Biochemistry

Biosynthesis and characteristics of anti-inflammatory proresolving derivatives of omega-3 and omega-6 polyunsaturated fatty acids

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Summary:

Anti-inflammatory pro-resolving mediators are endogenous lipid-derived compounds that are actively engaged in the resolution phase of acute inflammation. These mediators derive from polyunsaturated fatty acids (PUFA): lipoxins from omega-6 (ω6) arachidonic acid (AA), oxylipins from ω6 docosapentaenoic acid (DPA-ω6), resolvins series E from ω3 eicosapentaenoic acid (EPA), and resolvins-D, protectins and maresins all from ω3 docosahexaenoic acid (DHA). The formation of anti-inflammatory pro-resolving mediators occurs in a process called transcellular biosynthesis in which two types of interacting cells participate, present in the region of inflammation, i.e. neutrophilic granulocytes and other cells, such as epithelial cells, platelets, endothelial cells, or monocytes. Enzymes contributing to the biosynthesis of pro-resolving mediators include lipoxygenases (LOX-5, -12, -15) and cyclooxygenases (COX-2 and aspirin-triggered acetylated enzyme, i.e. ASA-COX2), as well as monooxygenases of the cytochrome P450 family. Some chemical reactions taking part in the biosynthesis of pro-resolving mediators, such as epoxidation or hydrolysis, may be enzyme-dependent or enzyme-independent. Pro-resolving anti-inflammatory mediators exert their biological activities in a receptor-dependent manner. Of their various biological effects, the most important include inhibition of leukocyte mobilization and traffic through endothelial or epithelial layers, suppression of pro-inflammatory cytokines release by different cells present in inflamed tissue, and stimulation of the phagocytic activity of monocytes/macrophages. This article presents the current knowledge on the mechanisms responsible for and conditions underlying the formation of pro-resolving mediators, describes their functional characteristics, and depicts new trends on a possibility of their use in therapy.

Key words: anti-inflammatory pro-resolving mediators, polyunsaturated fatty acids, arachidonic acid, 6-docosapentaenoic acid, eicosapentaenoic acid, docosahexaenoic acid, lipoxins, resolvins, protectins, maresins, oxylipins.

Introduction

The involvement and role of lipid mediators such as leukotrienes, prostaglandins, thromboxanes and platelet activating factor in the course of inflammation is part of the canon of the patophysiology of this process. The three first listed groups represent a numerous family of compounds known as eicosanoids, derived from arachidonic acid – a polyunsaturated fatty acid of the omega-6 series, which is a constituent of membrane phospholipids. Platelet activating factor (PAF) is in fact a family of many factors, derivatives of glycerophosphocholine. All these group of compounds are inflammatory mediators, involved in propagation of inflammatory reaction [10, 27, 35, 53].

Biosynthesis of eicosanoids is preceded by the release of arachidonic acid from membrane phospholipid pool upon the action of phospholipase A_2 (Fig. 1). Only the free acid becomes the substrate for the two types of oxygenases: cykloxygenase (COX) and lipooxygenase (LOX). Enzymes of the COX family initiate the arachidonic acid →//→ prostaglandins/thromboxanes transformation pathway, while the enzymes of the LOX family initiate the transformation pathway leading, among others, to leukotrienes. Although studies on the biological properties of the listed eicosanoids, particularly inflammatory mediators, are being continued, their general characteristics and mechanism of action are well known and included in university textbooks (e.g. [27, 53]); therefore, they will not be discussed in this study.

The subject of this study will include mediators of anti-inflammatory potential: lipoxins, oxylipins, resolvins, protectins and maresins, formed from both arachidonic acid and other polyunsaturated fatty acids (PUFAs) present in plasmatic membranes, representing lipids of both omega-6 (ω6), and omega-3 (ω3) series. The listed classes of mediators represent a numerous group of anti-inflammatory pro-resolving mediators. An overview of the role of these mediators in acute inflammation has been presented in the previous work of the current author [35] and in other studies [3-5, 34, 36, 52].

Currently, we shall focus on biosynthesis and conditions for formation of these lipid compounds. In addition, detailed characteristics of these mediators shall be presented. According to the latest concepts regarding the course of acute inflammatory reaction [5, 35, 52], fast and inconsequential resolution of this process requires active contribution of "agonist" mediators, such as pro-resolving mediators. They are generated locally, i.e. at the inflammation site, and exert specific actions which – as is currently believed – are required for the acute process not being transformed into a chronic one, often constituting a platform for the development of pathologies which may last for many years, sometimes throughout the remaining lifetime, often posing a hard-to-cure medical problem.

Anti-inflammatory arachidonic acid derivatives

Lipoxins

Lipoxins (LXs) are metabolites of a**rachidonic acid** (AA; C20:4-ω6) with anti-inflammatory and immunomodulatory properties. The history of lipoxins, dating back to early 1980s, is relatively long in comparison to the history of anti-inflammatory derivatives of omega-3 PUFAs, i.e. resolvins, (neuro)protectin and maresins, which spans the period of several recent years. Back at that time, a group of researchers led by the Nobel Prize winner of 1982, Bengt Samuelsson, described a new arachidonic acid transformation pathway, consisting in double transcellular oxidation catalyzed by lipooxygenases (LOX) and leading to formation of unstable 15*S*-epoxytetraenic acid and, subsequently, to two other structures, named lipoxins, as in words: ***lipox****ygenase* and ***inf****lammation* [41, 46]. Two lipoxins were identified: **LXA4** and **LXB4**, and their full names are respectively: 5*S*, 6*R*,15*S*-trihydroxy-7,9,13-*trans*-11-*cis*-eicosatetraenoic acid and 5*S*,14*R*,15*S*-trihydroxy-6,10,12-*trans*-8-*cis*-eicosatetraenoic acid.

Ten years after the discovery of lipoxins, a collaborator of B. Samuelsson, Charles N. Serhan showed that leukotriene LTA_4 might also be a substrate for the lipoxin synthesis [41, 43]. Several years later, Claria and Serhan reported formation of two lipoxin epimers [13].

The discovery of **15-epi-LXA4** and **15-epi-LXB4** was made in an *in vitro* experimental system, in which two types of human cells: human umbilical vein endothelial cells or epithelial (A549) cells were coincubated with neutrophils in the presence of acetylsalicylic acid (ASA). The studies involving the use of ASA (popular aspirin) led to two observations. The first one was easy to foresee and due to suppression of COX activity (which led to inhibition of the synthesis of proinflammatory prostaglandins and was associated with anti-inflammatory activity of the drug), and the other was unexpected, but associated with important consequences. It turned out that acetylated COX-2 (ASA-COX2), although incapable of promoting the synthesis of prostaglandins, inhibited another metabolic pathway of arachidonic acid, i.e. its transformation into 15-epi-lipoxins. The described biological system: coincubation of two types of cells in the presence of ASA, was subsequently used in numerous further experiments, in which another lipid mediators were discovered.

Synthesis of lipoxins

The synthesis of lipoxins from arachidonic acid (AA), although theoretically possible to occur in a single cell, usually occurs sequentially in two types of cells. Such a process is defined as transcellular biosynthesis; it is an example of cell-specific processes. Thus, biosynthesis of lipoxins requires cooperation of various types of cells present at the inflammation site, where said cooperation consists in transferring byproducts for further transformations.

Enzymes and/or chemical reactions (such as non-enzymatic processes) involved in lipoxin synthesis may differ depending on the type of cells involved in their formation. Fig. 1 presents metabolic pathways leading to formation of various signaling compounds, including lipoxins. Of note is the fact that the first stage determining further transformations is excision of AA from membrane phospholipids by means of the enzyme phospholipase A_2 (PLA_2). Free AA is a substrate for many enzymes of lipooxygenase (LOX) and cyclooxygenase (COX) families, as well as monooxygenases of the cytochrome P450 family. Action of these enzymes leads to formation of compounds of varied biological activity, such as prostaglandins, thromboxanes and leukotrienes. In contrast to these compounds, most of which are characterized by proinflammatory activity (prostaglandins, leukotrienes), lipoxins have an anti-inflammatory effect. Thus, the discovery of the AA →//→ lipoxins metabolic pathways changed the universal claim that the derivatives of the polyunsaturated omega-6 fatty acid, arachidonic acid (AA) are inflammatory mediators. Beyond doubt, lipoxins do not belong to this category.

There are at least three pathways to form lipoxins in different cell systems (Fig. 2), such as:

- **Epithelial cells – neutrophils**; the system involves sequential action of two types of lipooxygenases, i.e.: 15- and 5-LOX. First, the action of these enzymes leads to formation of 15*S*-hydro(peroxy)-eicosatetraenic acid, which is further transformed into intermediate 15*S*-hydro(peroxy)-5*S*, 6*S*-epoxytetraenic acid and next to lipoxins A_4 (LXA_4) and B_4 (LXB_4);

- **polynuclear neutrophils – platelets**; the system involves the sequence of 5-LOX and 12-LOX – the intermediate compound along this pathway is leukotriene A_4 (LTA_4);

- **neutrophils – vascular endothelial cells** or **epithelial cells** or **monocytes**; these systems involve COX2 and 5-LOX, where the former must be present in its acetylated form, as is the case in presence of acetylsalicylic acid (ASA). The action of ASA-COX2 leads to formation of 15*R*-hydroxy-ETE (15*R*-HETE), while the action of 5-LOX leads to 5*S*, 6*S*, 15*R*-epoxytetraenic acid. The final products of the aforementioned cell systems are 15*R*-epimers of lipoxins, i.e. 15-epi-LXA_4 and 15-epi-LXB4, commonly referred to as 15-epi-lipoxins or 15-epi-LXs or identified using other acronyms: AT-LXA_4 and AT-LXB_4, which underline the necessity of ASA; AT stands for aspirin-triggered. Both lipoxins are commonly referred to as ATLs. One must note that the biological activity of lipoxins and AT-lipoxins is similar. A proof for the formation of ATLs in humans was demonstrating the presence of ATL in the urine of healthy volunteers after administration of aspirin at the dose of 100 mg/day for ≥ 8 days, and in plasma following 8 weeks of treatment with low ASA doses [39].

