Specialized Pro-resolving Mediators in Atherosclerosis

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Atherosclerosis is one of the most important problems of modern medicine as it is the leading cause of hospitalizations, disability, and mortality. The key role in the development and progression of atherosclerosis is the imbalance between the activation of inflammation in the vascular wall and the mechanisms of its control. The resolution of inflammation is the most important physiological mechanism that is impaired in atherosclerosis. The resolution of inflammation has complex, not fully known mechanisms, in which lipid mediators derived from polyunsaturated fatty acids (PUFAs) play an important role. Specialized pro-resolving mediators (SPMs) represent a group of substances that carry out inflammation resolution and may play an important role in the pathogenesis of atherosclerosis. SPMs include lipoxins, resolvins, maresins, and protectins, which are formed from PUFAs and regulate many processes related to the active resolution of inflammation.

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1. Lipoxins

Lipoxins are the first identified class of SPMs. The chemical structure of lipoxins includes three hydroxyl residues and four double bonds. The origin from ω-6 arachidonic acid and the above structural features distinguish lipoxins from other SPMs, which are formed from ω-3 fatty acids.

Lipoxins are synthesized in two major pathways by the sequential action of lipoxygenase (LOX) enzymes, including 5-, 12-, and 15-LOX. The first pathway involves the enzymatic conversion of leukotriene A4 by 12-LOX [1]. The second pathway of lipoxin synthesis involves the action of 15-LOX and 5-LOX on arachidonic acid [2].

As previously noted, the subcellular localization of 5-LOX is at the intersection of pathways that determine the formation of pro-inflammatory leukotrienes or pro-resolving lipoxins. In particular, the nuclear localization of 5-LOX contributes to the biosynthesis of pro-inflammatory leukotriene [3]. This is because nuclear 5-LOX is located near the leukotriene A4 hydrolase, which leads to the conversion of arachidonic acid to leukotrienes (LTB4) [4][5][6]. The nuclear localization of 5-LOX is associated with its phosphorylation at Ser^{271} by MAPK-activated protein kinase 2 (MK2), which can be stimulated by MAPK p38 activation [3][5][6][7][8][9][10]. In contrast, the cytoplasmic localization of the unphosphorylated form of 5-LOX is associated with SPM formation. This is due to the proximity of 5-LOX to 12/15-LOX at the cytoplasmic localization, which promotes the conversion of LTA4 to LXA4.

It should be noted that 5-LOX activation is associated with five lipoxygenase activating protein (FLAP), which acts as an arachidonic acid transfer protein [11]. FLAP is a nuclear membrane protein and is required for the synthesis of both LT and LXA4/RvD1 [12]. Polymorphisms of the *ALOX5AP* gene encoding FLAP contribute to the risk of coronary heart disease in patients with familial hypercholesterolemia, as well as the development of myocardial infarction [13][14][15]. The FLAP antagonist BRP-201 causes a switch in the class of lipid mediators produced in human macrophages, shifting LT biosynthesis toward SPMs [16]. This may be related not only to FLAP inhibition but also to the stimulation of 15-LOX-1 activity in M2 macrophages [16].

Interestingly, however, the activation of MerTK in human macrophages, which is a macrophage receptor that mediates efferocytosis, leads to the ERK-mediated expression of sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2), which decreases cytosolic Ca^{2+} concentration [3]. This in turn suppressed Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) activity and reduced MAPK p38 and MK2 kinase activity. The resulting effect is an increase in the amount of the unphosphorylated cytoplasmic form of 5-LOX and an increase in SPM formation [3]. Thus, MerTK signaling in macrophages promotes the production of 5-LOX-derived SPMs and contributes to the process of inflammation resolution [17]. This has important implications for the coordination of the different mechanisms involved in the resolution of inflammation.

