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Inflammation: course and role of PUFA–derived lipid mediators in the resolution of inflammatory reaction

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Summary:

Inflammation is a complex process being a physiological defense reaction of living tissues to injury or infection. Many mediators generated locally and coming from other places to the area of damage/infection participate in inflammatory reaction, including those derived from immunological, hormonal and nervous system. The course of inflammation largely depends on nature of the causing factor (physical, chemical, biological) and extent of interference, yet a general pattern of sequential molecular and cellular events constitute a common inflammatory reaction independent on the site in an organism.

The course of an acute process can de described by three phases: initiation/development – plateau – resolution, in which specific pro- and anti-inflammatory mediators take part. Acute inflammation has several programmed phases, including complete resolution or progression to chronic inflammation. Para-inflammation is a process that in some aspects resembles inflammation, its course however does not proceed classical schema: acute → chronic inflammation. Para-inflammation may contribute to chronic age-dependent degenerative diseases.

Many mediators of inflammation (e.g. prostaglandins and leukotrienes) derive from omega-6 polyunsaturated fatty acid (PUFA) – arachidonic acid (AA). Studies on AA-derived pro-inflammatory mediators led to discovery of AA-derived anti-inflammatory compounds. They include: lipoxins – derived from AA, resolvins – derived from omega-3 and omega-6 PUFA, as well as (neuro-)protectin and maresin – derived from PUFA omega-3. Because of their role in resolution phase of inflammation, these anti-inflammatory mediators were named proresolving mediators. They are formed by two cooperating cells present in the region of inflammation in a process called transcellular biosynthesis with the aid of specific lipoxygenases and cyclooxygenases. Anti-inflammatory proresolving lipids are considered to become potential drugs.

This article surveys current knowledge on inflammation and the role of proresolving anti-inflammatory lipid-derived mediators, and their possible use in therapy.

Key words: inflammation, proresolving anti-inflammatory mediators, polyunsaturated fatty acids omega-6 and omega-3, lipoxins, resolvins, (neuro-)protectin, maresin, oxylipins

Inflammation: acute, chronic and para-inflammation

Every living organism has defence systems against adverse effects of tissue/organ damage. Regardless of the causing factors (chemical, physical, biological e.g. microorganisms and/or their toxins), the consequence of such damage is a homeostasis malfunction, that is a functional balance on the level of cell/tissue/organism. An organism answers with activation of adaptive reaction – complex, sequential and

interdependent regulatory mechanisms aiming at restoring the homeostasis. Their goal is not only to repair the damages, but also to protect against further damages. Regulatory mechanisms, that are reparative in nature, include humoral and homeostatic cellular responses as well as neurovascular response. They are connected to each other, playing a crucial role in the course of repair process and constitute the essence of the inflammation.

Inflammation (lat. *inflammatio*) is a non-specific, but predictable defensive reaction of living tissues and the whole organism to the damage, including four fundamental elements:

1) increased blood flow to the infected or damaged area,
2) increased permeability of capillary veins that contributes to a leak of bigger molecules from plasma to surrounding tissues,
3) leukocytes' migration from vessels to the damaged/infected area,
4) elimination of undesirable factors (phagocytosis, apoptosis).

Depending of the type, location and size of a damage as well as individual sensitivity and the scope of defensive reaction, the course of inflammation in a person, though qualitatively similar in every organism (Fig. 1), may progress in various manners. It may differ in dynamics and final effect. An inflammation may last few/several days → acute inflammation (*inflammatio acuta*), which may end with full healing without leaving morpho-functional marks, or may last for months, years → chronic inflammation (*inflammatio chronica*).

An inflammation may develop in several forms, i.e. serous including catarrhal inflammation (frequently occurring 'running nose'), purulent (usually triggered by the presence of pyogenic bacterium e.g. *Staphylococcus* or *Streptococcus*), fibrinous (i.a. bacterial infections), hemorrhagic (which leads to severe damage to the blood vessels), gangrenous, ulcerative or pseudomembranous. The list of diseases of chronic inflammatory origin includes i.a. atherosclerosis, asthma, rheumatoid arthritis, periodontitis, Alzheimer's disease, Crohn's disease, retinopathies and age-related macular degeneration (AMD). The course of such diseases may be persistent and continuous or recurrent.