Inactivation of lipoxins

Inactivation of lipoxins and AT-lipoxins in the inflammation region is important as it eliminates biologically active structures, thus contributing to termination of their effect. Studies showed that LXA_4 is a substrate for two enzymes: 15-hydroxyprostaglandin dehydrogenase (15-PGDH) and multifunctional eicosanoid oxidoreductase (EOR), including enzymes with affinity to both prostaglandins (PGR, prostaglandin reductase), and leukotrienes B_4 (LTB_4DH – LTB_4 dehydrogenase); sometimes, the lipoxin-inactivating enzymes are referred to using the common acronym PGR/LTB_4DH. These enzymes act on LXA_4, which leads to the formation of inactive compounds: 15-oxo-LXA_4 and 13,14-dihydro-15-oxo-LXA_4; the latter may be further transformed into 13,14-dihydro-LXA_4 [14]. Thus, the listed reactions include oxidation at position C15 and reduction of the C13=C14 bond. More recent data mention an additional lipoxin metabolic pathway, consisting in hydroxylation at position C20 [38]. One should mention that 15-epi-LXs are more resistant to inactivating enzymes than LXs, owing to which their body levels are higher and their effects are stronger.

During inflammation, multiple active compounds are synthesized; initially, they include inflammatory mediators, e.g. prostaglandins and leukotrienes, and later, they include also anti-inflammatory compounds, such as lipoxins, as well as resolvins and maresins (see below). Local inactivation of these compounds, similar to their inactivation in the inflammation area, fundamentally affects the course and outcome of inflammation. Thus, the role of enzymes degrading inflammatory mediators will be as important for the course of the inflammatory reaction as the role of mechanisms responsible for their formation and "supply".

Biological effects of lipoxins

Lipoxins, or, in particular lipoxin A_4 (LXA_4) and its 15-epi-LXA_4 – since it is these two compounds that are considered to be main representatives of the series (to date) – exert their action by inhibiting the receptor known as ALX [12]. Despite the fact that lipoxins A and B are structurally similar, LXB_4 and 15-epi-LXB_4 do not act via the ALX receptor. As suggested by functional test results,

there is most probably a B_4 lipoxin-specific receptor waiting to be discovered.

The ALX receptor was studied at the molecular level in the early 1990s [21]. It belongs to a numerous family of G protein-coupled receptors (GPCR); it consists of 351 amino acid residues and coded by a gene found in humans in chromosome 19q. ALX receptors are present in different cells, with particularly large numbers observed on leukocytes and in somewhat lower amounts on eosinophils, monocytes/macrophages, basophils, T-cells, dendritic cells, fibroblasts, renal mesangial cells, endothelial and vascular smooth muscle cells and hepatocytes.

The biological effects of stimulation of the ALX receptor are varied and location-dependent, i.e. cell-specific. For instance, in case of **neutrophils**. inhibition of chemotaxis, adhesion and transmigration can be observed, as well as reduction in degranulation, adhesion to the endothelium and homotypic aggregation, as well as reduction in IL-1β and IL-8 levels, expression of CD11b/CD18 (adhesion proteins). In case of **eosinophils**, inhibition of migration and degranulation, as well as eotaxin and IL-15 production. In case of **monocytes/macrophages**, intensification of: chemotaxis and adhesion to laminin as well as phagocytosis of apoptotic polynuclear leukocytes, and inhibition of IL-8 production, NF-κB activation and formation of the reactive oxygen radical: superoxide nitrate. In **T-cells** – inhibition of secretion of TNF-α, and in **dendritic cells** – reduction in IL-12 production; in **epithelial cells** – inhibition of IL-8 secretion and in **vascular endothelial cells** – enhanced expression of the tissue factor (TF) and heme-a oxygenase, formation of prostacylin (PGI_2) and reduction of: VEGF-dependent proliferation, adhesion and migration as well P-selectin expression.

The diversity of the effects of stimulation of the ALX receptor, and thus of the biological activity of LXA_4 and its 15-epimer (several of the above biological effects of LXA_4 can also be exerted by LXB4), makes lipoxins being considered as strong endogenous anti-inflammatory factors. The "disadvantage" of these compounds is that they undergo rapid enzymatic inactivation *in vivo* [38]. This makes exogenous lipoxins incapable of being used as anti-inflammatory drugs. However, the attempts to use synthetic and metabolically stable analogs of lipoxins and AT-lipoxins are continued with good results, which is a cause for optimism.

Soon, the treatment of inflammations, particularly acute inflammations, may include pro-resolving drugs, which would constitute a qualitatively novel strategy of treating these conditions. Lipoxin analogs currently studied for their potential used as drugs in humans include ATL analogs, e.g. 15(*R/S*)-methyl-LXA_4 ($ATLa_1$), 15-epi-16-(*para*-fluoro)-phenoxy-LXA_4 ($ATLa_2$; the compound is present as a methyl ester – *in vivo*, the ester is rapidly hydrolyzed by plasma and liver esterases into the free acid, which is the active compound), 3-oxy-15-epi-LXA_4 (ZK-994), o-[9,12]-benzo-ω6-epi-LXA_4 or 16-phenoxy-LXA_4 [15, 23, 26, 37, 38]. The synthesis of stable lipoxin analogues takes into account the fact that interaction of LXA_4 with the ALX receptor is highly stereospecific and requires certain structural and conformational arrangements being maintained, including the 5*S*,6*R*-orientation of hydroxyl groups and the presence of the C11=C12 double bond in *cis* position.

New and particularly interesting – particularly for ophthalmologists – is the fact that the stable analog of AT-lipoxin, ATLa, showed pro-resolving effects in acute inflammatory reactions in ocular tissue and effectively blocked corneal neovascularization – phenomena induced in mice by administration of micropellets containing IL-1β and/or VEGF-A [22].

Summarizing the effects of lipoxins and AT-lipoxins, one may conclude that these compounds, as well as their metabolically stable analogs, exert anti-inflammatory action by active contribution at the active inflammatory reaction resolution phase [40]. *In vivo*, the anti-inflammatory effect is a resultant of multidirectional effects of lipoxins in several types of cells involved in the inflammatory process. The most important effects of lipoxins (characterized by anti-inflammatory and pro-resolving properties) include, on one hand, reduction/inhibition of neutrophil function and transmigration through "barriers" of epithelial and endothelial cells, and on the other hand, suppression of the release of pro-inflammatory cytokines by T-cells and stimulation of phagocytic activity of monocytes and macrophages.

Attempting to classify the biological effects of lipoxins into classical anti-inflammatory and pro-resolving effects, the division may be as follows: the group of anti-inflammatory effects would include the effects dependent on specific signals generated by neutrophils, i.e. the reduction of: CD11b/18, production of reactive oxygen species, activation of NF-κB, secretion of pro-inflammatory cytokines/chemokines and the increase of production/enhancement of the activity of anti-inflammatory cytokines/chemokines. The group of pro-resolving effects (dependent on specific „signals" generated by monocytes/macrophages) would include: the increase/enhancement of Ca^{2+} ions mobility, adhesion and chemotaxis, as well as

stimulation of macrophages to phagocytize apoptotic neutrophils in the area of inflammation.

Finally, it has to be mentioned that the spectrum of biological effects (both anti-inflammatory and pro-resolving) of lipoxins may be wider than that presented above, as there are premises indicating that these compounds may enter interactions with receptors other than ALX, such as $CysLT_1$ (antagonistic effects observed in macrovascular epithelial cells and mesangial cells → suppression of the effects of leukotriene LTD_4) and nuclear aryl hydrocarbon receptor AhR (*aryl hydrocarbon receptor*), which is a ligand-activated transcription factor controlling the expression of different gene sets; LXs are direct agonists of this receptor → anti-inflammatory effects) [12, 23, 39]. In terms of the overall effect of lipoxins, of importance may be also the inhibitory effect of signals generated by ALX and $CysLT_1$ receptors on the function of growth factor receptors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) or connective tissue growth factor (CTGF) – such interactions may lead to suppression of processes dependent on these factors, such as angiogenesis, proliferation and fibrosis [12, 23, 39].

Anti-inflammatory derivatives of omega-3 polyunsaturated fatty acids

Resolvins - the name is derived from words ***resol****ution* and ***in****teraction*, referring to the c*ell-cell interaction* required for the synthesis of the compound or **in**flammation, as in case of lipoxins. Resolvins are a family of derivatives of eicosapentaenoic acid (E series) and docosahexaenoic acid (D series).

Resolvin E series – eicosapentaenoic acid derivatives (EPA)

The discovery of resolvin E series dates back to the year 2000 [1]. At that time, an observation was made regarding unexpected, albeit resembling the case of lipoxins, effect of the acetylsalicylic acid (ASA) on COX-2 in human vascular endothelial cells (exposed to TNF-α in order to stimulate COX-2 expression) and the capability of the acetylated enzyme (ASA-COX2) to catalyze the transformation of **eicosapentaenoic acid** (EPA; C20:5-ω3) to 18R-hydro(peroxy)-eicosapentaenoic acid, or 18*R*-H(p)EPE. After being uptaken by neutrophils present in the culture, 18*R*-H(p)EPE was transformed by the action of neutrophil-derived 5-LOX into 5*S*-hydro(peroxy)-18*R*-hydroxy-EPE, or 5*S*-H(p)-18*R*-HEPE, then to 5*S*(6)-epoxy-18*R*-HEPE and finally to 5*S*,12*R*,18*R*-triHEPE (Fig. 3). The last structure is that of **resolvin-E1** (**RvE1**), or 5*S*,12*R*,18*R*-trihydroxy-6*Z*,8E,10*E*,14*Z*,16*E*-eicosapentaenoic acid [1] (Fig. 3).