Lipoxin A4 (LXA4 or (5S,6R,15S)-Trihydroxy-(7E,9E,11Z,13E)-eicosatetraenoic acid) and lipoxin B4 (LXB4 or (5S,6E,8Z,10E,12E,14R,15S)-5,14,15-Trihydroxy-6,8,10,12- icosatetraenoic acid) have currently been identified. In addition, their epimers, such as 15-epi-LXA4 and 15-epi-LXB4, are known. The formation of lipoxin epimers is associated with an aspirin-dependent pathway, which is an important therapeutic effect of this medicine [18]. Aspirin modifies cyclooxygenase-2 (COX2) by acetylation in Ser^{530}. This modification, limits the access of arachidonic acid to the catalytic core of COX-2 and promotes the switch from the production of PGH2, a prostaglandin precursor, to 15-R-HETE ((15R)-15-hydroxy-5,8,11-cis-13-trans-eicosatetraenoic acid), which is then converted by 5-LOX to 15-epi-LXA4 [19][20]. This pathway can be realized during intercellular interactions between leukocytes and endothelial cells [18]. In this case, the transcellular biosynthesis of aspirin-triggered lipoxins (ATLs) is carried out through the formation of 15R-HETE by the endothelium and its delivery to the adherent leukocytes [18][21]. In turn, 15-epi-lipoxin A4 via eNOS and iNOS induces NO synthesis, which mediates the anti-inflammatory effects of aspirin by negatively regulating leukocyte–endothelial interaction [22].

Statins, such as atorvastatin, also have the ability to enhance 15-epi-LXA4 formation. It is known that 15-epi-LXA4 is formed from 15R-HETE by the action of 5-LOX. By regulating and activating COX-2 and 5-LOX, statins can demonstrate anti-inflammatory and anti-atherosclerotic actions [19]. In addition, lovastatin increased the levels of 14,15-EET via CYP450, which increased the production of 15-epi-LXA4, which, however, has been shown in airway mucosa and requires additional research [23]. Moreover, the phosphorylation of 5-LOX at Ser^{523} by protein kinase A (PKA), which is induced by atorvastatin and pioglitazone, determines the formation of the anti-inflammatory 15-epi-LXA4 or pro-inflammatory LTB4 [24]. Atorvastatin and pioglitazone have been shown to increase 5-LOX levels in the cytosolic fraction [24]. This is because phosphorylation at Ser^{271} can promote [5][25], and phosphorylation at Ser^{523} by protein kinase A inhibits the nuclear import of 5-LOX [26][27].

Lipoxins and epi-lipoxins exert their action through the lipoxin A4 receptor/formyl peptide receptor 2 (ALX/FPR2, also called ALX receptor, FPR2 receptor, ALX/FPR, and FPRL1) [28]. The ALX/FPR2 mRNA levels were shown to be significantly elevated in atherosclerotic lesions compared with control healthy vessels. Moreover, in the region of human atherosclerotic lesions, ALX/FPR2 was expressed primarily on macrophages, as well as on VSMCs and endothelial cells [29]. The results suggest a dual role of ALX/FPR2 signaling in atherosclerosis. It is to promote disease progression by increasing the size of the atherosclerotic lesion, but atherosclerosis is characterized by a more stable plaque phenotype [30]. This is consistent with evidence that ALX/FPR2 promotes pro-inflammatory signaling in leukocytes, leading to accelerated atherosclerosis, while ALX/FPR2 expression in VSMCs potentially increased plaque stability [30]. Notably, in addition to transducing the anti-inflammatory effects of LXA4, the ALX/FPR2 receptor may also mediate the pro-inflammatory effects of serum amyloid A (SAA) and several other peptides [31][32][33][34][35].

In addition to ALX/FPR2, lipoxin A4 is considered as a ligand of the aryl hydrocarbon receptor (AhR) [36]. ATLs also bind to the CysLT1 receptor (Cysteinyl leukotriene receptor 1), while competing with leukotriene LTD4 [37]. A higher expression of the CysLT1 receptor has been reported in human carotid atherosclerotic lesions. This is consistent with evidence that the pro-inflammatory environment in atherosclerosis contributes to increased CysLT1 receptor expression through the stimulation of VSMCs [38][39]. For example, LPS stimulation has been shown to induce CysLT1 receptor expression in human coronary artery VSMCs [39][40].