In contrast to short-lasting acute inflammation, chronic inflammation frequently leads to various dysfunctions and tissue damage, where inflammatory process takes or took place. Its occurrence is usually associated with a negative end of an acute inflammation, which as a result of partial healing turns into a chronic form. Even though such scenario occurs certainly in many cases, it is worth mentioning that, as it is assumed in some cases originating in inflammation (based on results of modern diagnostics), no evident, classic lesions indicating any ongoing inflammatory processes are observed. It applies also to routinely performed diagnostic tests typical for inflammation.

To the group of such diseases belongs serious, age-related ophthalmological condition, resulting from degenerative lesions of 'retinal pigment epithelium – photoreceptor cells' complex in the area of the macula, know under shortened name AMD [25, 26, 50]. This category of conditions includes also a number of neuropsychiatric diseases, which are a consequence of chronic neurodegenerative process, and also diabetes mellitus type, 2 and the above-mentioned arteriosclerosis or asthma [13,15, 21, 24, 46, 49]. Patients suffering from mentioned diseases do not recall in the past any major acute inflammatory episode which may become a cause of chronic process. Consequently, a chronic inflammation does not necessarily have to be preceded by an acute inflammatory process. The process, which resembles in some aspects an inflammation, but is not a typical inflammation, is more and more frequently described in scientific literature as *para-inflammation* [20, 30, 50].

The essence of para-inflammation process is well conveyed by the situation taking place in an ageing organism. Even though the pathogenesis of various age-related conditions of acknowledged or supposed inflammatory grounds is well known, it is often hard to find a specific factor (damage/injury to the tissue or bacterial infection) triggering an acute inflammatory reaction or supporting the condition of chronic inflammation. In an ageing organism various cellular and organic dysfunctions (mulfunctions) appear. They reflect either an accumulation of diversified undegradable products of metabolism, e.g. material known as lipofuscin, or other deposits with potential cytotoxic properties (i.a. protein or lipoprotein), or an inability to rebuild worn-out or dying cells, especially so-called postmitotic cells. Sometimes, such age-related deposits accumulating in excess in lysosomes or outside the cell, which can not be degraded, may induce an immunological reaction being enough for initiating inflammatory process, which, however, never attain acute phase. Para-inflammation may be described as an adaptive response of the tissue to widely understood, harmful stress or dysfunctions (mulfunctions). Many factors lying on the border of pathology can create a stressful situation for a cell/organ. In addition to the above-mentioned ones, it may also be an excess of reactive oxygen species, lingering hyperglycemia or cholesteremia. In sample situations cells/organs are functioning, but functional tension borders on evident malfunctions. Such state of danger or 'smouldering' dysfunction may be recognized by

non-specific (innate) mechanisms of immunological system, whose role is to initiate repairing actions by e.g. starting 'inflammation programme' aiming at restoring homeostasis.

The course of inflammatory process

The course of classic inflammation and *para-inflammation* process may differ both quantitatively (individually variable severity of different symptoms, clinical and biochemical indicators of inflammation) and qualitatively (differences concern especially the course of chronic inflammation – continuous course, remissions, relapses, various acuteness). That is why applying common algorithm of sequences of physiological and biochemical processes related to inflammation may give rise to some difficulties.

While considering inducing factors and the 'realization' paths of inflammatory reactions, Medzhitov [20] proposed the following general sequence: inducers → sensors → mediators → effectors. Expanding of this sequence would concern the observed differences in the course of inflammation. To the group of inducers of inflammation several factors may be counted, namely exogenous factors (bacteria or other factors e.g. allergens, foreign bodies, toxic substances, irritant factors) and endogenic factors (coming from cells, tissues, plasma and extracellular matrix).