Resolvin-E2 (**RvE2**), or 5*S*,18*R*-diHEPE (5*S*,18*R*-dihydroxyeicosapentaenoic acid) was found to be formed simultaneously with RvE1. RvE2 is a product of the reaction of peroxidation of 5*S*-H(p)-18*R*-HEPE, which is also an intermediate in the synthesis of RvE1 (Fig. 3).

Formation of resolvins of the E series resembles the process of lipoxin formation and is a result of the process described as transcellular synthesis. These qualitatively novel EPA metabolites showed anti-inflammatory activity in different cell systems and inflammation models. The activity consisted in activation of the process of resolution of acute inflammatory reaction. The biological activity profiles and strengths of RvE1 and RvE2 are similar, although some differences can be observed. According to data available to date, the range of RvE1 effects is wider than that of RvE2. RvE1 and RvE2 regulate (inhibit) infiltration– transendothelial migration of neutrophils into the inflammation area, stimulate macrophages to phagocytize apoptotic neutrophils and reduce the release of pro-inflammatory cytokines (Table 1). Resolvins promote the stage of inflammation healing, i.e. katabasis or resolution [19]. The strength of both resolvins is similar after intravenous (i.v.) administration; however, following intraperitoneal (i.p.) administration, the effect of RvE1 is stronger than that of RvE2. In addition, RvE1 affects: thrombocytes (disturbing thromboxane-dependent platelet aggregation), T-cells (enhances the expression of the chemokine receptor CCR5), dendritic cells (inhibits IL-12 migration and production) and eosinophils (inhibits allergen-dependent mobilization of eosinophils). In addition, RvE1 alleviates colitis and prevents osteoclast-dependent bone destruction [1, 2, 19, 44].

Comparison studies showed that in some biological systems, the anti-inflammatory effects of RvE1 were stronger that these of aspirin, and even these of dexamethasone [1, 44].

RvE1 exerts its biological action by the ChemR23 receptor, showing 36% structural similarity to the ALX receptor [2, 19]. Stimulation of the ChemR23 receptor activates a series of signaling processes, including MAP kinase cascade. ChemR23 is also activated by the peptide ligand – chemerin, which has anti-inflammatory properties [11]. RvE1 may also interact with the leukotriene LTB_4 receptor BLT1, expressing an interaction profile characteristic for that of a partial agonist. This interaction led to suppression of the LTB_4→BLT_1 signal in neutrophils [2].

Human neutrophils synthesize larger amounts of RvE2 compared to RvE1. However, RvE2 does not interact with the ChemR23 receptor, and thus the

molecular mechanism of receptor signaling induced by this resolving remains unknown [56].

It is assumed that resolvins are formed in the final stage of acute inflammation as a result of interactions between two types of cells (transcellular biosynthesis). However, studies in healthy volunteers receiving fish oil (containing 1 g of EPA and 0.7 g of DHA) with aspirin (160 mg), revealed presence of RvE1 in plasma samples in the amounts of 0.1-0.4 ng/mL, suggesting that biosynthesis of resolvins may take place in healthy humans, without any inflammation process detected [1].

Resolvin D series – docosahexaenoic acid derivatives (DHA)

Resolvins of the D series, i.e. compounds derived from **docosahexaenoic acid** (DHA; C22:6-ω3), were detected in the exudate from mice with chemically induced inflammation receiving DHA and aspirin [47]. Reactions of **AT-RvD** and **RvD** formation were essentially similar to these involved in the synthesis of resolvins of E series (transcellular biosynthesis), with the difference consisting in a larger number of resolvins being formed (four compounds per series): RvD1–RvD4 and AT-RvD1–AT-RvD4. In case of AT-RvD resolvins, the starting metabolite of DHA (formed as a result of ASA-COX2 action) is 17R-H(p)DHA, which is next transformed, via 7*S*-hydro(peroxy)- and 7*S*(8)-epoxy- forms, into AT-RvD1 and AT-RvD2. Transformations of 17R-H(p)DHA → 4S-hydro(peroxy)-derivatives → 4S(5)-epoxy-derivatives lead to formation of resolvins D3 and D4, i.e. AT-RvD3 i AT-RvD4 (Fig. 4).

LOX-LOX-dependent pathways of transformation of DHA into D1-D4 resolvins (RvD1, RvD2, RvD3 and RvD4) are shown in Fig. This figure also contains full chemical names of the compounds. According to a recent publication by Calder [8], there may be more resolvins in the D series: in his work, author suggested two new compounds, resolvins D5 and D6, but did not present the mechanism of their formation.

Inactivation

Inactivation of RvD1 and resolvins of E series involves the same enzymes as lipoxins, i.e. 15-PGDH and EOR; however, catalytic capacity of these enzymes is slightly lower in case of resolvins (reactions are slower). The aforementioned enzymes catalyze transformation of resolvins into 8-oxo- and 17-oxo-derivatives. An interesting observation was made in the comparison studies of metabolism of RvD1 and AT-RvD1 (the latter differs from RvD1 only with the configuration of the 17-hydroxyl group – 17*R*), which showed that only the first compound, i.e. RvD1 was rapidly inactivated [54].

Biological effects

In contrast to numerous known biological effects of resolvins of the E series, information regarding resolvins of D series is relatively scarce and describes mostly the use of resolvin D2 in animal models. First observations revealed the capacity of these compounds (administered to mice by intravenous route) to inhibit mobilization and infiltration of leukocytes in the mouse dorsal air pouch inflammation model [15] caused by TNF-α and in zymosan-induced peritonitis [47]. Protective effect of resolvins of the D-series was also reported with respect to renal damage or function loss due to hypoxia and following reperfusion [20].

Recent reports [51] have stated the protective effect of RvD1 when injected at very low doses of 0.01-10 ng *i.v.*, in inflammation caused by oxidative stress; peritonitis in mice was induced by *i.p.* administration of a cytotoxic and pro-inflammatory aldehyde, i.e. 4-hydroxynonenal (HNE), which is formed *in vivo* in the peroxidation of lipids, including numerous polyunsaturated fatty acids. Suppression of leukocyte infiltration was proportional to the RvD1 dose being used and was between 30 and 70% [51]. Table 1 Presents the effects of resolvins on different cells participating in the inflammatory process.

RvD1 has also inhibited IL-1β expression in microglial cells [25] and reduced vasoobliteration and neovascularization in retinopathy [16]. Recent reports extended the range of ocular effects of RvD1 and RvE1, which inhibited the pro-inflammatory signaling generated in choroid endothelial cells and leukocytes as well as transmigration of leukocytes through the endothelium *in vitro* [55].

(Neuro)Protectin – a docosahexaenoic acid derivative (DHA)

First observations showing the capacity of the central nervous system (CNS) tissues, including retina, to transform docosahexaenoic acid (DHA) upon catalysis with lipoxygenases (LOX) date back to the year 1984. The results of further studies showed a "beneficial" effect of the fatty acids of the omega-3 series (EPA and DHA) within the CNS. As early as in these times, that is more than two decades ago, the role of diet rich in these acids (especially DHA) in maintaining proper brain function was underscored. However, at that time nobody expected that certain metabolites of DHA, such as compounds of the type of hydroxydocosanoids might have unique

protective properties that would justify naming them protactins or neuroprotectins.

Biosynthesis of (neuro)protectin

The substrate for the synthesis of **protectin** is **docosahexaenoic acid** (DHA; C22:6-ω3). At the first stage of biosynthesis, LOX transforms DHA into 17*S*-H(p)DHA – a structure that next undergoes enzymatic epoxidation to form 16*S*(17)-epoxydocosatriene. Finally, the docosatrienoic compound is transformed by enzymatic hydrolysis into 10*R*,17*S*-dihydroxy-docosa-4*Z*,7*Z*,11E,13E,15*Z*,19*Z*-hexaneoic acid, i.e. **protectin D1** (**PD1**); the suffix D1 presents the nature of the compound: D provides information about the origin, i.e. DHA, while 1 stands for the first compound in the series. If biosynthesis takes place within the CNS, the generated compound is called **neuroprotectin D1** (**NPD1**); if biosynthesis takes place outside the CNS, the compound is called PD1. Fig. 6 presents the DHA transformation pathways with emphasis on the pathway leading to protectin generation.

In physiological conditions, biosynthesis of neuroprotectin takes place mostly in the structures/organs containing large amounts of DHA. The CNS, and particularly the retina, belong to this group of organs; It is the DHA content that makes the retina a unique organ in the animal and human system [32, 33]. The specific and effective DHA transport system within mammal bodies ensures high supply of DHA from the gastrointestinal tract into the retinal pigment epithelium (RPE) and photoreceptors [31]. It should be noted again that polyunsaturated fatty acids, particularly those of the omega-3 series (EPA, DPA, DHA, and, to a large extent, the precursor of these compounds, i.e. α-linolenic acid, C18:3-ω3), belong to the so-called essential fatty acids (EFAs), which cannot be synthesized in sufficient amounts in the human body, and which thus must be introduced with food or as diet supplements. The presence of this most unsaturated, fatty acid, containing six double bonds, in plasmatic membranes of photoreceptors and, in particular, their external segments (containing visual pigments responsible for absorption of light photons), is essential to maintain both the functional "plasticity" of the cell/plasma membrane and the compartmentalization of processes associated with perception of visual sensations. In contrast to other lipid membrane components, DHA present in the membranes of the RPE-photoreceptor complexes shows high mobility and dynamics, also with regard to generation of NPD1.

