi.org/10.1016/j.cjca.2011.10.013.
23. Zheng F, Xing S, Gong Z, Xing Q. NLRP3 inflammasomes show high expression in aorta of patients with atherosclerosis 2013;22:746–50. https://doi.org/10.1016/j.hlc.2013.01.012
24. Menu P, Pellegrin M, Aubert J-F, Bouzourene K, Tardivel A, Mazzolai L, et al. Atherosclerosis in ApoE-deficient mice progresses independently of the NLRP3 inflammasome 2011;2:e137. https://doi.org/10.1038/cddis.2011.18.
25. Prabhu SD, Frangogiannis NG. The Biological Basis for Cardiac Repair After Myocardial Infarction: From Inflammation to Fibrosis 2016;119:91–112. https://doi.org/10.1161/CIRCRESAHA.116.303577.
26. Frangogiannis NG. Chemokines in ischemia and reperfusion 2007;97:738–47.
27. Bujak M, Frangogiannis NG. The role of Interleukin-1 in the pathogenesis of heart disease 2009;57:165–76. https://doi.org/10.1007/s00005-009-0024-y.
28. Dobaczewski M, Bujak M, Zymek P, Ren G, Entman ML, Frangogiannis NG. Extracellular matrix remodeling in canine and mouse myocardial infarcts 2006;324:475–88. https://doi.org/10.1007/s00441-005-0144-6.
29. Patti G, Mega S, Pasceri V, Nusca A, Giorgi G, Zardi EM, et al. Interleukin-1 receptor antagonist levels correlate with extent of myocardial loss in patients with acute myocardial infarction 2005;28:193–6. https://doi.org/10.1002/clc.4960280409.
30. Toldo S, Mezzaroma E, Van Tassell BW, Farkas D, Marchetti C, Voelkel NF, et al. Interleukin-1β blockade improves cardiac remodeling after myocardial infarction without interrupting the inflammasome in the mouse 2013;98:734–45. https://doi.org/10.1113/expphysiol.2012.069831.
31. Bujak M, Dobaczewski M, Chatila K, Mendoza LH, Li N, Reddy A, et al. Interleukin-1 receptor type I signaling critically regulates infarct healing and cardiac remodeling 2008;173:57–67. https://doi.org/10.2353/ajpath.2008.070974.
32. Thaik CM, Calderone A, Takahashi N, Colucci WS. Interleukin-1 beta modulates the growth and phenotype of neonatal rat cardiac myocytes 1995;96:1093–9. https://doi.org/10.1172/JCI118095.
33. Gurantz D, Cowling RT, Varki N, Frikovsky E, Moore CD, Greenberg BH. IL-1beta and TNF-alpha upregulate angiotensin II type 1 (AT1) receptors on cardiac fibroblasts and are associated with increased AT1 density in the post-MI heart 2005;38:505–15. https://doi.org/10.1016/j.yjmcc.2004.12.015.
34. Bujak M, Frangogiannis NG. The role of TGF-beta signaling in myocardial infarction and cardiac remodeling 2007;74:184–95. https://doi.org/10.1016/j.cardiores.2006.10.002.
35. Bauer J, Huy C, Brenmoehl J, Obermeier F, Bock J. Matrix metalloproteinase-1 expression induced by IL-1beta requires acid sphingomyelinase 2009;583:915–20. https://doi.org/10.1016/j.febslet.2009.02.008.
36. Berk BC, Fujiwara K, Lehoux S. ECM remodeling in hypertensive heart disease 2007;117:568–75. https://doi.org/10.1172/JCI31044.
37. Coxon A, Bolon B, Estrada J, Kaufman S, Scully S, Rattan A, et al. Inhibition of interleukin-1 but not tumor necrosis factor suppresses neovascularization in rat models of corneal angiogenesis and adjuvant arthritis 2002;46:2604–12. https://doi.org/10.1002/art.10546
38. Szekely Y, Arbel Y. A Review of Interleukin-1 in Heart Disease: Where Do We Stand Today? 2018;7:25–44. https://doi.org/10.1007/s40119-018-0104-3.
39. Mitrokhin VM, Mladenov MI, Kamkin AG. IL-1 provokes electrical abnormalities in rat atrial myocardium 2015;28:780–4. https://doi.org/10.1016/j.intimp.2015.08.006.
40. Monnerat G, Alarcón ML, Vasconcellos LR, Hochman-Mendez C, Brasil G, Bassani RA, et al. Macrophage-dependent IL-1β production induces cardiac arrhythmias in diabetic mice 2016;7:13344. https://doi.org/10.1038/ncomms13344.
41. Buckley, L. F., & Abbate, A. (2018). Interleukin-1 Blockade in Cardiovascular Diseases: From Bench to Bedside. BioDrugs: Clinical Immunotherapeutics, Biopharmaceuticals and Gene Therapy, 32(2), 111-118. 10.1007/s40259-018-0274-5. https://doi.org/10.1007/s40259-018-0274-5
42. Baum JR, Long B, Cabo C, Duffy HS. Myofibroblasts cause heterogeneous Cx43 reduction and are unlikely to be coupled to myocytes in the healing canine infarct 2011;302:H790–800. https://doi.org/10.1152/ajpheart.00498.2011.
43. De Jesus NM, Wang L, Herren AW, Wang J, Shenasa F, Bers DM, et al. Atherosclerosis exacerbates arrhythmia following myocardial infarction: Role of myocardial inflammation 2015;12:169–78. https://doi.org/10.1016/j.hrthm.2014.10.007.
44. Cheng T, Wang X-F, Hou Y-T, Zhang L. Correlation between atrial fibrillation, serum amyloid protein A and other inflammatory cytokines 2012;6:581–4. https://doi.org/10.3892/mmr.2012.934.