Depending on the 'activating' factor further course of inflammatory reaction may be diversified. Examples of the above-mentioned sequence are listed below [according to 20]:

- bacterial lipopolysaccharide (inducer), TLR4 (sensor), TNFα/IL-6/PGE2 (mediator), endothelium cells/leukocytes/hepatocytes/other (effectors)
- allergen (inducer) → IgE (sensor) → vasoactive amines (mediator) → endothelium/smooth muscles cells (effectors)
- collagen (inducer) → Hageman factor (sensor) → bradykinin (mediator) → endothelium/smooth muscle cells (effectors)

As mentioned, several kinds of responses with cellular and humoral responses among them determine the course of an inflammatory reaction. The first one depends on the inflow and activation of some types of cells, whose activity contributes to specific dynamics of inflammatory reaction, also owing to the production of signal compounds i.e. inflammatory mediators and proteolitic enzymes (Fig. 1). Among the cells participating in the inflammatory reaction there are blood cells (neutrophil granulocytes, also called neutrophils, lymphocytes, monocytes, eosinophil granulocytes, basophil granulocytes and plateles), endothelium and connective tissue cells (macrophages, fibrobasts, mast cells i.e. mastocytes) (Fig. 2).

Plasma factors participate in the humoral response. They reflect changes in the complement system, blood coagulation, fibrinolysis and the system producing kinines (bradykinin), which may trigger not only local, but also systemic reactions. Other important components of intercellular connective tissue, so-called intercellular matrix, e.g. collagen, proteoglycans, laminins, fibronectins or small fragments of hyaluronan also possess pro-inflammatory activity [1, 9, 28]. The aforesaid systemic response of neurovascular character, in addition to local consequences may have also general ones.

Circulatory or haemodynamic lesions responsible for signs such as flushing and oedema are the first response of the tissue/organism to a damage. They appear after few/several minutes after a stimulus starts operating. Leukocytes which activities determine the development and the course of inflammatory process already in this initial phase, reach the damage area. Migration of leukocytes is defined by the term transmigration (diapedesis) and it is preceded by other steps as margination, rolling, activation and tight adhesion. Those steps are under strict control of many factors participating in the inflammation and show in a harmonic way the development of inflammatory reaction. A detailed description of the steps may be found in other work of the author [31], as well as in Kelly's et all [12], thus they will not be discussed herein.

After reaching the target and depending from the properties of leukocytes (granulocytes – neutrophils) as well as other cells participating in an inflammation (see Fig. 2), the cells initiate the defence reaction. Being activated, the cells begin producing i.a. pro-inflammatory cytokines e.g. interleukins IL-1α /β, IL-6, IL-8 and TNF-alpha (tumour necrosis factor). While being outside the circulation, the granulocytes transform into microphages and monocytes into macrophages. Their role is to phagocytose for exapmple microbes, if there is a bacterial infection, or dying (apoptotic) cells in the area of injury/damage. There are other inflammatory mediators occurring locally and in bodily fluids that emerge in the area of inflammation: histamine, serotonin, C-reactive protein (CRP), kinines, platelet-activating factor (PAF) and metabolites of arachidonic acid such as leukotrienes, prostaglandins, thromboxane. What follows afterwards is a vascular reaction (increase of permeability of vascular endothelium) and pain reaction (resulting from the presence of inflammatory pain mediators – mainly kinines and prostaglandins). In the inflammatory focus lowering of pH takes place, as well as haemolysis of erythrocytes, aggregation and adhesion of platelets to detaching