LXA4 and LXB4 are characterized by multiple anti-inflammatory effects. They contribute to the inhibition of neutrophil transendothelial migration stimulated by LTB4 [41]. Although neutrophils are rarely found in atherosclerotic plaques, they are actively involved in the pathogenesis of atherosclerosis by contributing to inflammation [42]. Neutrophils also contribute to the destabilization of atherosclerotic plaques [43]. In contrast to the fact that LTC4 and LTD4 increased the adhesion of PMN to the endothelium, partially stimulating the mobilization of P-selectin, lipoxins can weaken the P-selectin-mediated adhesion of PMN to endothelial cells [41]. Lipoxin A4 and 15-epi-lipoxin A4 have been shown to modulate the expression of adhesion molecules on human leukocytes in whole blood and to inhibit neutrophil adhesion to endothelial cells [44]. Lipoxin A4 and lipoxin B4 inhibit neutrophil chemotactic responses stimulated by leukotriene B4 and N-formyl-L-methionyl-L-leucyl-L-phenylalanine [45]. In addition, LXA4, 15-epi-LXA4, and their synthetic analogues selectively reduce azurophilic PMN degranulation [46].

It should be noted that lipoxins have different effects on PMN and monocytes [47]. In contrast to the described effect on PMN, LXA4 and LXB4 stimulate monocyte chemotaxis and adhesion, which may play a role in physiological monocyte movement and/or pathological processes [47]. In addition, lipoxins increase the uptake of apoptotic neutrophils by macrophages [48], which promotes the clearance of apoptotic leukocytes by macrophages at the site of inflammation [48][49][50].

LXA4 and 15-epi-LXA4 also inhibit peroxynitrite formation, nuclear factor-κB (NF-kB) and AP-1 (activator protein-1) activation, and *IL-8* gene expression in leukocytes [51]. In addition, ATLs can impair angiogenesis by inhibiting endothelial cell proliferation and migration [52].

Recent studies convincingly show that VSMCs are actively involved in the pathogenesis of atherosclerosis [53]. They are the main cell type that is present at all stages of atherosclerotic plaque development. VSMCs exhibit phenotypic plasticity [54]. The cells derived from VSMCs are the main source of atherosclerotic plaque cells and the extracellular matrix [54]. VSMCs have been shown to have specific receptors for ATLs and resolvin E1, such as ALX/FPR2 and ChemR23. Because of this, ATLs and resolvin E1 can act on VSMCs to provide a protective phenotypic switch for these cells and may thus have further potential to prevent atherosclerosis [21]. In particular, the lipid mediators ATLs and RvE1 have been shown to be involved in counteracting the regulation of PDGF-stimulated VSMC chemotaxis [21]. In another study, the 15-epi-lipoxin A4 signals through ALX/FPR2 in vascular smooth muscle cells and protects against intimal hyperplasia after carotid artery ligation [30].

In a study evaluating the effect of lipoxin A4 on myocardial ischemia-reperfusion injury following cardiac arrest in a rabbit model, the inhibitory effect of LXA4 on NF-κB, IL-1β, IL-6, and TNF-α expression, as well as the infarct ratio and apoptotic index values, was shown. Another positive role was the improvement of the IL-10 expression, hemodynamic indices, and myocardial structure and function [55].

The regulation of reverse cholesterol transport is an important mechanism, the disruption of which is closely related to the formation of froth cells in the vascular wall. This process involves the active participation of ABCA1, a member of a large family of ABC transporters. ABCA1 regulates the reverse transport of cholesterol to extracellular acceptors, thereby regulating cholesterol accumulation in macrophages, and through this mechanism may be related to the involvement of these cells in inflammation. Interestingly, LXA4 can induce a dose-dependent increase in ABCA1 and LXRa expression and through this mechanism may be involved in the regulation of reverse cholesterol transport in THP-1 macrophage-derived foam cells [56]. These findings significantly broaden the view on the function of LXA4 in inflammation, as the decreased expression and functional activity of ABCA1 leads to impaired reverse cholesterol transport in macrophages and their inflammatory activation. Thus, the anti-inflammatory role of LXA4 mediated by increased ABCA1 expression represents an important antiatherogenic mechanism.

The involvement of lipoxins in cholesterol metabolism may also be mediated through the increased expression of another representative of the ABC transporters, Abcb11. Abcb11 provides lipid homeostasis through regulation of biliary lipid secretion. Lipoxins cause an increase in Abcb11 expression through a posttranscriptional and posttranslational mechanism involving MAPK p38 activity [57].