Although the reactions of NPD1/PD1 biosynthesis are well known, initiation of the process of neuroprotectin generation is not fully understood; it is uncertain whether actual inflammatory process with cell influx into the inflammation area is necessary for the synthesis, as discussed in other articles by the authors [34, 35]. This type of doubts are justified by the fact that cultured human RPE cells (ARPE-19 – spontaneously transformed RPE cells), or human brain cells are capable of synthesizing NPD1 e.g. under conditions of hypoxia, oxidative stress and the presence of cytotoxic bis-retinoid A2E, as well as in the presence of IL-1β and calcium ionophore A23187 [24, 28, 29]. Docosanoid formed in these conditions showed neuroprotective properties, e.g. preventing cell apoptosis caused by oxidative stress and induction of COX-2 stimulated by the presence of pro-inflammatory cytokine. These and other observations were decisive for the 10R,17*S*-dihydroxydocosahexaenoic acid being called "neuroprotectin" (NPD1) [6, 24, 28, 29, 45].

It cannot be excluded that the DHA→//→NPD1 transformation is a kind of defensive reaction occurring in threat situations, e.g. in inflammation or neurodegeneration (according to the most recent concepts, chronic inflammation and microglia are crucial as the factor inducing and maintaining neurodegeneration). It should be mentioned that some well known endogenous factors are capable of stimulating biosynthesis of NPD1 in RPE cells; they include, for example, brain-derived neurotrophic factor (BDNF), fibroblast growth factor-2 (FGF-2), leukemia inhibitory factor (LIF), and even anti-angiogenic pigment epithelium-derived factor (PEDF). It was also reported that the presence of NPD1 leads to upregulation of the expression of anti-apoptotic and downregulation of the expression of proapoptotic proteins of the Bcl-2 family, resulting in a drop in proapoptotic activity of caspase -3 and suppression of the apoptotic process [6, 24].

To date, no specific receptor of NPD1/PD1, through which the protectins might exert their biological effects, was identified. However, the concept of receptor-dependent nature of the mechanism of action of (neuro)protectin is predominant. Extensive research is currently conducted to find such receptors within the retina and the brain.

It is assumed that the lack of (neuro)protectin may contribute to the acceleration of the development of degenerative pathologies such as age-related macular degeneration (AMD) or Alzheimer's disease [6, 24].

NPD1/PD1 exert many effects in line with their classification as pro-resolving factors, e.g. inhibition of expression of genes encoding

proinflammatory compounds such as IL-1, COX-2 and B94 (a pro-inflammatory element induced by TNFα) and cytokine exodus protein-1 (CEX-1, an inflammatory response and oxidative stress marker); other effects of (neuro)protectins are listed in Table 1.

Maresins – *docosahexaenoic acid derivatives (DHA)*

Maresin – the name is derived from three words: ***ma***crophage, ***res***olution and ***in***flammation.

Maresins are the most recent component of the family of endogenous pro-resolution mediators of the acute inflammation phase. An article published in January 2009 presented the results of recent research by Serhan *et al.*, suggesting a novel pathway of docosahexaneoic acid (DHA) transformations [49]. Using the advanced, complex techniques of lipid analysis (mediator lipidomics) allowing to isolate, extract and identify various (including stereospecific) metabolites of polyunsaturated fatty acids, including DHA, the Serhan's group managed to identify hitherto unknown DHA metabolites produced in exudates collected from mice with peritonitis (induced by zymosane) and by macrophages present in the exudates.

The researchers demonstrated that besides the already known metabolites, such as 17*S*-hydroxy derivatives of DHA (a precursor of the synthesis of D-series resolvins and protectins), hitherto unknown 14*S*-hydroxy derivatives of DHA were also present. After adding DHA or synthetically obtained 14*S*-H(p)DHA to the activated macrophage-containing suspension, presence of qualitatively new DHA metabolites containing two hydroxyl groups and characterized by biological activity similar to that of resolvin E1, originating from EPA (RvE1, containing three hydroxyl groups in positions 5*S*, 12*R* i 18*R*) and of protectin D1, originating from DHA (PD1, with two hydroxyl groups in positions 10*R* and 17*S*) was revealed. The newly identified compound turned out to be 7*S*,14*S*-dihydroxydocosa-4*Z*,8,10,12,16*Z*,19*Z*-hexaneoic acid, i.e. **7S,14S-dihydroxy-DHA** or 7*S*,14*S*-diH-DHA, or 7*S*,14*S*-diHDHA – all notations relate to **maresin** (**MaR1**). Of note is the lack of stereochemistry indications at positions 8, 10 and 12, which might, but does not have to represent 8*E*, 10*Z* and 12*E* configurations. It turned out that double oxidation of DHA, leading to formation of MaR1, was sequentially catalyzed by two enzymes: 12- and 5-LOX (Fig. 7).

Biological activity of MaR1 involves multidirectional interactions leading to restriction of accumulation of polynuclear leukocytes in inflammation area due to stimulation of phagocytic activity of macrophages (Table 1). Since MaR1 appears in the inflammatory reaction resolution phase, it is another proresolving mediator. MaR1 is thought to exert its biological activity via a specific receptor different from the receptor for resolvins and protectins, and remaining to be identified.

Anti-inflammatory derivatives of omega-6 docosapentaenoic acid (DPA-ω6)

The idea of searching for novel resolvins not associated with the omega-3 acids is related to recent observations, gathered since 2007 and focusing on the anti-inflammatory potential of oil produced by *Schizochytrium sp.* microalgae. The oil contains 40% DHA, 2.5% EPA and 15% DPA-ω6. The product is commercially available under the name of DHASCO-S (DHA-S^{TM}), derived from DHA Single Cell Oil (Martek Biosciences Corporation). In contrast to another oil product from Martek, known as DHASCO-T (DHA-T^{TM}), produced by microalgae *Crypthecodinium cohnii* and containing 40% of DHA (with trace amounts of other polyunsaturated fatty acids), DHASCO-S showed stronger anti-inflammatory effect in the rat inflammation model (hind paw edema caused by administration of mucous polysaccharide present in red algae – carrageenan induction test) [30].

Direct comparison of the relative strength of anti-inflammatory activity of individual polyunsaturated fatty acids present in the studied oils showed the following results: DPAn-6 (DPA-ω6) > DHA > EPA, while the studies of biological effects of combinations of ethyl esters of these acids: DHA + EPA and DHA + DPAn-6 (DPA-ω6), both in carrageenan test and in the test of *in vitro* migration of neutrophils and other phages stimulated by the chemotactic factor *N*-formyl-Met-Leu-Phe (fMLP) suggested that DPAn-6 (DPA-ω6) has high anti-inflammatory potential, either by itself, or via its metabolites [30].[1]

Detailed studies of the biological activity of DPA-ω6 and its various derivatives in two animal models of acute inflammation (mice, rats) [17] and in the murine model of delayed hypersensitivity [18] showed that the active compounds of high anti-inflammatory potential are two oxylipid derivatives formed from DPA-ω6 upon treatment with 15-LOX, i.e. 17*S*-hydroxydocosa-4Z,7Z,10Z,13Z,15E-pentaenoic acid (**17*S*-hydroxy-DPAn-6** or **17*S*-HDPAn-6** or 17***S*-DPA-ω6**) and

[1] In their work [30], Nauroth JM et al. consequently use the abbreviation DPAn-6 for the docosapentaenoic acid of the omega-6 series, while in this study, this acid is referred to as DPA-ω6; both abbreviations are equivalent.

10S,17*S*-dihydroxydocosa-4Z,7Z,11E,13Z,15E-pentaenoic acid (**10S,17*S*-diHDPAn-6** or **10S,17*S*-HDPA-ω6**). Due to their activity in the final phase of acute inflammations, these compounds were nicknamed **DPA-ω6 resolvins**. The popular name of these resolvins is oxylipins. Of note are particularly the data showing the anti-inflammatory activity *in vivo* in the delayed hypersensitivity model, where 17SHDPA-ω6 resolvin at doses as low as 5 μg/kg body mass caused statistically significant effect comparable to the effect of dexamethasone at the dose of 500 μg/kg body mass [18].

Formation of DPA-ω6 resolvins (oxylipins) was demonstrated both in *ex vivo* conditions, with DPA-ω6 incubated in the environment containing fresh whole human blood, and *in vivo*, where rats received DPA-ω6-enriched diet for 19 days. In the first model the main identified metabolite was 17*S*-HDPA-ω6, while in the second model, presence of 17*S*-HDPA-ω6 was detected in blood, bronchi, heart and, in smaller amounts, in small intestine, lungs and kidneys. Other studies showed that under *in vivo* conditions, formation of oxylipins from DPA-ω6 was higher than formation of DHA-derived resolvins. It should be mentioned that DPA-ω6 resolvins (oxylipins) were not detected in biological systems in which the ω6-precursor had not been used [17].

The aforementioned studies revealed yet another important observation of potential practical importance. It turned out that the metabolic stability of DPA-ω6 resolvins (oxylipins) and, for comparison, the 17-hydroxy derivative of DHA (all compounds were incubated at a concentration of 10 μM in microsomal human liver extract) was the highest for 10,17-HDPA-ω6 and 17-HDPA-ω6. Thus, the DPA-ω6 derivatives are metabolically more stable, which is a parameter of high importance when designing potential drugs. Finally, another practical hint was the fact that supplementation with DPA-ω6-containing products led to *in vivo* synthesis of pro-inflammatory oxylipins, which may interfere with the course of the inflammatory process.