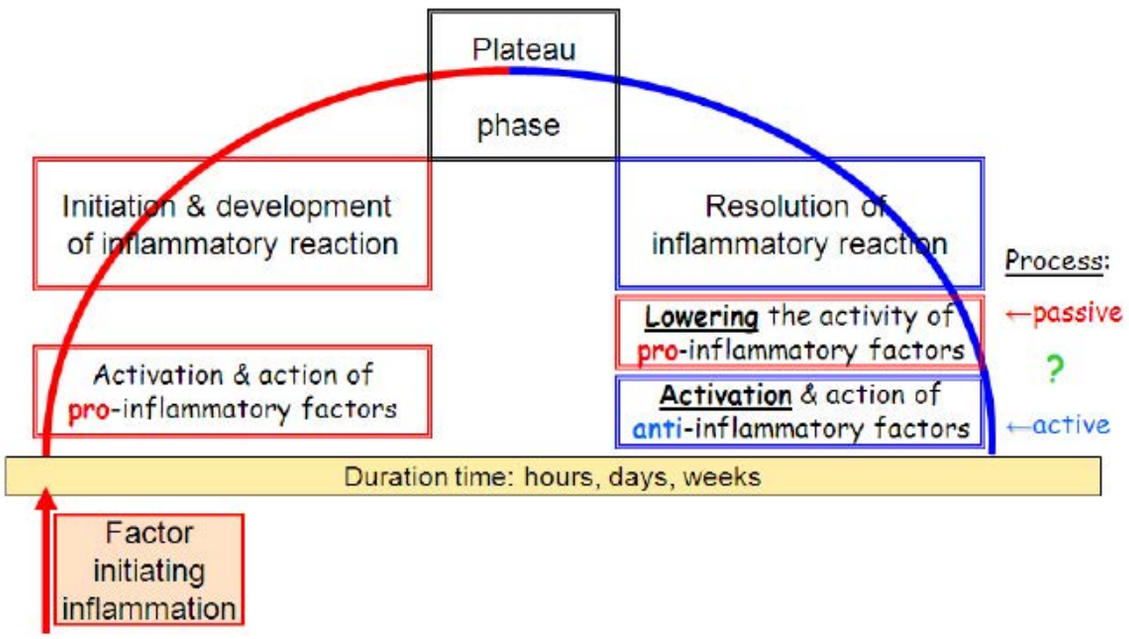

Figure 1: Diagram showing the course of acute inflammatory reaction. The attention should be paid to two possibilities discussed in the paper of ending (resolving) of inflammatory reaction:
1. by lowering the activity of pro-inflammatory agents as a result of their inactivation or elimination, and
2. resulting from activation and action of proresolving anti-inflammatory agents.
The first process has passive character by nature, whereas the second one is an active process.

epithelium from microvessels, what results in the formation of microclots.

Therefore, the course and duration of the process depends on several mediators that participate in the inflammatory reaction. What is curious, the profile of activity of such mediators may change depending on coexisting molecular and cellular conditions in which an inflammation is progressing. That is why an inconsistent classification of pro-inflammatory ediators may be encountered [1]. The above-mentioned pro-inflammatory mediators and inflammatory reactions refer to the most important mechanisms and constitute only the outline of a complex adaptation process. Further review of mechanisms governing inflammatory process together with the characteristics of other mediators and signals may be found in recent English [4, 9, 17, 20, 48, 50] or Polish [6, 19, 24, 30, 42] review articles.

Resolution of acute inflammatory reaction – passive or active process

Clinical symptomatology has been well-known for a long time both for cardinal signs of inflammation i.e. elevated temperature, redness, swelling, pain and loss of function (described by Roman physicians; the first four were described by Celsus, while the last one was introduced by Galen; the fifth sign was renewed in 19c. by Virchow) and for (patho-)morphological manifestation. However, many detailed molecular and cellular mechanisms being the cause of (or taking part in) inflammatory process including *para-inflammation* were identified quite recently [2-6, 20, 30, 37, 42, 50].

In spite of the extensive knowledge the resolution of acute inflammatory process still remains unsolved (Fig. 1). The last stage of acute inflammation process – the resolution is very important for a patient, because, if proceeding without any problem, it decreases or even eliminates the risk of possible complications and pathology development. If the resolution of acute inflammation does not occur, the acute

[1] One of the widely-used classification of inflammatory mediators is based on their biochemical properties. According to such classification mediators may be divided into seven groups: 1. vasoactive amines (histamine, serotonin); 2. vasoactive peptides (e.g. substance P, kinines, fibrinopeptides A and B, products of proteolysis of Hageman factor, thrombins, plasmins); 3. components of complement system (especially anaphylotoxins: C3a, C4a and C5a); 4. lipid mediators (eicosanoids, platelet-activating factor); 5. pro-inflammatory cytokines (e.g. TNF-alpha, IL-1, IL-6, IL-8); 6. chemokines; and 7. proteolytic enzymes (e.g. elastins, cathepsins, matrix metalloproteinases).

