Biomolecular Paradigm of Active Resolution Mechanisms in Heart

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Inflammation is a complex program of active processes characterized by the well-orchestrated succession of an initiation and a resolution phase aiming to promote homeostasis. When the resolution of inflammation fails, the tissue undergoes an unresolved inflammatory status which, if it remains uncontrolled, can lead to chronic inflammatory disorders due to aggravation of structural damages, development of a fibrous area, and loss of function. Various human conditions show a typical unresolved inflammatory profile. Inflammatory diseases include cancer, neurodegenerative disease, asthma, right heart disease, atherosclerosis, myocardial infarction, or atrial fibrillation. New evidence has started to emerge on the role, including pro-resolution involvement of chemical mediators in the acute phase of inflammation. Although flourishing knowledge is available about the role of specialized pro-resolving mediators in neurodegenerative diseases, atherosclerosis, obesity, or hepatic fibrosis, little is known about their efficacy to combat inflammation-associated arrhythmogenic cardiac disorders. It has been shown that resolvins, including RvD1, RvE1, or Mar1, are bioactive mediators of resolution. Resolvins can stop neutrophil activation and infiltration, stimulate monocytes polarization into anti-inflammatory-M2-macrophages, and activate macrophage phagocytosis of inflammation-debris and neutrophils to promote efferocytosis and clearance.

Keywords: inflammation ; right heart disease ; atrial fibrillation ; resolution ; arrhythmias ; specialized pro-resolving mediators ; resolvins

1. Introduction

Cardiac diseases, including atrial fibrillation (AF), the most common form of arrhythmia, are characterized by an unresolved inflammatory status [1][2][3]. In response to cardiac injury, apoptotic cardiomyocytes (CM) contribute to activating the inflammatory status regulated by pro-inflammatory signals released by cardiac cells and recruited inflammatory cells [4]. These events characterize the acute phase of inflammation, aiming to promote wound cleaning and to start the healing process [5]. Resolution-promoting signals are then secreted to stop acute inflammation via the initiation of the resolution phase, allowing the maintenance of homeostasis [6]. Cardiac fibroblasts (FB) are sensitive to circulating and CM-originated inflammatory signals [7]. When resolution is successfully activated, pro-resolution processes promote FB-secreted collagenous material to consolidate the extracellular matrix, compensate for the loss of apoptotic CM, and preserve the mechanical stability of the myocardium to protect the heart from rupture and failure [5][8]. In contrast, myocardial remodeling could become dangerous when the acute inflammatory period is prolonged and when the resolution response fails to occur [5][9]. This can lead to a switch into a persistent inflammatory status instead of resolving the inflammation [5][10].

Chronic inflammatory signals promote fibrotic tissue deposition, constituting a “stiff” layer on the myocardium [11]. Such fibrous zones are non-contractile and electrical insulator areas that disrupt the normal propagation of action potential can cause conduction slowing, refractoriness and AF [12][13] (**Figure 1**). Pro-resolution therapeutic strategies are poorly described in the field of anti-arrhythmic drug-development and arrhythmia-management.