Conclusion

When analyzing biosynthesis and properties of anti-inflammatory pro-resolving mediators, it is finally worth turning our focus to their precursors, i.e. the polyunsaturated fatty acids. They are commonly referred to as PUFAs or LCPUFAs, as in long-chain PUFAs. These acids are prevalent in living organisms, both vegetable and animal, starting from the simplest, single-cell organisms and ending at the most complex ones, including the human. They are nearly ubiquitous and indispensable for both normal cell structure and normal course of numerous physiological processes. PUFAs are integral components of plasmatic membranes, playing numerous roles [32, 33]. Despite PUFAs being so important, not all living organisms are capable of synthesizing them in sufficient amounts – therefore, they must be supplied from the outside. Humans are one of such organisms.

The function of fatty acids is determined by their chemical structure (having or not having double C=C bonds between carbons in the hydrocarbon chain) and spatial conformation (*cis* or *trans* forms), which is associated with the presence or absence of such bonds. The number of C=C bonds is decisive of the degree of unsaturation of each PUFA, while location of the last C=C bond (starting at the carboxyl end) in relation to the last carbon labeled by the Greek letter omega (ω, Ω), regardless of the length of the structure, decides whether the compound belongs to the omega-3, omega-6 or even omega-9 series. In other words, the last C=C bond may be treated as the first double bond in relation to the omega carbon; if it is present at position 3 → omega-3 (ω3) acids, position 6 → omega-6 (ω6) acids, position 9 → omega-9 (ω9) acids [32, 33].

Arachidonic acid, often mentioned in this study and a precursor of numerous both pro- and anti-inflammatory mediators (the latter including lipoxins), is a fatty acid of the omega-6 series; the series is started with linolic acid (C18:2ω6), having two double C=C bonds. Transformations of the lipid compounds of the omega-6 series are completed with docosapentaenoic acid (C22:5ω6), having 5 C=C bonds and known under the acronym DPA-ω6 (to differentiate from DPA-ω3, i.e. docosapentaenoic acid of the omega-3 series). Pro-resolving mediators – oxylipins – are formed from DPA-ω6. Transformations of omega-3 fatty acids, including three precursors of numerous pro-inflammatory mediators as discussed in this work: EPA→DPA-ω3→//→DHA, are started with α-linolenic acid (C18:3ω3), containing 3 C=C bonds, and completed with the already mentioned docosahexaenoic acid (DHA; C22:6ω3), characterized by six double C=C bonds. Reactions leading to increase in the number of double bonds and elongation of the hydrocarbon chain are catalyzed by enzymes known as desaturases and elongases, respectively, with the last stage of transformations in both series being the so-called β-oxidation, requiring translocation of appropriate substrates from endoplasmic reticulum to peroxisomes. The presence or absence of particular desaturases or elongases is decisive whether the particular cell/tissue or organ/organism is

capable of producing the particular acid. In addition, insufficiency of formation of certain acids may be due to the fact that the same enzymes take part in transformations of lipids in the omega-3, omega-6 and omega-9 series, competing for substrates. For instance, increased supply of omega-6 or omega-9 acids (common in popular vegetable oils), would cause reduction in production of omega-3 acids. And, in reverse, intensive intake of fish rich in omega-3 acids with simultaneous reduction in the supply of vegetable products would disturb the omega-3/omega-6 equilibrium in favor of the former. Proper omega-3/omega-6 ratio should be in the range of 1/2-4. Fig. 8 presents a scheme of transformations of omega-3 and omega-6 fatty acids (arrows at appropriate acids indicate their capability of being further transformed into compounds of high biological activity, including pro-inflammatory mediators).

First reports turning attention to the possibility of new (as it was referred to at that time) transformations of arachidonic acid into lipoxins, 15-epi-lipoxins, as well as docosahexaenoic acid into (neuro)protectin were published over 25 years ago [7, 46]. At that time, only few researchers believed that these studies would point out a novel direction for research - important not only for the purposes of gaining new knowledge, but also for practical applicability. Studies on metabolically stable analogs of lipoxins and resolvins have recently crossed the border of experiments and laboratory trials and entered the phase of functional and clinical trials [3, 5, 8, 9, 35, 40, 50].

Capability of pharmacological control of inflammation, including the process known as parainflammation may contribute to satisfactory therapeutic success in case of many diseases of unfavorable course, especially of the chronic type, such as asthma, coronary disease or rheumatoid arthritis, as well as certain diseases of the organ of vision [35, 36]. Of note are dynamically expanding studies of the role of (neuro)protectins in the physiology and certain pathophysiological conditions, as well as promising attempts to use such mediators in animal models of neurological and psychiatric disorders, as well as in clinical practice of management of such disorders, including Alzheimer's disease, and ophthalmological disorders such as age-related macular degeneration (AMD), which may lead to blindness [6, 24, 36].

The importance of the problem of rapid and complete resolution of inflammatory reaction without pathomorphological and/or physiological traces may be proven by very dynamic and extensive research on anti-inflammatory pro-resolution mediators: lipoxins, resolvins, protectins, maresins and oxylipins. The number of experimental and clinical data on the effects of these mediators, either formed endogenously or administered externally (for therapeutic reasons) is growing rapidly, ensuring optimistic attitude among physicians and a wide group of patients with inflammatory diseases, which are not easy to treat. Unique and extensive studies, e.g. those led by the unquestionable leader in the area of lipid pro-inflammatory mediators, Charles N. Serhan (Harvard Medical School, Boston, MA), continuously provide new information [42, 48, 50], contributing to the expansion of knowledge of the course of inflammation, the resolution of inflammation and potential use of pro-inflammatory mediators in therapy.

The practical aspect of the cited works is associated with yet another fact, i.e. the potential to regulate the supply of the precursors of the pro-inflammatory mediators of interest, i.e. polyunsaturated fatty acids, by means of appropriately profiled diet or supplementation with PUFA-containing products [32, 33]. Many products containing fatty acids, both of the omega-3 and the omega-6 series, as well as combinations thereof, are available at the market. Reasonably taken, these products may prove very useful, if not as drugs, then surely as auxiliary agents in the treatment of many disorders. It should be kept in mind that many metabolites of these acids, particularly of these being of high interest to a large part of the society (EPA and DHA), include compounds of high biological activity and anti-inflammatory and (neuro)protective profile.

Acknowledgements:

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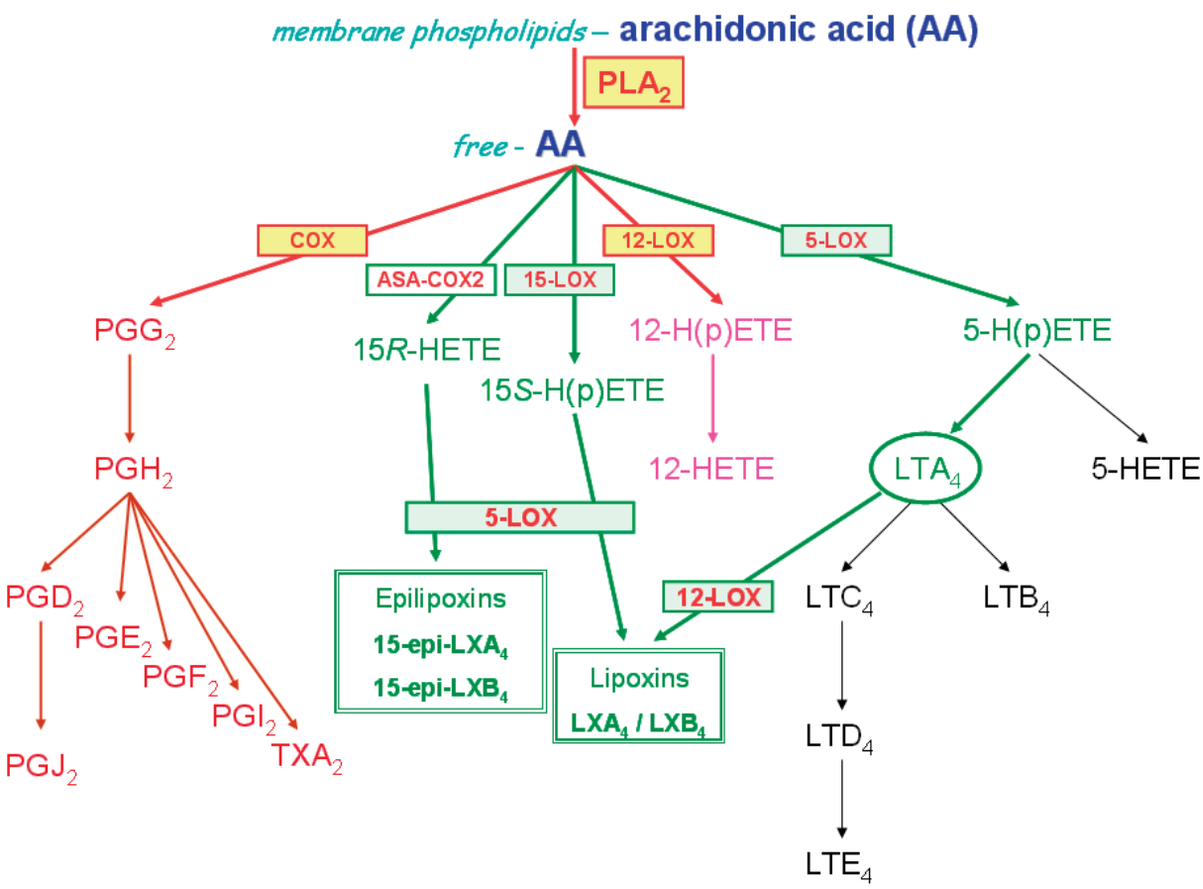


Figure 11: Metabolic pathways of a polyunsaturated omega-6 fatty acid, arachidonic acid (AA; C20:4-ω6). See text for explanations.