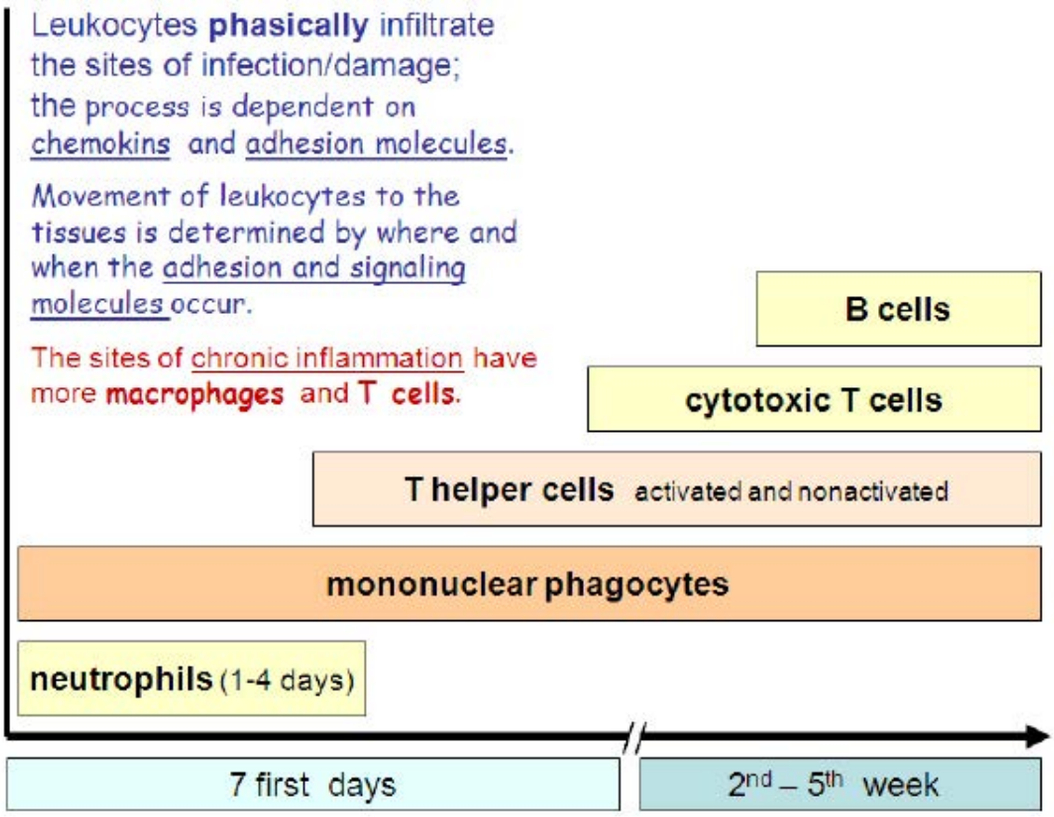

Figure 2: Sequential occurrence of various cells in the area of short- and long-lasting acute inflammation. Description in the text

process consistently transforms into the chronic one, which may proceed in two manners: either symptomatically, when the patient complains of specific ailments and additional tests confirm the presence of functional and/or morphological lesions of a cell/tissue or other pathology, or asymptomatically – without any visible clinical symptoms or measurable laboratory parameters of the inflammation. Being often underestimated, the new situation takes place, which is a potential cause of further health complications that may occur in any moment in life (e.g. the above-mentioned AMD pathology [23, 33]).

So why in some, quite frequent cases the inflammation does not end rapidly, but stretches in time and transforms into a chronic form? The question concerns the resolution of acute inflammatory process, therefore the mechanism which governs the full healing process. It may be assumed that if the damaging and triggering inflammatory reaction factor was not too heavy and lasted for a short period of time, the whole reconstructive process will proceed fast, without exposing for complications in the form of transition to chronic phase. If the cause of inflammation happened to be an infection, the organism has to manage to annihilate a microbial invasion.