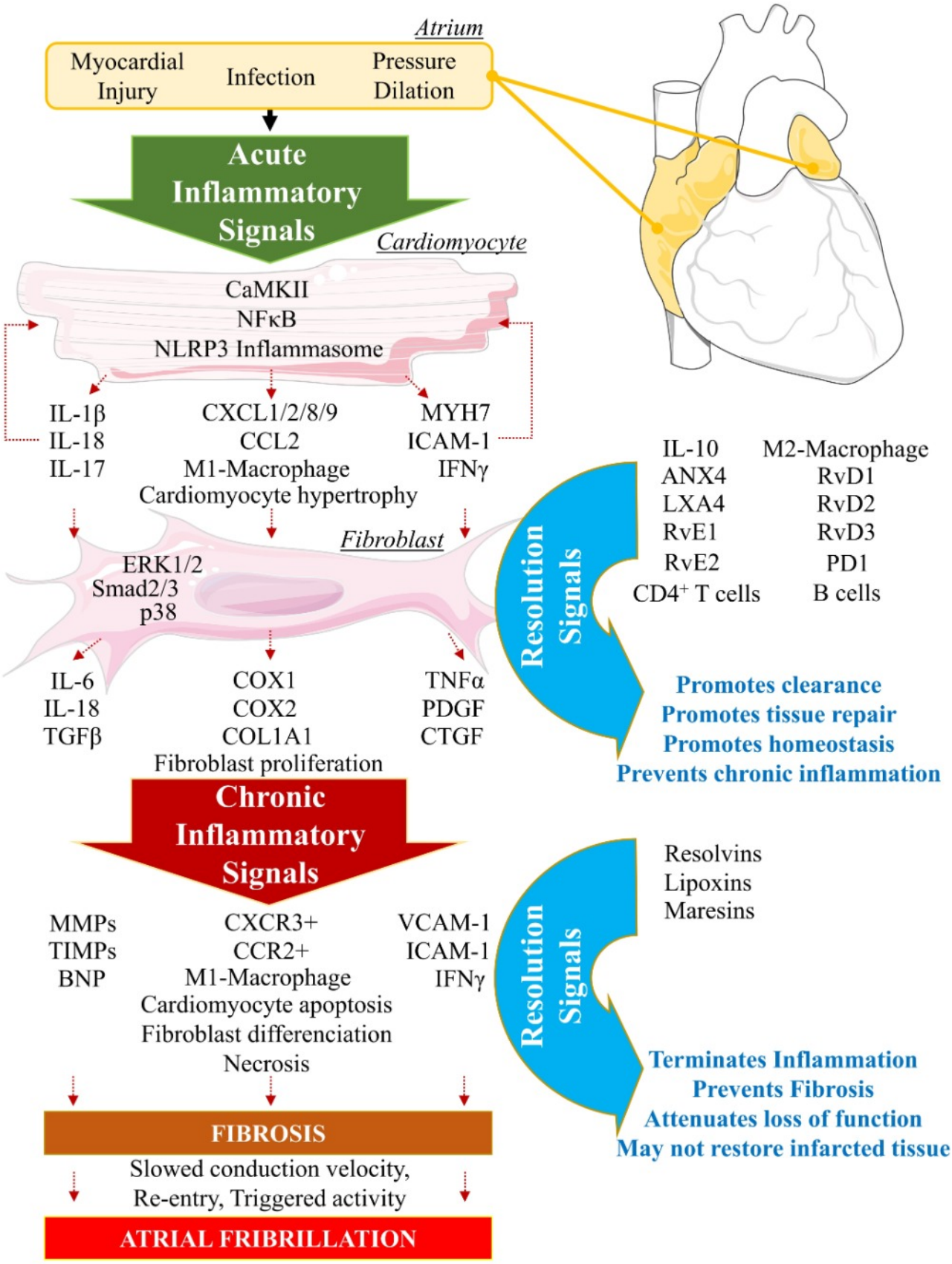

Figure 1. Biomolecular orchestration of cellular events from cardiac insult to resolution opposed to persistent arrhythmogenic inflammation. Longstanding exposure of the atrium to myocardial injuries, infections or chronic pressure and dilation provokes the normal initiation of acute inflammation. In cardiomyocytes (CM), intracellular inflammatory response involves CamKII, NF-kB or NLRP3 inflammasome pathways activation, which contribute to CM deregulation of structural genes (*Myh7*), and secretion of proinflammatory cytokines including interleukins (IL-1β, IL-18) and chemokines (CXCL, CCL), leading to promotion of proinflammatory (M1)-macrophage infiltration. Proinflammatory signals contribute to the activation of cardiac fibroblasts (FB). FB activate additional pro-inflammatory signals (TGFβ, TNFα, PDGF) provoking FB differentiation into myo-FB, aiming to promote repair and wound healing, if the resolution signals are properly activated in response to inflammation initiation. Resolution mediators, including IL-10, LXA4, D- and E-series resolvins, contribute to terminate M1-macrophages infiltration, facilitate anti-inflammatory (M2)-macrophages polarization and phagocytosis, while activating CD4+ T cells and B cells efferocytosis, leading to homeostasis. When Resolution fails to occur, inflammation is

perpetuated via FB and myoFB secretion of chronic-inflammation-promoting mediators (MMPs, IFNγ, CXCR3+, M1-macrophages) leading to CM necrosis, and loss of function. Resolution signals can be promoted to limit chronic inflammation-induced damages. If failed resolution mechanisms persist, the myocardium is exposed to the development of fibrosis, slowed conduction velocity, triggered activity, re-entry and increased susceptibility to arrhythmias, including atrial fibrillation.