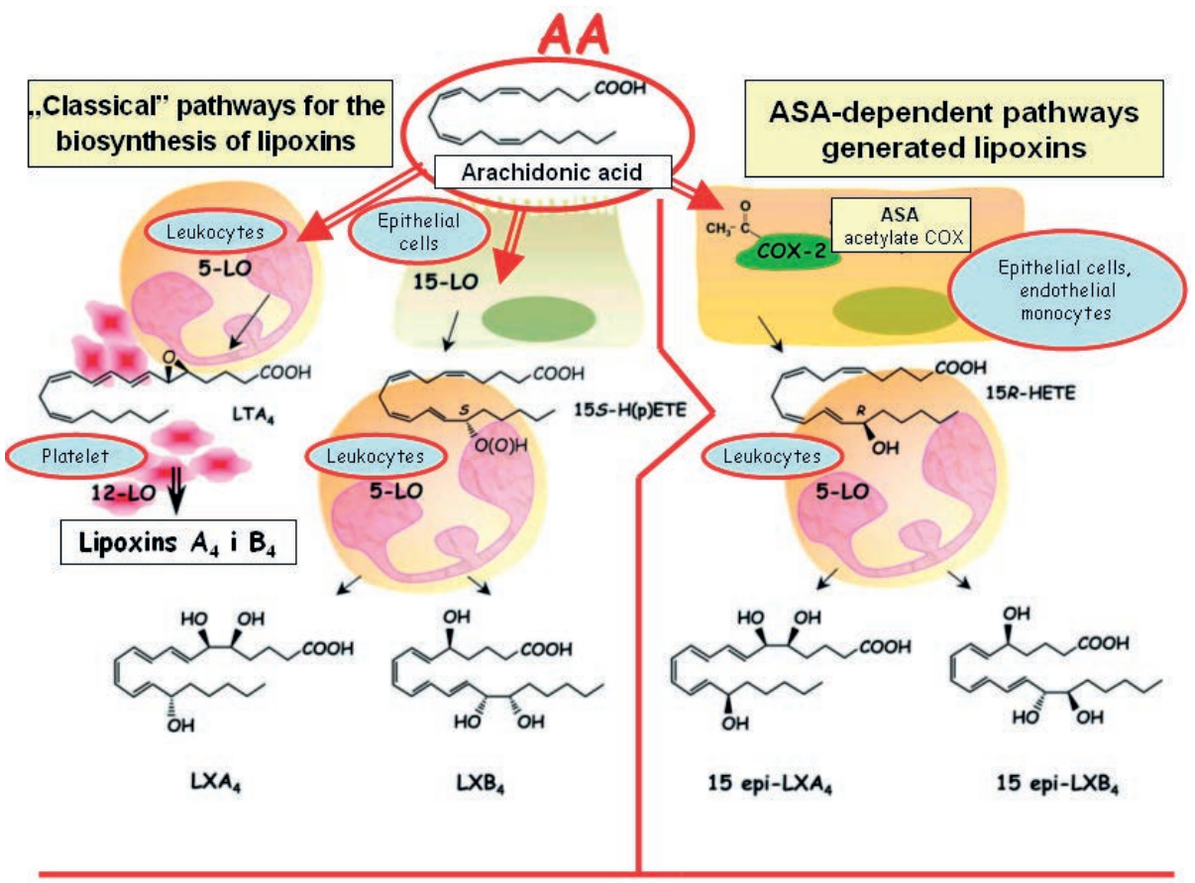


Figure 12: Transcellular synthesis of lipoxins (LXA_4 and LXB_4) and epilipoxins (15-epi-LXA4 and 15-epi-LXB_4)..

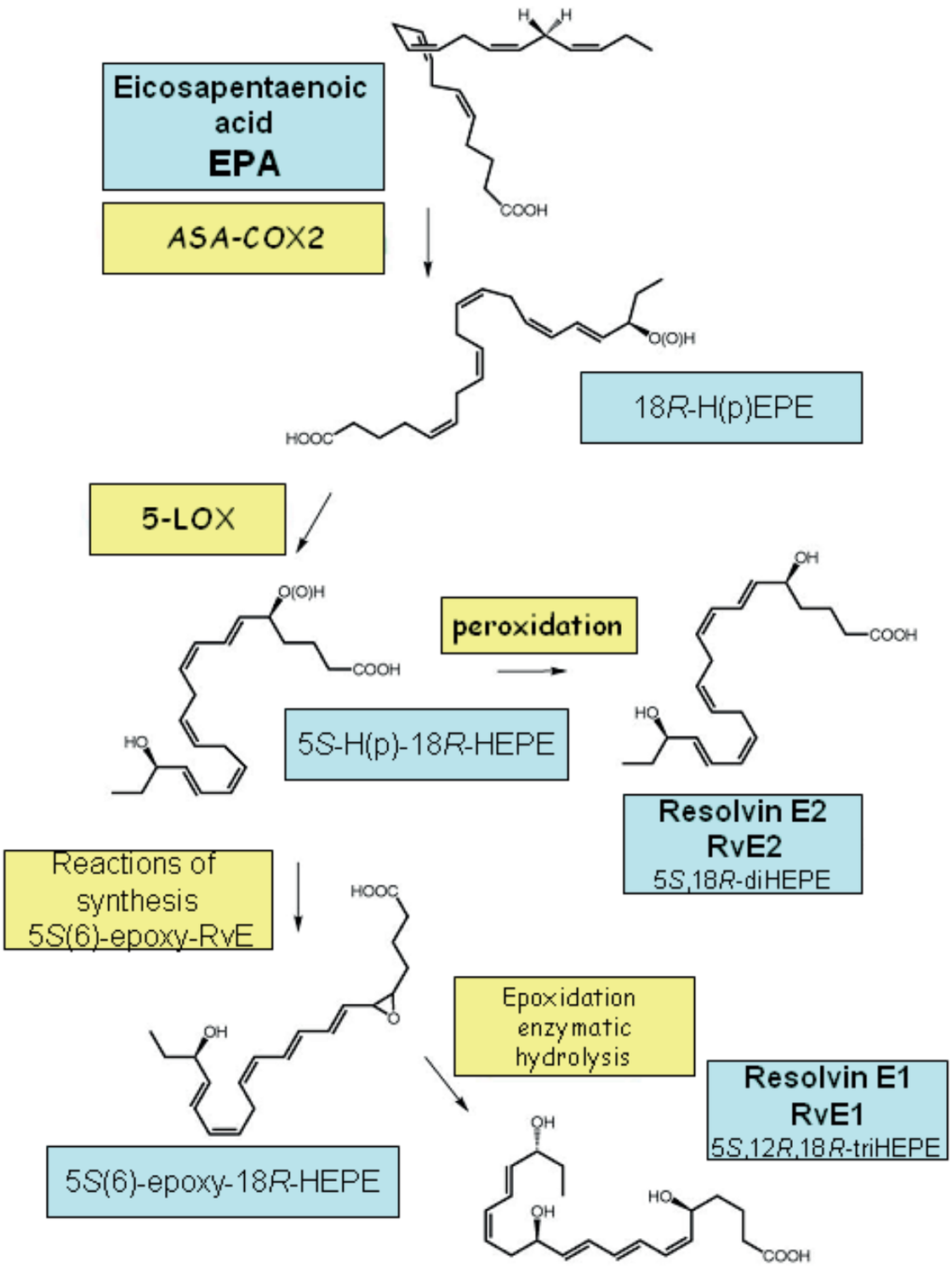


Figure 13: Pathways of biosynthesis of resolvin E series from eicosapentaenoic acid (EPA; C20:5-ω3).