This aspect may prolong the duration necessary for recovery and restoring the homeostasis. However, in this case the risk of potential distant complications still remains, because the endogenous (physiological) or exogenous (therapeutic, e.g. antibiotic therapy) treatment may not result in full eradication of an intruder, whose presence may be felt unexpectedly in distant time from invasion, e.g. Chlamydia pneumonia infections and further complications) [2].

Apart from pro-inflammatory cytokines that participate in development and implementation of the 'inflammation programme', anti-inflammatory cytokines can be found in the area of inflammation, i.a. IL-4, IL-10 or TGF-β. Moreover, the activity of kininases occurs which contributes to decreases in the concentration of kinines and afterwards the concentration of anti-inflammatory endogenous corticosteroids. The presence of listed anti-inflam-

[2] Infections caused by Chlamydia pneumoniae usually affect children (upper respiratory tract infections – rhinitis, pharyngitis) and are benign or asymptomatic with tendency to self-healing. They are hard to detect, often resistant to antibiotic therapy and easily transform into a chronic form, whereas microbes may survive in the tissues for a very long time (an asymptomatic carrier or chronic infection with subclinical course)

matory factors as well as a number of observations pointing at the participation of other direct or indirect anti-inflammatory mechanisms suggests that the resolution of acute inflammation is not a passive process that results from neutralisation or spontaneous elimination of damaging (pro-inflammatory) factor. On the contrary, the resolution seems to be an active process, in which mediators specifically programmed for the participation in the final phase of inflammatory response are present. Such mediators are lipid compounds with an anti-inflammatory and proresolving potential, i.e. *anti-inflammatory proresolving mediators*, whose name refers to the term describing the final phase of inflammation – *the resolution of inflammation* [3]. In order to highlight their active participation in resolution of acute inflammatory reaction, such compounds are also called *proresolving agonists*. They constitute a large group of mediators derived from polyunsaturated fatty acids omega-6 (lipoxins and oxylipins) and omega-3 (resolvins, maresin, (neuro-)protectin). Figure 3 shows chemical structures and characteristics or three omega-6 and omega-3 polyunsaturated fatty acids (arachidonic acid, AA; eicosapentaenoic acid, EPA, docosahexaenoic acid, DHA), from which the majority of proresolving mediators is derived. Figure 3 does not show below-mentioned (in the next subchapter) omega-6 docosapentaenoic acid (DPA-ω6), which is a compound closing 'classic' conversion of omega-6 acids (linoleic acid → // → AA → // → DPA-ω6) [27, 28]. It has been suggested that the conversion of acute inflammation into a chronic one is related to functional malfunctions in the resolving phase – the resolution. It is supposed to result from dysfunction of proresolving mediators (proresolving agonists). Such a view on healing of inflammatory process and formation of chronic inflammation is quite inventive, but based on more and more conclusive scientific evidence.