Thus, lipoxins are involved in the regulation of many pathophysiological mechanisms that are associated with the development of atherosclerosis. Recent evidence of the deficient production of 15-epi-LXA4 in patients with peripheral arterial disease suggests a protective role for lipoxins in atherogenesis [21]. Despite higher levels of circulating LXA4 in patients with coronary heart disease, lower local levels of LXA4 were observed in rabbit atherosclerotic vessel walls. It was also found that LXA4 inhibited oxLDL-induced regulation of CD36 and reduced oxLDL-induced macrophage apoptosis and foam cell formation [58].

It has also been shown that decreased serum LXA4 levels correlate with the development of metabolic syndrome [59]. In this regard, the assessment of LXA4 levels can be used for the early detection and prevention of metabolic syndrome.

Thus, lipoxins are considered to be an important tool that provides control of inflammation and regulation of inflammation resolution. The role of lipoxins in the prevention of atherosclerosis is a subject for study in order to find new drugs that could increase the effectiveness of treatment.

2. Resolvins

Resolvins (Rvs) are a family of bioactive derivatives of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Their synthesis from docosapentaenoic acid (DPA) and clupandonic acid (cis-7,10,13,16,19-Docosapentaenoic acid) has also been described [60]. Resolvins are small lipid molecules with anti-inflammatory and immunoregulatory properties [61][62]. The term “resolvins” is related to their function (short for resolution phase interaction products) and was first used to describe this group of substances [63][64]. Thus, Rvs have both pro-resolution anti-inflammatory and immunoregulatory properties. There are many studies that have shown the potential beneficial effects of resolvins on the course of various inflammatory processes and the therapeutic value from the use of this group of substances [60][65][66][67][68][69].

Among resolvins, there are the D-series resolvins (RvD) and the E-series resolvins (RvE) [61][70]. The main difference and the reason for the division into groups is the initial product for the synthesis and the slight differences in the chemical structure. RvD is biosynthesized from DHA, RvE is from EPA [71][72].

Currently, six representatives of RvD are known: RvD1 to RvD6. The key enzymes for their synthesis are LOX-15, LOX-5, and for some subtypes, such as aspirin-triggered RvD (AT-RvD), acetylated cyclooxygenase-2 (COX-2) and cytochrome P450 [73][74].

There is information in the literature about the possibility of using RvD1 for the therapy of certain diseases, such as Parkinson’s disease and Alzheimer’s disease [75][76], the prevention of proarrhythmic atrial remodeling [77], and others [78][79][80][81][82][83]. The mechanism of the anti-inflammatory action of RvD1 includes a stimulatory effect on ALX/FPR2 [84]. ALX/FPR2 is a G-protein-coupled receptor (GPCR) and can, depending on the ligand, exert both pro-inflammatory (agonists: N-formyl-Met-Leu-Phe-Lys (fMLFK), amyloidogenic proteins and antibacterial peptides) [85][86] and anti-inflammatory effects (agonist—RvD1, AT-RvD1, RvD3, LXA4, ATLs, Annexin A1) [86][87]. The ALX/FPR2 receptor is expressed on macrophages, endothelial cells, and smooth muscle cells, among others [30]. The effect of RvD1 on ALX/FPR2 alters the intracellular Ca^{2+} content through CaMKII and the subsequent inhibition of MAPK p38 phosphorylation [6][86][88][89]. The antioxidant effect of RvD1 is realized by reducing the activation of NF-κB and increasing the synthesis of antioxidant compounds, thereby reducing the formation of reactive oxygen species (ROS).

A number of studies have established a protective or neutral effect of the ALX/FPR2 receptor in macrophages on the development of atherosclerotic lesions [30]. This indicates the possibility of using the ALX/FPR2 receptor as a therapeutic target in atherosclerosis. However, one should not forget that the effects of ALX/FPR2 stimulation can be the opposite depending on the ligand.

In addition to their effects on ALX/FPR2, RvD1, other resolvins (RvD3, RvD5), and synthetic analogues of BDA-RvD1 (benzo-diacetylenic-17R-RvD1-methyl ester) act on DRV1 (the receptor is also known as GPR32). DRV1 is widely expressed in monocytes and macrophages and is also present in neutrophils and lymphocytes and on the membrane of cardiomyocytes [84][86][90][91][92]. In contrast to ALX/FPR2, the DRV1 receptor lacks murine homologues, which significantly complicates the in vivo study of the mechanisms of regulation by this receptor [40]. The main role of the receptor is to enhance phagocytosis, reduce PMN infiltration [93][94], and participate in the processes of inflammation resolution [95][96][97].