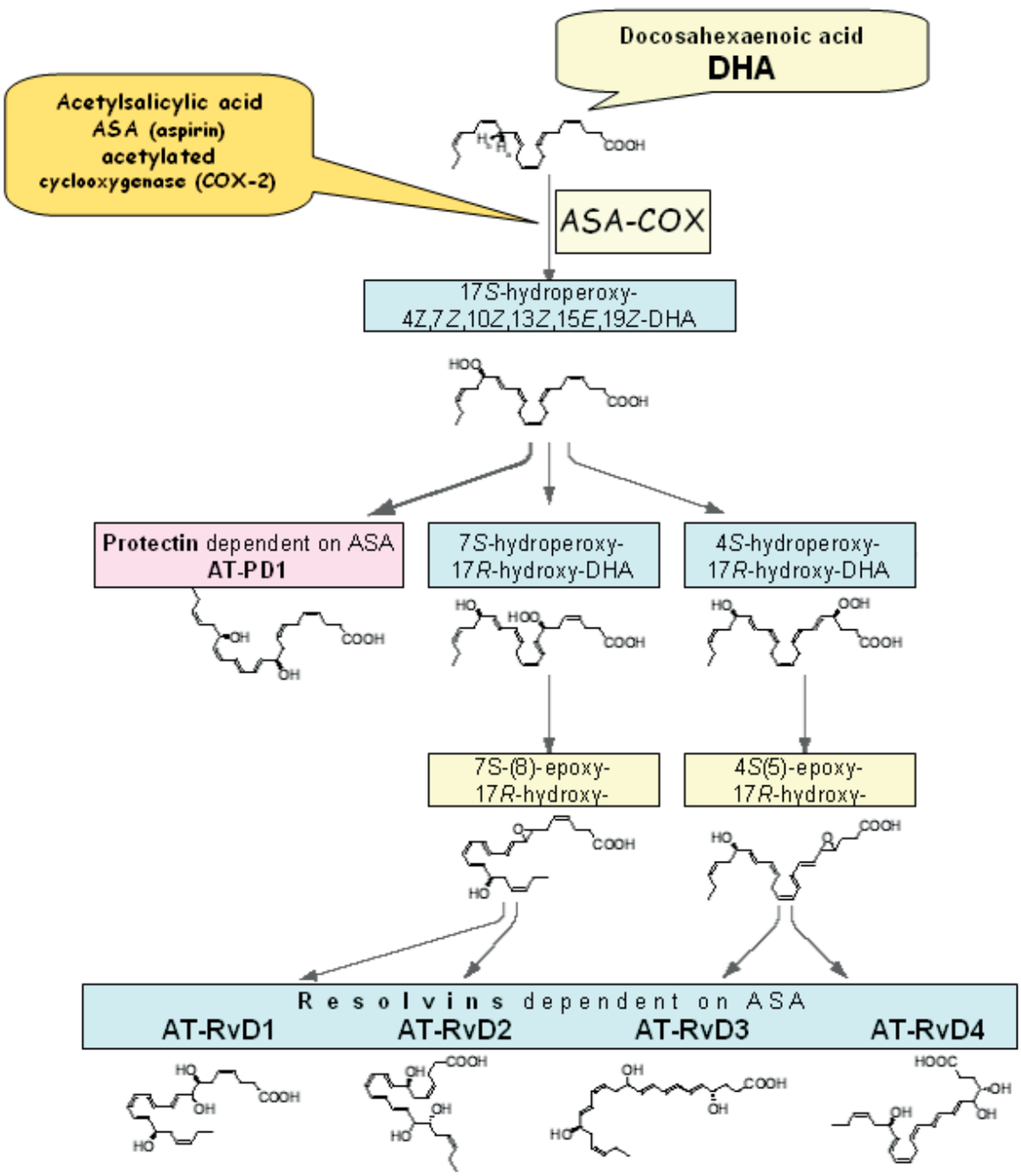
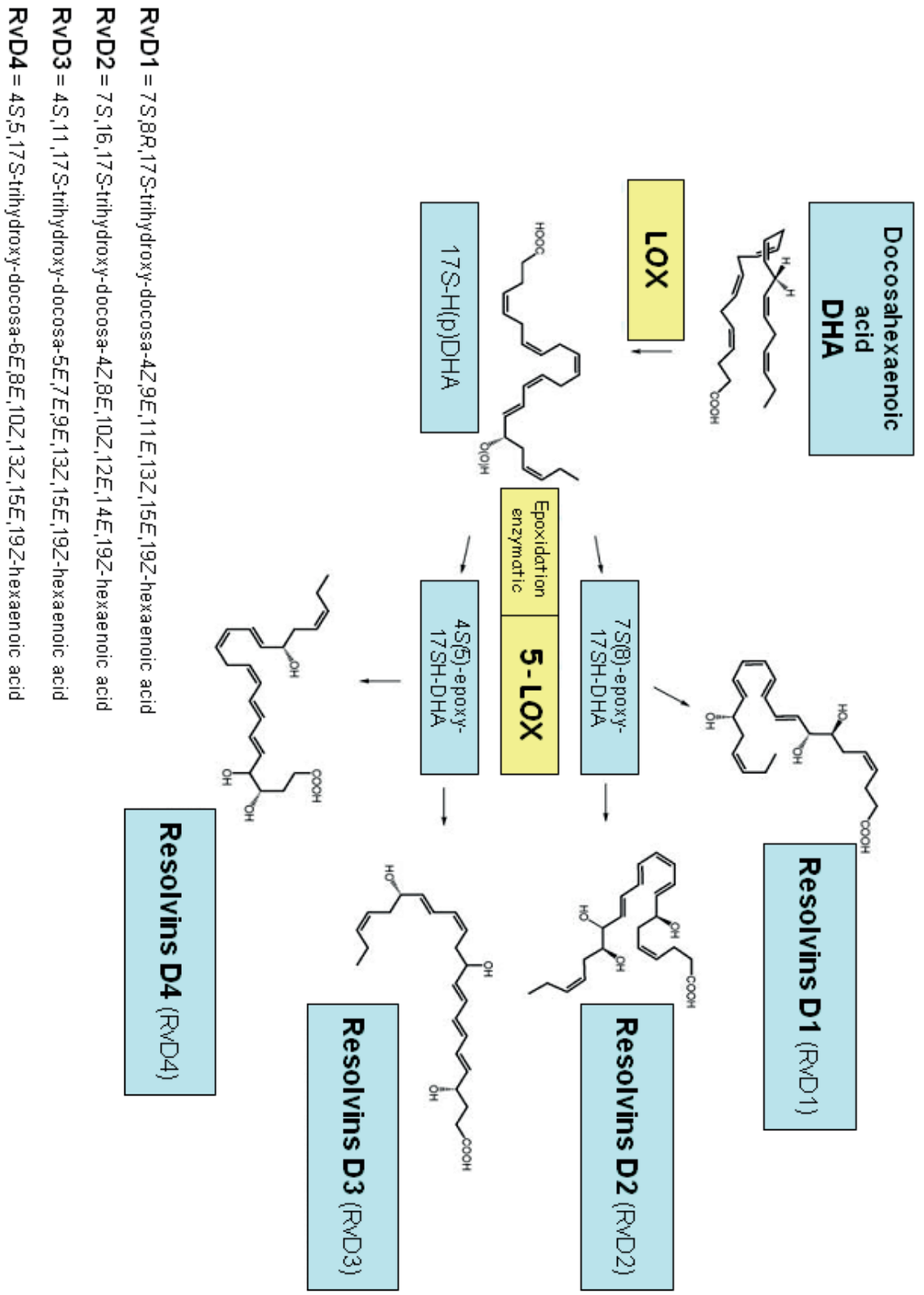


Figure 14: Pathways of biosynthesis of aspirin-triggered resolvin D series form docosahexaenoic acid (DHA; C22:6-ω3) with contribution from acetylated COX-2 (ASA-COX2).



RvD1 = 7*S*,8*R*,17*S*-trihydroxy-docosa-4*Z*,9*E*,11*E*,13*Z*,15*E*,19*Z*-hexaenoic acid

RvD2 = 7*S*,16,17*S*-trihydroxy-docosa-4*Z*,8*E*,10*Z*,12*E*,14*E*,19*Z*-hexaenoic acid

RvD3 = 4*S*,11,17*S*-trihydroxy-docosa-5*E*,7*E*,9*E*,13*Z*,15*E*,19*Z*-hexaenoic acid

RvD4 = 4*S*,5,17*S*-trihydroxy-docosa-6*E*,8*E*,10*Z*,13*Z*,15*E*,19*Z*-hexaenoic acid

Figure 15: Pathways of biosynthesis of resolvin D series from docosahexaenoic acid (DHA; C22:6-ω3).

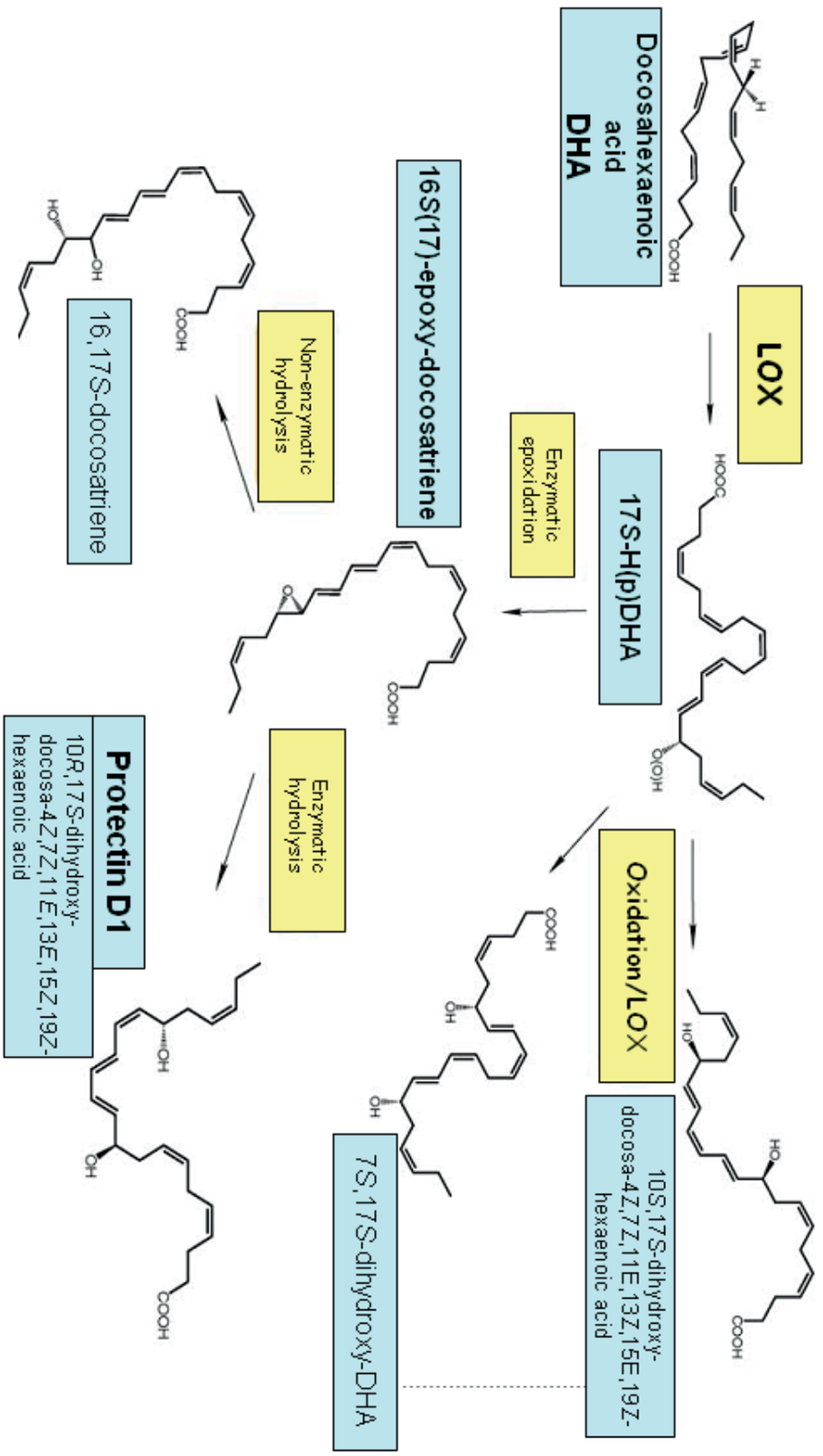


Figure 16: Pathways of biosynthesis of (neuro)protectin D1 from docosahexaenoic acid (DHA; C22:6-ω3).