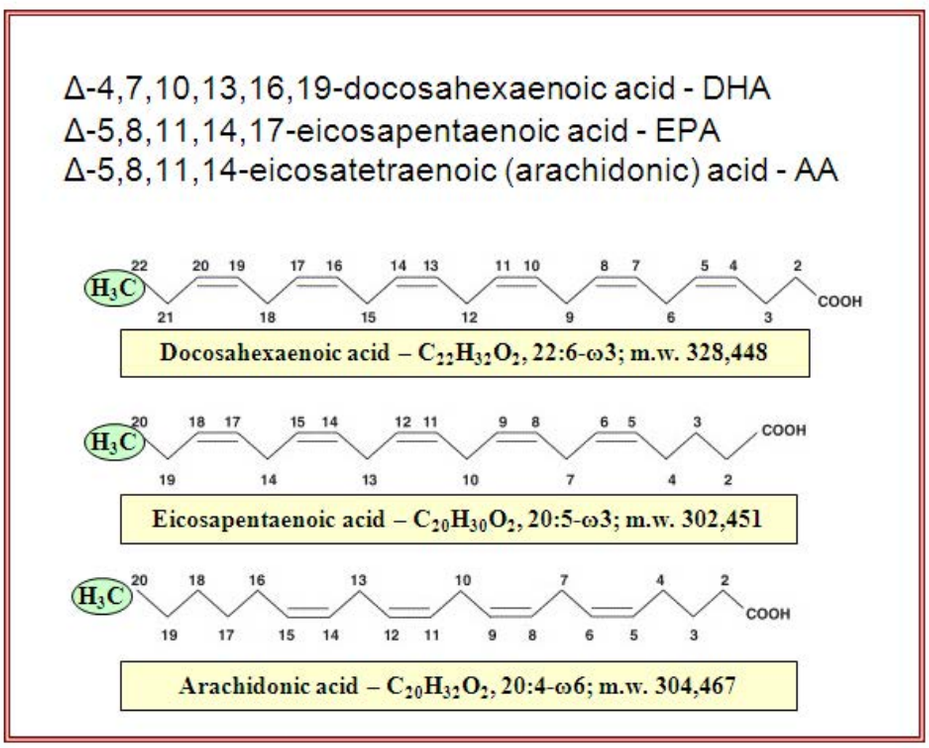

Figure 3: Chemical structures and basic characteristic of three omega-3 (EPA, DHA) and omega-6 (AA) PUFA.

[3] *Resolution* (Eng.) = *resolution* (Lat.) = *katabasis* (Gr.) = *katabaza* (Polish equivalent) i.e. delitescence or absorption (e.g. of infiltration, exudate). This is the last phase of inflammation, a return from the phase of active inflammatory process to recovery, which also refers to the abatement of the illness (pathology) and return to homeostasis (physiology). According to 'Wielki Słownik Medyczny' (published by PZWL in 1996), *resolution* = *catabasis* is the final stage of acute inflammation course, which depends on factor causing inflammation, reactive properties of a tissue and whole organism and leads either to recovery (return to the initial state) or turns into a chronic inflammation.

The role of omega-6 and omega-3 PUFA-derived lipid mediators in the resolution of acute inflammatory reaction

As mentioned before, the acute inflammation is a defense reaction of an organism for tissue damage and disturbed homeostasis on the cellular and tissue level. Restoring the homeostasis on every level of cellular and tissue organization requires activation of both local and systemic mechanisms. However, the activation of local mediators – especially those produced from substrates present in the area of inflammation – guarantees fast response exactly through localized actions. Proresolving mediators, thus mediators having anti-inflammatory potential, participate in the final phase of acute inflammatory reaction. Their local biosynthesis and presence in the area of inflammation is a natural response of cells/tissues threatened by functional destabilisation accompanying or being a result of inflammatory reaction. Proresolving mediators seem to be similar to a physiological 'handy' weapon used by an organism forced to defend itself, especially that they are derived from polyunsaturated fatty acids (PUFAs) present in plasma membrane of each cell and delivered with food or by supplementation, and transported to the area of inflammation [11, 27, 28]. Anti-inflammatory proresolving mediators i.e. lipoxins, resolvins, oxylipins, (neuro-)protectin and maresin are derived from four PUFAs either from the family of omega-3 acids (ω3; EPA and DHA) and from the family of omega-6 acids (ω6; AA and DPA) [3, 7, 8, 22, 38-40, 43-45]:

- **Arachidonic acid** (**AA**; **C20:4-6**) **lipoxins** (LXA4 and LXB4) and AT-lipoxins (15-epi-LXA4 and 15-epi-LXB4);
- **Eicosapentaenoic acid** (**EPA; C20:5-3**)**resolvins E** (RvE1 and RvE2);
- **Docosahexaenoic acid** (**DHA; C22:6-3**)**resolvins D** (RvD1, RvD2, RvD3, RvD4) and **AT-resolvins-D** (AT-RvD1, AT-RvD2, AT-RvD3, AT-RvD4); (**neuro-**)**protectins**(docosatriens; NPD1/PD1) **maresins** (MaR1);
- **Docosapentaenoic acid omega-6** (DPA-ω6; C22:5-6) **oxylipins** – resolvins (17-HDPA-ω6, 10,17-HDPA-ω6).