RvD1 has a regulatory effect on neutrophil migration through the endothelium [98][99], promotes neutrophil efferocytosis, and activates M2 type macrophages [100]. Other resolvins act similarly, affecting neutrophils and macrophages, and thereby exerting an anti-inflammatory effect [89][101]. In macrophages, RvD1 inhibits the release of pro-inflammatory cytokines such as IL-6 and TNF-α [64][102][103] and enhances the production of anti-inflammatory cytokines. The RvD1 levels have been shown to be reduced in individuals with carotid atherosclerosis [104][105]. A number of works by other researchers demonstrate the effect of RvD1 on atherosclerotic plaque stability; in addition, RvD1 contributes to the reduction in necroptotic cells (NCs). In addition, RvD1 activates the PI3K/Akt pathway, which reduces the negative effects of ischemia and reduces infarct size [105]. Thus, RvD1 may be a marker for the diagnosis of complications and a potential link in the therapy of atherosclerotic lesions [105][106][107]. RvD1 enhances necroptotic cell clearance by stimulating fatty acid oxidation and the oxidative phosphorylation of macrophages via AMPK signaling [107].

Of interest is the information that RvD1 regulates a number of microRNAs (miRNAs) targeting cytokines and some proteins involved in the immune system, which may contribute to the resolution of inflammation [96].

Another member of the resolvins, RvD2, has an important role in atherosclerotic lesions. RvD2, like RvD1, has anti-inflammatory properties in various pathological conditions [108][109], including vascular conditions [110]. This action is associated with the regulation of PMN infiltration, the effect on macrophages due to increased phagocytosis, and a decrease in the synthesis of PAF (platelet activating factor), LTB4, and PG [72]. RvD2 may be involved in the regulation of nitric oxide production. It has been shown to play a role in nitric oxide production as well as in the modulation of leukocyte adhesion receptor expression, which reduces the interaction between leukocytes and endothelium [111]. In addition, RvD2 promotes the release of prostacyclin from vascular endothelial cells [90][111]. All of these effects together indicate an important role for RvD2 in protecting the vascular wall from atherosclerotic lesions.

RvD3 has a specific role in the resolution of inflammation. It is synthesized in the late stages of inflammation resolution, characterized by the appearance and increased accumulation 24 h after the onset of inflammation. High

levels persist for up to 72 h, which corresponds to the stage of inflammation resolution. RvD3, due to its high activity, helps to reduce PMN infiltration into tissues and the production of inflammatory mediators. In addition, it enhances the phagocytosis and efferocytosis of macrophages. 17R epimer (AT-RvD3), whose biosynthesis is triggered by aspirin, has similar properties [91][112].

RvD4 reduces the effects of deep vein thrombosis by regulating neutrophil infiltration and increasing monocyte levels and enhancing phagocytosis, whereas its metabolite, 17-oxo-RvD4, has virtually no involvement in phagocytosis and has no anti-inflammatory activity compared to RvD4 [113][114][115].

The therapeutic use of RvD1 in atherosclerosis contributes to plaque stabilization by reducing focal necrosis and oxidative stress; RvD2 and Mar1 have a similar effect in preventing atheroprogression [116][117]. In addition, the effects of RvD1 have been described as decreasing the number of neutrophils in the inflammatory zone and switching the macrophage phenotype toward M2 in the spleen and left ventricle [118][119]. However, RvD1 is chemically a complex molecule that is difficult to synthesize; so, more simply organized compounds with the ability to activate FPR2 or DRV1/GPR32 receptors have gained an advantage [120].

The resolvins E series (RvEs) includes resolvin E1 (RvE1), resolvin E2 (RvE2), resolvin E3 (RvE3), and resolvin E4 (RvE4) [121]. The substrate for their synthesis is eicosapentaenoic acid (EPA) [122][123]. The key enzymes of synthesis are endothelial aspirin acetylated COX-2, CYP450, and leukocyte 5-LOX (for RvE1 and RvE2) and 15-LOX (for RvE3 and RvE4) [124][125][126].