Among cardiac disorders with an important inflammatory impact, right heart disease (RHD) is a pathological condition in which the right ventricle (RV) suffers from a structural and electrical remodeling that strongly affects cardiac physiological functions [14]. Right heart structure, heart chambers, and the circulatory system are vulnerable to morphological modifications that may result from hypertension-promoting cardiac conditions, including pulmonary artery hypertension (PAH), chronic obstructive pulmonary disease (COPD) or pulmonary embolism [15]. Volume- and pressure-overload conditions associated with structural remodeling negatively impacts the cardiac function, particularly because of the induced inflammatory status, and can potentially result in myocardial fibrosis in response to a chronic rise in blood pressure, myocardial tissue stretching, or myocardial injury [16]. In the RV and the right atrium (RA), electrical remodeling is at the origin of potential tachycardia and arrhythmias, including ventricular fibrillation or/and atrial fibrillation (VF and AF) [17][18]. In response to structural remodeling, pro-inflammatory cytokines, and chemokines such as IL-1β, IL6, IL18, TGF-β, or CXCL1/2 stimulate fibroblasts (FB) differentiation into myofibroblasts (myo-FB) associated with a gradual loss of function in the myocardium [19][20]. Events and conditions promoting the development of cardiac fibrosis in the atrial tissue are associated with arrhythmogenic structural and functional modifications, promoting AF [3][21][22] (**Figure 1**).

2. Biomolecular Paradigm of Active Resolution Mechanisms in the Heart

2.1. Initiation Phase of Inflammation: Central Regulatory Role of Arachidonic Acid

During the initiation of acute inflammation, phospholipase A2 (PLA2) levels are increased at the site of injury [23]. PLA2 produces arachidonic acid (AA: 5, 8, 11, 14-eicosatetraenoic acid) by hydrolyzation of the sn-2 ester bond of cellular phospholipids [23]. Patients with coronary artery disease show increased levels of lipoprotein-associated PLA2 (Lp-PLA2) [24]. Elevated levels of Lp-PLA2 have been suggested as an important risk factor of cardiovascular diseases [25]. Paradoxically, when Lp-PLA2 hydrolyzes the platelet-activating factor (PAF), its enzymatic activity is associated with anti-inflammatory properties [26]. The underlying mechanisms governing this paradox will be discussed below.

2.1.1. Arachidonic Acid Metabolism by Cytochrome P450

AA is an essential polyunsaturated fatty acid (omega-6 PUFA) that can interact with cytochrome P450 (CYP450) enzymes to undergo monooxygenation or epoxidation and produce hydroxyeicosatetraenoic acids (19- and 20-HETEs) and dihydroxyeicosatrienoic acid (diHETrEs) [27] (**Figure 2**). These molecules act as hormone-like autocrine and paracrine agents to promote vasoconstriction, vascular permeability, polymorphonuclear leukocytes (PMN), and proinflammatory (M1)-macrophages chemotaxis, and proinflammatory signaling [28].