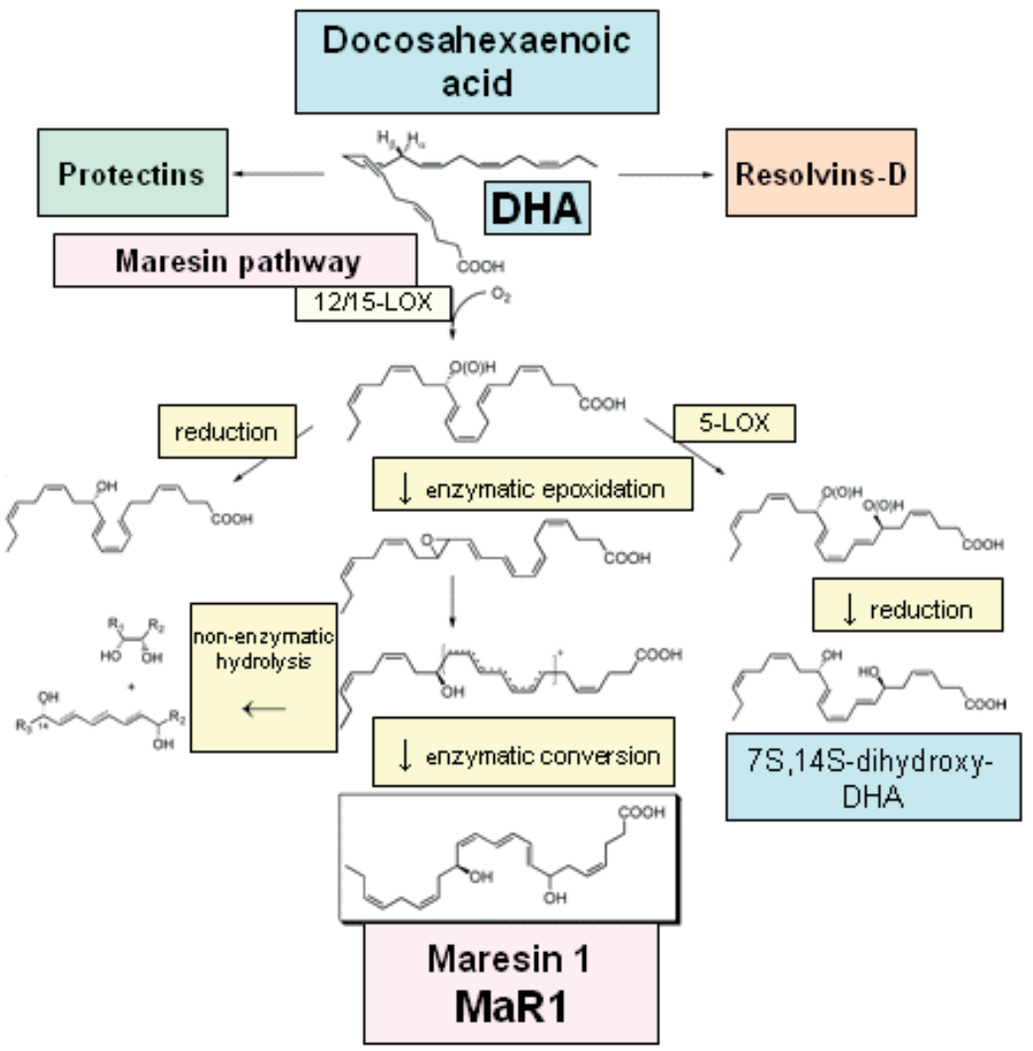


Figure 17: Pathways of biosynthesis of maresin from docosahexaenoic acid (DHA; C22:6-ω3). .

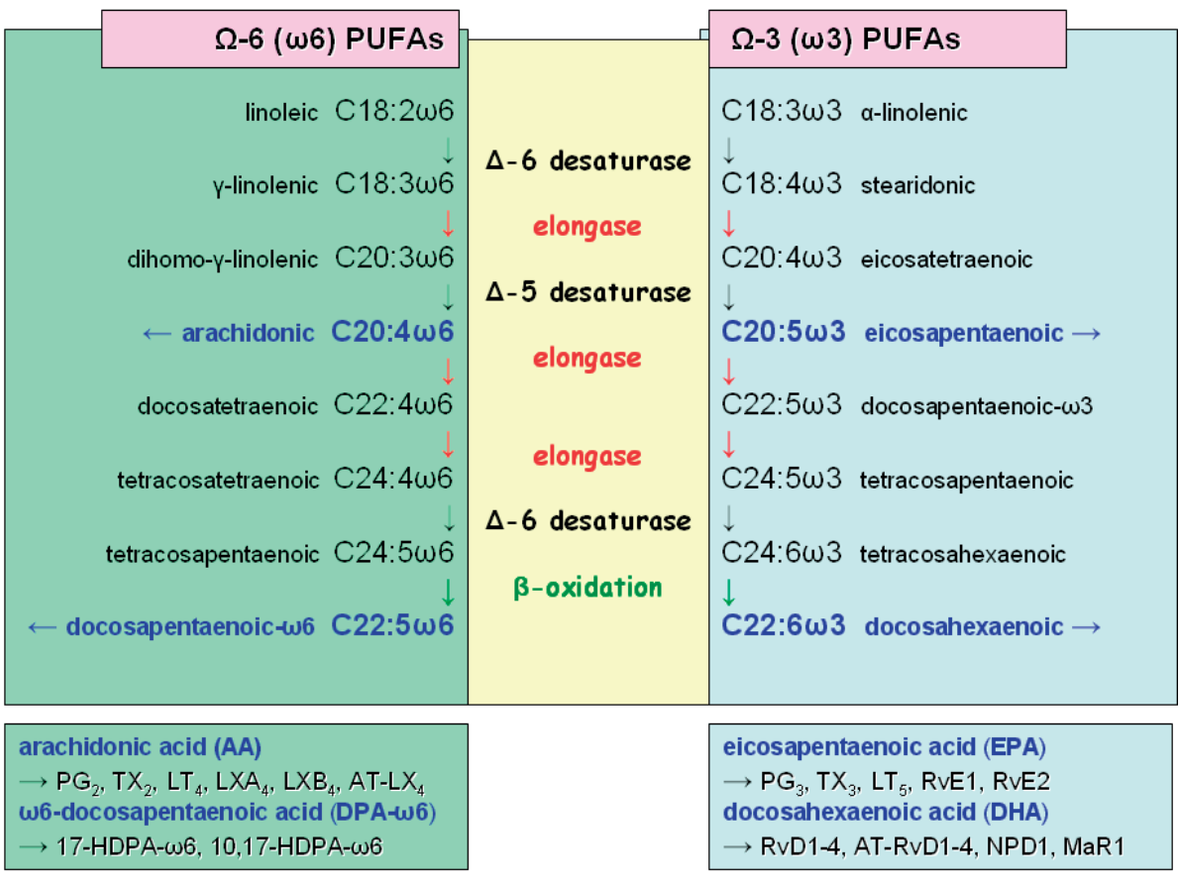


Figure 18: List of biological effects of anti-inflammatory pro-resolving mediators resulting from their impact on neutrophils, macrophages, dendritic cells, lymphocytes and thrombocytes. ↑ is for: increase, enhancement or activation; ↓ is for: drop, reduction or inhibition of activity.

Table 3: List of biological effects of anti-inflammatory pro-resolving mediators resulting from their impact on neutrophils, macrophages, dendritic cells, lymphocytes and thrombocytes. ↑ is for: increase, enhancement or activation; ↓ is for: drop, reduction or inhibition of activity.

Neutrophils	**RvE1 / RvE2 / RvD1 / AT-RvD1 / PD1**	↓ neutrophils mobilization
	PD1	↑ CCR5 expression
	RvE1 / AT-RvD1	↓ transmigration through the endothelium and epithelium ↓ expression of L-selectin and CD18 in neutrophils and monocytes ↓ leukocyte-endothelial interactions
	MaR1	↓ neutrophils migration; ↑ monocytes migration
Macrophages	**RvE1**	↑ phagocytize apoptotic neutrophils ↑ phagocytes removal by the lymphatic system
	PD1	↓ release TNF through macrophages of bone marrow origin
	PD1 / RvE1	↑ phagocytosis stimulation of apoptotic thymocytes through macrophages ↓ leukocyte-endothelial interactions
	RvD1	↓ release of pro-inflammatory cytokines by macrophages
	MaR1	↑ Zymosan phagocytosis stimulation by macrophages
Dendritic cells	**RvE1**	↓ IL-12 production by the dendritic cells ↑ dendritic cells population development inducing apoptosis of T lymphocytes
Lymphocytes	**PD1**	↓ T-cells migration and ↓ secretion of TNFα and IFNγ
	RvE1 / RvD1	↑ CCR5 expression on T lymphocytes
Thrombocytes	**RvE1**	↓ platelet aggreagtion actvation ADP & receptor TBX dependent (but not aggregation initiated by colagen)

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