RvE1 and RvE2 are the most widely described and are the main representatives of the E-series resolvin family. RvEs exert their anti-inflammatory effects through their action on the E-series resolvin receptors (ERV), also known as chemokine-like receptor 1 (CMKLR1) or chemerin receptor 23 (ChemR23) [127]. ERV is expressed in neutrophils, monocytes, macrophages, and dendritic cells [128][129][130][131][132][133][134][135][136].

RvE1 has anti-inflammatory and pro-resolving effects through several mechanisms, in particular by reducing neutrophil migration [124][130][137][138][139][140], increasing the activation of the efferocytosis process of apoptotic neutrophils by macrophages [138][139], inhibiting the release of inflammatory mediators [141][142], and by regulating the monocyte-macrophage system [86][143][144]. In addition, RvE1 increases the expression of C-C chemokine receptor type 5 (CCR5), which also demonstrates the involvement of RvE1 in resolving inflammation [145].

RvE1 administration to ApoE*3-Leiden transgenic mice significantly reduces interferon gamma (IFN-γ), disintegrin, and metalloproteinase domain-containing protein 17 (ADAM17) and TNF-α, which are directly involved in atherogenesis. This occurs by regulating the expression of the genes encoding them. Moreover, against the background of ADAM17 reduction, the process of efferocytosis is activated and inflammation signaling is inhibited as ADAM17 influences MerTK, which in turn regulates efferocytosis and inflammation resolution in vivo [7][146]. In experimental animal models, RvE1 administration has been shown to suppress atherogenesis and vascular inflammation, which is an interesting subject for study in terms of new approaches to preventing atherogenic

complications [147]. RvE1 reduced the area and severity of atherosclerotic lesions in experimental animals, favoring RvE1's effect on the risk of plaque rupture [148].

RvE2 is another member of the RvEs family. Its chemical structure is very similar to RvE1 [74][137]. Resolvin RvE2 is known to be a substance with potent anti-inflammatory properties that inhibits zymosan-induced PMN infiltration in experimental peritonitis in mice. RvE2 is present in the blood plasma of healthy people [127] and is synthesized by PMN in significant amounts [74][137]. At concentrations of 1–10 nM, it has a direct regulatory effect on human neutrophil chemotaxis processes and promotes the activation of phagocytosis and the production of anti-inflammatory cytokines. In addition, it prevents platelet aggregation, indicating its protective properties and role as a local mediator of tissue homeostasis during inflammation resolution [127][149].

RvE3 and RvE4 are less studied compared to the aforementioned E-series resolvins. They are synthesized mainly by neutrophils and macrophages under hypoxia and have the ability to inhibit neutrophil migration and stimulate the efferocytosis of senescent red blood cells (SRBC) and apoptotic neutrophils by M2 macrophages [71][121][150]. This is confirmed in experiments on human cells and in vivo experiments in mouse models of inflammation [71][72][150]. Moreover, resolvin RvE3 in experiments suppresses the process of the chemotaxis of polymorphonuclear leukocytes [121].

Pathways of therapeutic action on ERV1/ChemR23 receptors can be used to reduce inflammation in cardiovascular diseases, such as atherosclerotic vascular lesions. RvE1 is known to have anti-inflammatory effects in vessels and to attenuate atherosclerotic vascular lesions both in monotherapy and in combination with statins without affecting cholesterol levels and lipid spectrum [148]. Influencing vascular inflammation with inflammation resolution mediators represents a new approach to preventing atherosclerotic vascular lesions [147].

Analysis of the above data points to the important role of D-series and E-series resolvins in the mechanisms of inflammation resolution. Their dysregulation may be part of the pathogenesis of many inflammatory diseases, including atherosclerosis.

3. Protectins

Protectins (PDs) are other members of the SPM family that can be formed from the two omega-3 PUFAs, docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) [151]. PDs have three conjugated double bonds located between the 10th and 17th carbon atoms and are chemically E,E,Z-docosatrienes. The best-known member of this SPM group, Protectin D1 (PD1 or 10R,17S-dihydroxy-docosa-4Z,7Z,11E,13E,15Z,19Z- hexaenoic acid), is a dihydroxylated noncyclic docosatriene, which is formed by lipoxygenation and hydrolysis of an epoxy intermediate.