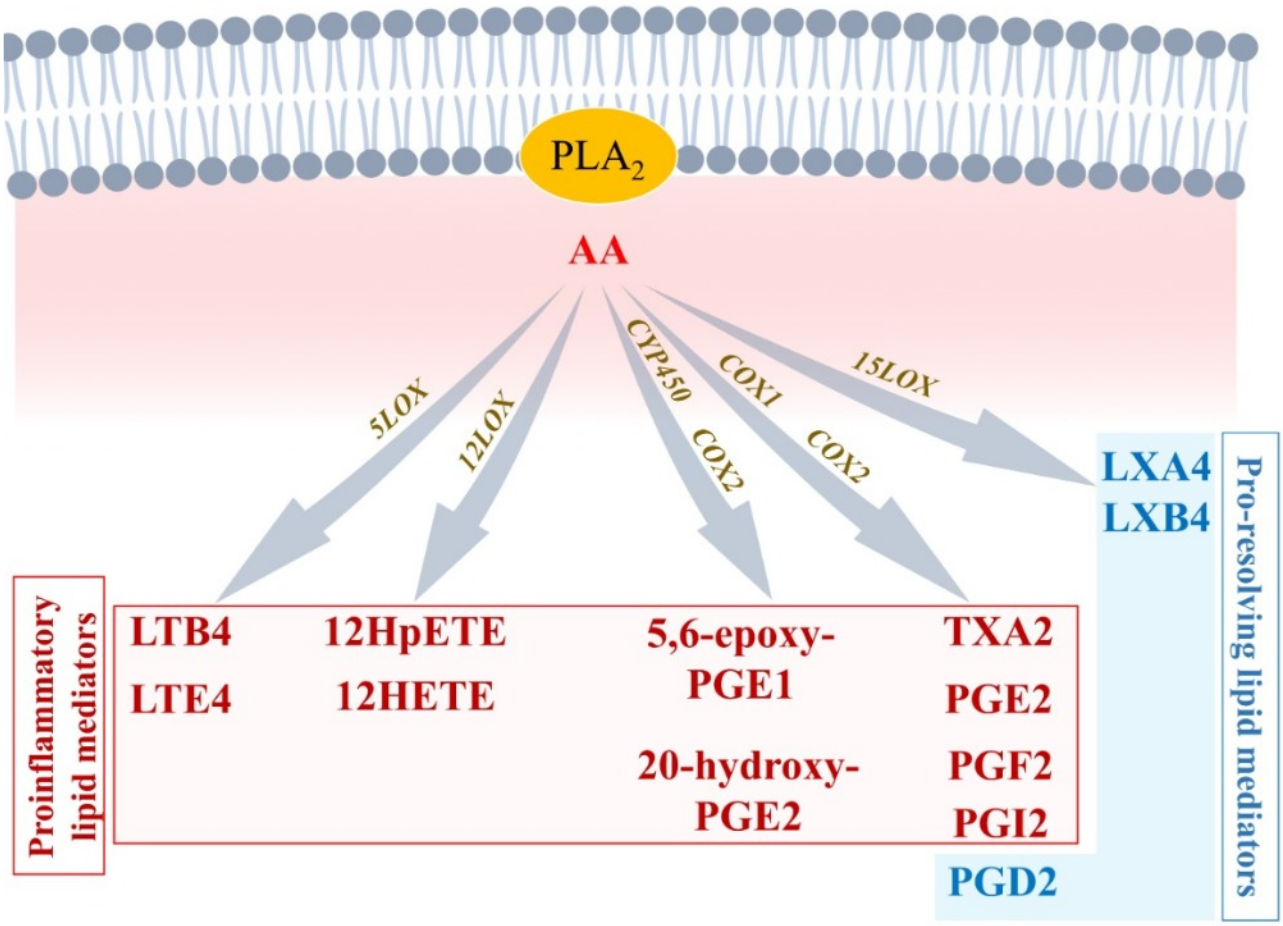

Figure 2. Arachidonic acid-derived lipid mediators. Arachidonic acid (AA) interaction with COX1, COX2, 5LOX, 12LOX, or CYP450 enzymes mainly leads to the production of proinflammatory lipid mediators including leukotrienes, thromboxanes, and prostaglandins. AA interaction with COX1/2 or 15LOX can generate pro-resolution mediators including PDG2, LXA4, and LXB4.

2.1.2. Arachidonic Acid Metabolism by COX1 and COX2

AA can directly interact with COX1 and COX2 to produce prostaglandin H2 (PGH2), an intermediate metabolite that is converted into bioactive proinflammatory lipid mediators such as thromboxane A_2 (TXA_2), prostaglandin A_2 (PGA_2), PGB_2, PGE_2, and PGI_2 (**Figure 2**). These AA metabolites have been shown to be elevated in various cardiovascular conditions, including hypertension, atherosclerosis, vasculopathy, and myocardial infarction [29]. AA-derived lipids mediate vasoconstriction, increase vascular permeability, and stimulate expression of proinflammatory chemokines (complement component (C): C3b, C5a; chemokine C-X-C motif ligand 1 (CXCL1), CXCL2, CXCL8) and interleukins (IL1β, IL6, IL8, IL18, tumor necrosis factor alpha (TNFα)) to promote polymorphonuclear leukocytes (PMN) and proinflammatory-(M1)-macrophages chemotaxis and adhesion, by increasing expression of intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion molecule 1 (VCAM1), and e-selectin (SELE), which act on endothelial cells to promote the adherence of neutrophils to the blood vessel wall [29][30]. These inflammatory biomarkers have been described to promote the development and progression of cardiovascular diseases including cardiac arrhythmias and AF [11][12][22].

2.1.3. Arachidonic Acid Metabolism by 5-LOX

AA can also interact with 5-LOX to produce 5-Hydroperoxyeicosatetraenoic acid (5-HpETE), which promotes vasoconstriction. 5-HpETE can be metabolized either by leukotriene (LT) C-synthase to produce LTC4, LTD4, and LTE4, or by LTA-hydrolase to produce LTB4 via LTA4, which are all leukotrienes playing proinflammatory properties by amplifying PMN and M1 macrophages influx in the injured tissue [31] (**Figure 2**). HETEs have been shown to activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) signaling to promote abnormal CM hypertrophy [32].

Evidence shows that AA-derived metabolites' receptors are expressed on most cardiac cells including CM and FB [33]. In CM, inflammation signaling promotes NFκB activity and the assembling of the NACHT, LRR, and PYD domains containing protein 3 (NLRP3) inflammasome, leading to secretion of IL-1β and increased inflammatory status [34]. Patients with AF have shown increased expression of IL-1β and NLRP3 inflammasome components [35]. Normal initiation of inflammation must be followed by bio-molecularly orchestrated cellular processes aiming to terminate the inflammatory state and

promote resolution [36]. In this purpose, lipid-mediator (LM) class switching is a key event that could be defined as a transition phase between the end of inflammation-initiation and the beginning of resolution [37].

2.2. Lipid-Mediator Class Switching: Transition from Pro-Inflammatory to Pro-Resolution Signals

During the initiation phase of inflammation, neutrophils have an intense apoptotic and phagocytic activity [38]. This activates intracellular accumulation and extracellular secretion of 12/15-LOX in the damaged tissue. This accumulation of 12/15-LOX activates lipid-mediator-class switching from proinflammatory to pro-resolution mediators [39]. AA is then enzymatically metabolized by 12/15-LOX into lipoxins, including lipoxin (LX) A4 and LXB4 (**Figure 2**). LXA4 activates its transmembrane specific-receptor lipoxin A4 receptor or formyl peptide receptor 2 (ALX/FPR2) expressed on PMN and macrophages to limit further leukocyte trafficking, stimulate monocyte recruitment, promote anti-inflammatory (M2)-macrophage polarization, and activate phagocytosis and elimination of debris [39]. LXA4 has been shown to be significantly decreased in patients with chronic heart failure [40]. Recent studies have shown that LXA4 attenuates myocarditis by inhibiting NFκB and PI3K/Akt signaling pathways. 15-epi-LXA4 promotes initiation of resolution after myocardial infarction [41][42]. This activity of LXA4 suggests that, in arrhythmogenic conditions, anti-resolution signals promote the diminution of LXA4 production or/and LXA4-associated activity and signaling [42]. LXA4 could be an interesting candidate in the prevention of inflammation-induced substrate of arrhythmias, including AF.

2.3. Resolution of Inflammation: SPMs-Mediated Efferocytosis and Homeostasis

Along with AA, other essential n3PUFAs are delivered with edema fluids at the site of injury. Among them, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) compete with AA to be enzymatically metabolized by either CYP450, 5LOX, 12LOX, 15LOX, or aspirin-acetylated COX2 [43]. Knowing that AA-derived metabolites are crucial in the initiation of normal inflammation, and that EPA and DHA products are important in resolution, it is understandable that optimal healthy conditions must promote a fair balance between AA, EPA, and DHA concentrations. Hence, in opposition to what has long been thought, it is not recommended to completely annihilate AA-derived metabolites (i.e., by using COX inhibitors) to guaranty homeostasis [44] (**Figure 2** and **Figure 3**).