The first descriptions of PD1 linked its action to protection against oxidative stress in brain and retinal tissues; so, it was named Neuroprotectin D1 (NPD1) [152][153]. Subsequent studies have expanded the understanding of its

functions in different tissues. PD1 is known to be produced by PMNs [154], macrophages [155], and eosinophils [156] [157].

Protectins exert their anti-inflammatory effect through a special kind of G-protein-coupled receptor, GPR37 (G-protein-coupled receptor 37) or PAELR (parkin-associated endothelin receptor-like receptor) [151]. The strength of the anti-inflammatory effect of protectins is related to the stereochemistry of the molecules. For example, the R-epimer of PD1 has greater activity than the S-epimer [151][158].

PD1 exhibits potent anti-apoptotic and anti-inflammatory activity. The anti-inflammatory effects of PD1 include the inhibition of neutrophil migration [159] and the reduction in TNF-α and IFN-γ production by neutrophils [160]. In addition, PD1 regulates CCR5 expression in neutrophils [145] and stimulates macrophage phagocytosis and efferocytosis [91][161][162]. PD1 contributes to the reduction in neutrophil infiltration of tissues and increases the phagocytic activity of macrophages to engulf apoptotic neutrophils [138]. This is an important part of the mechanism of inflammation resolution and may be part of the early anti-inflammatory response in CHD. An increase in the level of protectins in the first hours after myocardial infarction, with a subsequent decrease to normal values, has been shown. Moreover, the PD2n-3 DPA and PD1 levels were positively correlated with the number of neutrophils after the onset of myocardial infarction. These data suggested the involvement of protectins as a counteracting mechanism to attenuate the negative effect of the initial neutrophil increase after ST-elevation myocardial infarction (STEMI) [163].

At present, in addition to PD1, protectin DX (PDX or 10S,17S-dihydroxy-4Z,7Z,11E,13Z,15E,19Z-docosahexaenoic acid) is well known. PDX is a geometric stereoisomer of PD1. PD1 and PDX differ in the geometry of the double bonds in the conjugated triene, which is E,Z,E for PDX and E,E,Z for PD1, as well as in the configuration of the carbon 10, which is S in PDX and R in PD1. Despite the similarity in chemical structure, the biological properties of PD1 and PDX are different [164]. Moreover, the biological activity attributed to PD1 may be related to its PDX isomer [164]. PDX inhibits COX-1 and COX-2, thereby reducing the formation of pro-inflammatory prostaglandins [165]. Unlike PD1, PDX inhibits platelet aggregation by inhibiting COX-1. PDX also inhibits TxA2-induced platelet aggregation [164][166]. Both the formation and the action of endogenously formed thromboxane can be a target for PDX [165]. PDX also reduces the production of ROS and COX activity and the release of myeloperoxidase from neutrophils [164][167]. However, PDX has no effect on the 5-LOX pathway, which produces LTB4 [167].

PD1 metabolic products such as 22-OH-PD1 (22-hydroxy-PD1 or 10R,17S,22-trihydroxy-4Z,7Z,11E,13E,15Z,19Z-docosahexaenoic acid), which also exhibit potent anti-inflammatory activity [168], are also of interest. 22-OH-PD1 is an omega-oxidation product of PD1 and contributes to the inhibition of PMN chemotaxis. Aspirin-triggered PD1 (AT-PD1 or 17-epi-PD1, i.e., 10R,17R-dihydroxy-4Z,7Z,11E,13E,15Z,19Z-docosahexaenoic acid) is a potent anti-inflammatory molecule that is formed with aspirin. AT-PD1 contributes to the resolution of inflammation by reducing the transendothelial migration of PMNs, as well as by enhancing the efferocytosis of apoptotic PMNs by macrophages [158].

Thus, the role of protectins in the resolution of inflammation and in the pathogenesis of atherosclerosis is of clinical interest and requires further research [63].