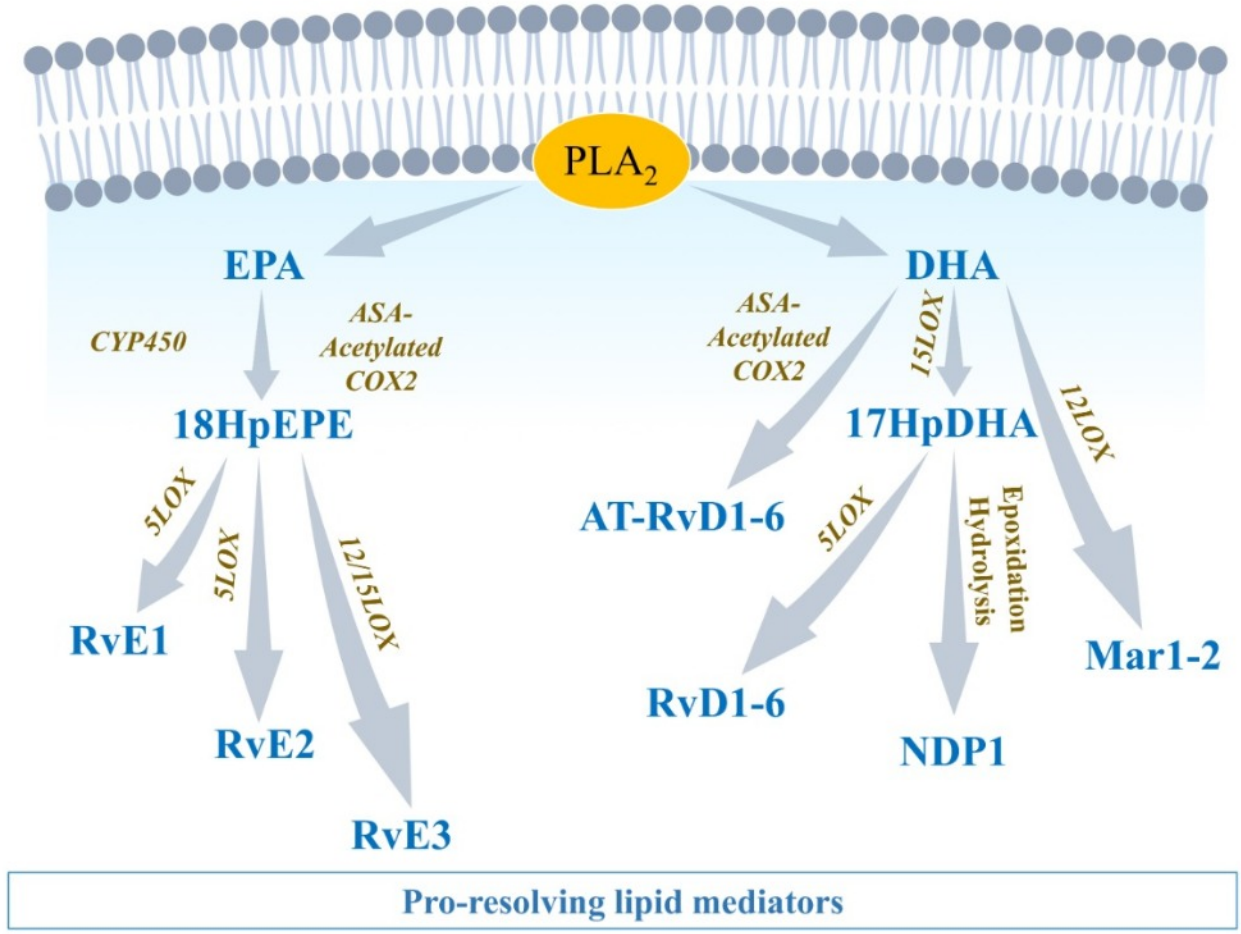

Figure 3. Eicosapentaenoic acid-, and docosahexaenoic acid-derived lipid mediators Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) compete with AA in interacting with COX1/2, 5LOX, 12LOX, and 15LOX. Lipids produced from EPA and DHA metabolism include E-series resolvins (RvE1-3) and D-series resolvins (RvD1-6), respectively, which are involved in pro-resolution mechanisms.

2.3.1. EPA-Derived Specialized Pro-Resolving Mediators

EPA is metabolized by CYP450 or aspirin-[ASA]-acetylated COX-2 into 18-HpEPE (18R-hydroperoxy-5Z, 8Z, 11Z, 14Z, 16E-eicosapentaenoic acid), which itself can interact with either 5LOX to produce E-series resolvins (Rvs), RvE1 and RvE2 or 15LOX to produce RvE3. E-series Rvs activate specific receptors such as chemokine-like receptor 1 (CMKLR1), also known as chemerin receptor 23 (ChemR23) (receptor of RvE1), or antagonize proinflammatory leukotriene receptors, such as leukotriene B4 receptor 1 (BLT1), expressed on PMN cell membrane, to stop the expression of chemoattractants, limit neutrophils adhesion/infiltration, and promote phagocytosis of apoptotic neutrophils and efferocytosis [45] (**Figure 3**).

2.3.2. DHA-Derived Specialized Pro-Resolving Mediators

DHA can be metabolized by 12LOX to produce maresins (MaR1-2), or 15LOX to produce D-series resolvins (RvD1-6) and neuroprotectin D1 (NPD1) [46]. DHA interaction with aspirin-acetylated COX2 results in aspirin-triggered resolvins (AT-RvD1-6), which have been described to have similar properties as their classic homologs of the D-series Rvs [47] (**Figure 3**). D-series resolvins activate specific receptors such as ALX/FPR2 (receptor of RvD1), G-protein-coupled receptor 32 (GPR32: receptor of RvD1 and RvD3), and GPR18 (receptor of RvD2) that are expressed on vascular endothelial cells [37]. The activation of these signals promotes eNOS and P-ERK1/2 signaling, vascular permeability to non-phlogistic monocytes, cessation of PMN infiltration, macrophage polarization into M2-macrophages, M2-macrophages phagocytosis of cellular debris, and maintenance of homeostasis [37][45] (**Figure 4**).