4. Maresins

Maresins (MaRs), other SPMs, are derived from ω-3 docosahexaenoic acid (DHA) [169]. They are produced by macrophages, for which they received their name (MAcrophage, RESolving INflammation) [169]. Several members of this class have been described: MaR1, MaR2, MaR1-d5, MaR2-d5, MCTR1, MCTR2, MCTR3, of which the last three maresins are conjugated substances (maresin conjugate in tissue regeneration, MCTR) [170]. Their chemical structures are close to each other, which explains their common functions and the mechanism of anti-inflammatory action, but at the same time, maresins differ in their activity and specificity [171]. In addition, there is evidence for maresin-like (L) mediators, such as maresin-L1 and maresin-L2, which are enantiomers of each other. They, like the true maresins, have anti-inflammatory and reparative effects but are produced by both activated macrophages and leukocytes and platelets, with maresin-L1 being produced 10 times more than its enantiomer, maresin-L2 [172] [173].

Maresin biosynthesis starts with a substrate, which is DHA. The key enzyme of the synthesis is 12-LOX [174][175]. MaR1 was first described as a product of DHA conversion by macrophages derived from human monocytes [169] and is a dihydroxylated docosatriene isomer of PD1 [164]. However, unlike protectins, which can be produced by neutrophils, maresins are mainly produced by M2 macrophages and provide a potent anti-inflammatory effect. By providing resolution of inflammation, MaR1 has analgesic and regenerative effects, and an antiaggregant effect has also been found, indicating a protective role, including in vascular damage [72][176][177][178][179][180][181].

Maresins, being isomers, are capable of transferring into each other. Enzymes such as epoxide hydrolase [182], soluble epoxide hydrolase [183], leukotriene C4 synthase and glutathione S-transferase MU 4, gamma-glutamyltransferase, and dipeptidase [174][184][185], which catalyze the transition to one or another maresin, play a key role in this process.

The mechanism of the anti-inflammatory action of MaRs is to enhance the phagocytosis and efferocytosis of macrophages and to limit the penetration of polymorphonuclear leukocytes [117][181][183][186][187][188]. In addition, MaRs contribute to the reduction in inflammatory mediators such as IL-6, IL-1β, and TNF-α [108][189] and increase the production of anti-inflammatory mediators (IL-10) [174][190]. The biological role of MCTR conjugated maresins, which appear at a later stage, is to regulate the mechanisms of inflammation resolution and tissue regeneration [72] [179][181].

Two receptors are targeted by MaR1: retinoic acid-related orphan receptor-α (RORα) and Leucine-rich repeat-containing G-protein-coupled receptor 6 (LGR6) [191][192]. Specific MaR1 binding enhanced efferocytosis and phagocytosis and also promoted phosphorylation of several proteins, including ERK and cAMP responsive element-binding protein (CREB1) [192]. The property of MaR1 to suppress oxidative stress, presumably through activation of the Nrf2-mediated HO-1 signaling pathway, has been described [193].

MaR1 directly enhances neutrophil activation and plays an important role in switching macrophages from the M1 to the M2 phenotype [180][181][194]. MaR1 mainly acts on vascular endothelial cells and VSMCs and promotes the reduction in TNF-α-induced monocyte adhesion to the endothelium. In addition, it has an antioxidant effect, which is manifested through its effect on the factor NF-κB [195]. When the levels of MaR1 and RvD2 decreased, the progression of atherosclerosis was observed, which may be associated with impaired efferocytosis against the background of the reduction in these mediators [117]. There is evidence that RvD2 and MaR1 prevented the progression of atherosclerosis by causing a change in the macrophage profile toward a reparative phenotype, which secondarily stimulated collagen synthesis in smooth muscle cells [117]. This indicates a homeostatic effect of MaR1 on vascular cells, which is of no small importance in acute and chronic vascular inflammation and can be used as a therapeutic target in vascular lesions [195].

MaR2 showed similar effects to MaR1, limiting PMN infiltration and enhancing phagocytosis, while being 2–3 times less active than MaR1 [171].

MCTR1, MCTR2, and MCTR3 maresin conjugates are involved in tissue regeneration and the regulation of PMN infiltration [170][193]. In a mouse model, MCTR1 has been shown to promote the accumulation of M2 macrophages and significantly accelerate the resolution of inflammation [196]. In addition, it contributes to a decrease in the production of inflammatory cytokines such as TNF-α, IL-1β, and IL-6. In addition, all MCTRs interact with CysLT1, reducing vascular permeability and affecting cardiac function [170].

Thus, MaRs provide a regulatory influence on the processes of inflammation resolution and are of interest in the pathogenesis of atherosclerosis [197][198].

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