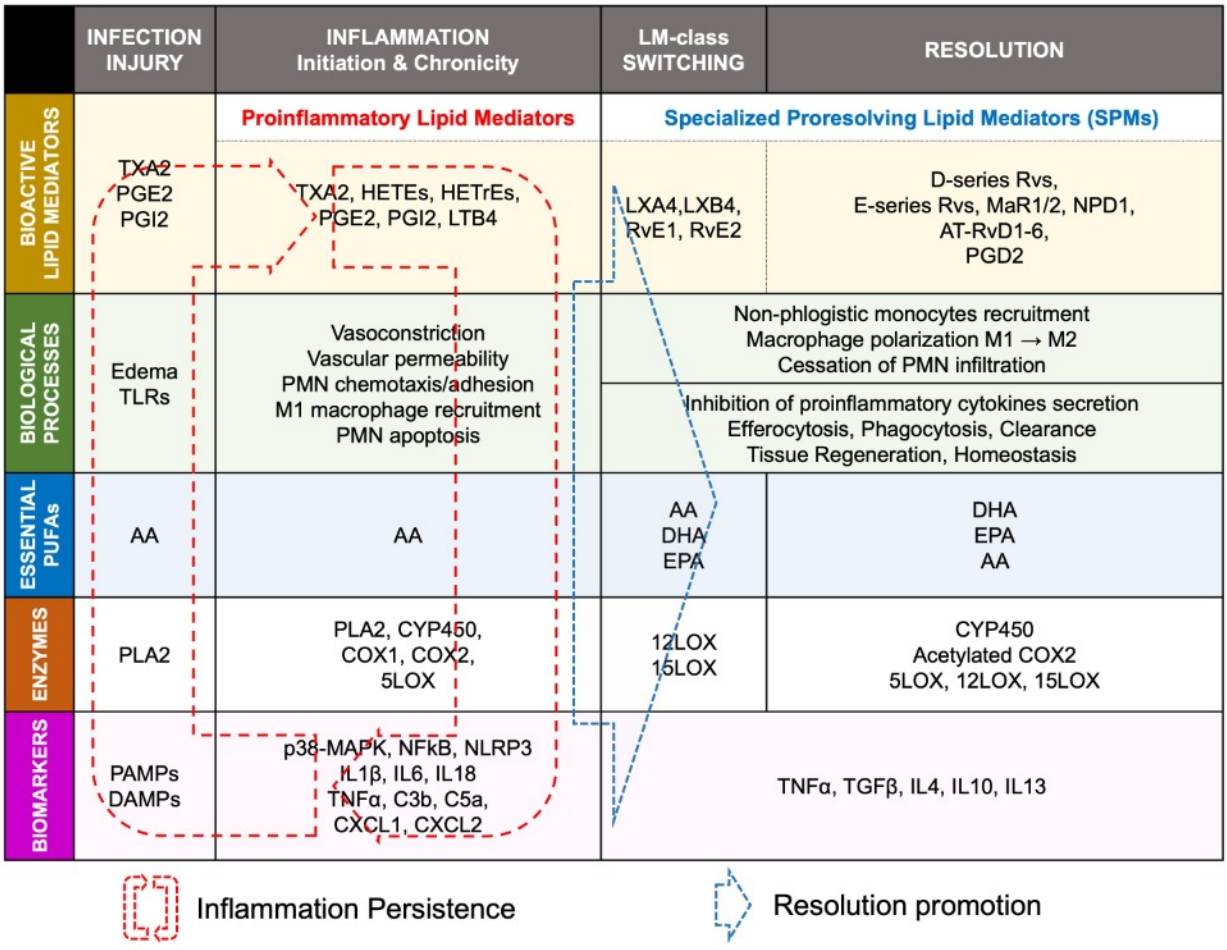

Figure 4. Categorization of inflammation- and resolution-promoting agents. In response to pathogens or injury stimuli (PAMPs, DAMPs), phospholipase A2 (PLA2)-induced biosynthesis of arachidonic acid (AA) leads to the production of proinflammatory lipid mediators including thromboxanes, leukotrienes, and prostaglandins. Such events mark the initiation phase of acute inflammation characterized by PMN chemotaxis, pro-inflammatory-[M1]-macrophages recruitment, and enhanced proinflammatory signals (NLRP3 inflammasome, NF-κB, IL-1β, CXCL1/2). Phagocytic M1-macrophages release 12/15 LOX, which promotes the activation of lipid-mediators (LM) class switching, where AA, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) interact with 12LOX and 15LOX enzymes to be metabolized into specialized pro-resolving mediators (SPMs) including PGD2 from AA, D-series resolvins from DHA, or E-series resolvins from EPA. SPMs promote anti-inflammatory (M2)-macrophage recruitment, inhibition of proinflammatory cytokines' secretion, termination of inflammation, and regeneration of optimal functions. When the resolution mechanisms fail to occur, inflammation is perpetuated. Inflammatory mediators are overexpressed, leading to persistence of cellular damages, necrosis, fibrosis, loss of function and cardiac vulnerability to arrhythmias, and heart failure. Strategies

promoting the augmentation of pro-resolution mechanisms can potentially limit, or eventually reverse, some chronic-inflammation-induced cardiac disorders.

2.3.3. Arachidonic Acid-Derived Specialized Pro-Resolving Mediators

The metabolism of AA by COX does not only generate proinflammatory components. PGD2 has been shown to play an important role in resolution of inflammation [48]. PGD2 interacts with prostaglandin-D2-receptor 1 and 2 (DP1/2) expressed on T helper type (Th2) cells and dendritic cells that are involved in efferocytosis, phagocytosis, and clearance, to promote elimination of debris and pathogens, and induce complete resolution [48]. The interaction of AA with CYP450 can lead to production of epoxyeicosatrienoic acids (EETs) that are converted by soluble epoxide hydrolase (sEH) into dihydroxyeicosatrienoic acids (DiHETrEs). Although DiHETrEs are toxic, it has been shown that EETs mostly play a beneficial role by promoting vasorelaxation, and cardioprotective effects [49] (**Figure 2** and **Figure 4**).

2.4. 'Failed Resolution Mechanisms' in the Development of Chronic Inflammation and Heart Diseases

Lipid mediator (LM) production and signaling are fundamental in the regulation of the normal process of acute inflammation from its initiation to its resolution [46]. When the cardiac tissue undergoes a chronic inflammatory status, the crucial phase of LM class switching, which promotes the end of PMN infiltration and the activation of efferocytosis, may have failed to promote the shift of the cellular and lipidic accumulation from proinflammatory to pro-resolution mediators in the injured tissue [39]. Pathologic failure in the production of 12/15 LOX by immune cells including eosinophils, PMN, lymphocytes, and macrophages, leads to a lack of metabolization of AA into lipoxins (LXA4, LXB4) [38]. Lipoxins are essential to activate the cessation of neutrophil recruitment and the infiltration of non-phlogistic monocytes in the site of injury, which is the first step of resolution [38][39]. Moreover, lack of 12/15LOX prevents the production of D-series Rvs from DHA and RvE3 from EPA [38][50] (**Figure 3**). This may contribute to an annihilate resolution. Then, more proinflammatory LMs (Prostaglandins, leukotrienes) are produced from AA enzymatic interactions with the other enzymes available (COX2, CYP450, 5LOX) [50]. Abnormal accumulation of proinflammatory signaling promotes the prolongation of the initiation phase, characterized by the persistence of the external, cellular, and molecular signs of inflammation. This chronic inflammatory status leads to the development of fibrosis and loss of function [40][50]. If the local production of 12/15LOX is restored, or if the bioavailability of resolvins and lipoxins is increased (from diet or endogenous biosynthesis) at the site of injury, the tissue may enter the resolution phase via termination of proinflammatory signals, reduction of fibrosis, wound healing, and restoration of homeostasis [39][51][52] (**Figure 1** and **Figure 4**).

The detailed biomolecular characterization of inflammation–resolution remains partially understood in cardiac conditions. Moreover, each cardiac disease may display specific biomarkers involved in the incidence of the disorder. Although recent studies suggest a role of SPMs in ischemia-reperfusion [42][53] and pulmonary arterial hypertension-induced right atrial arrhythmogenic substrate [54], further fundamental research and clinical studies are required to assess whether resolution-promoting strategies and cytokine therapies could be an efficient approach to prevent and treat cardiac diseases, including hypertrophic cardiomyopathy, dilated cardiomyopathy, valvopathy, myocardial infarction, or arrhythmias.

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