Derived from four PUFAs, the anti-inflammatory lipid mediators identified so far constitute 8 families (lipoxins, AT-lipoxins, resolvins-E, resolvins-D, AT-resolvins-D, maresins, protectins, oxylipins), each containing 1 to 4 active compounds. In total

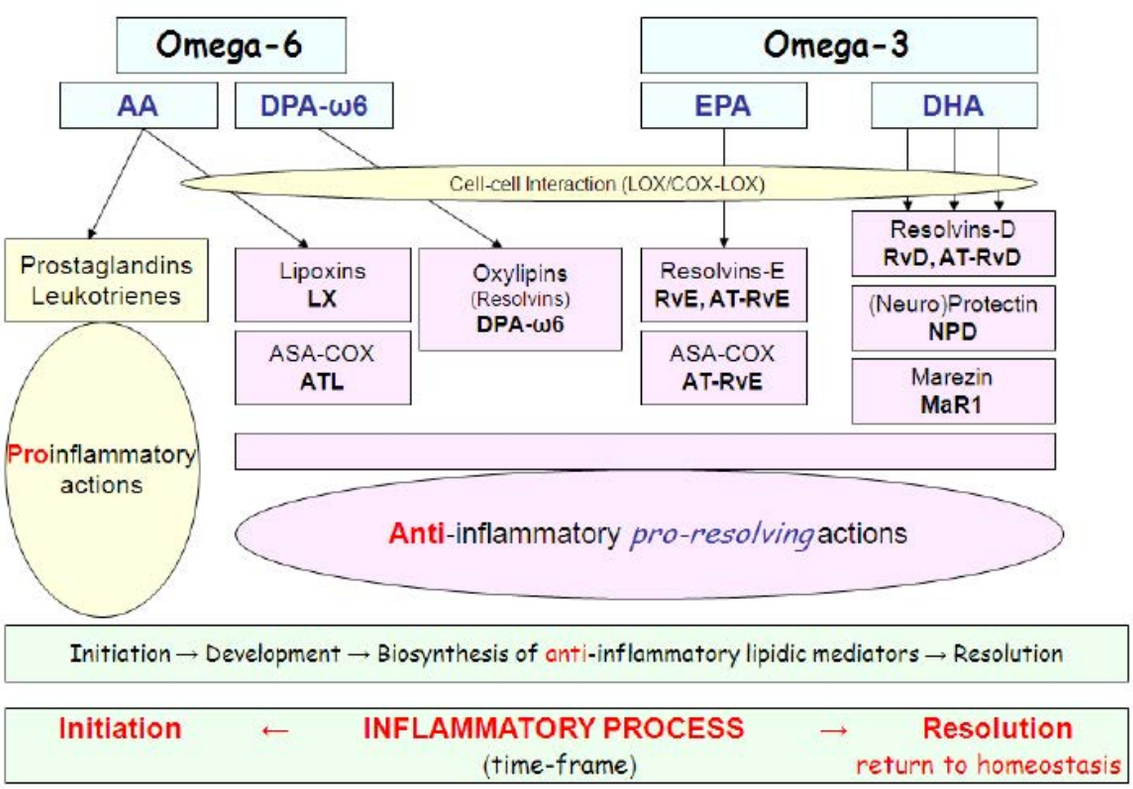

Figure 4: Temporal course of acute inflammatory reaction taking into consideration pro-inflammatory and anti-inflammatory (proresolving) lipid mediators. Description in the text

there are 18 such well-characterized, biologically active compounds, but their number may increase rapidly, because in *in vivo* conditions the possibility of various enzymatic and non-enzymatic changes of many PUFAs including the formation of stereoisomeric compounds differing in biological properties [2, 3, 30, 39, 41].

The production of the above-mentioned anti-inflammatory lipid mediators takes place in cell-specific process defined as a transcellular biosynthesis. Two different cells present in the area of inflammation participate in this process, e.g. leukocytes – platelets, epithelial cells – leukocytes or endothelial cells/epithelial cells/monocytes – leukocytes. Being present in specified cells, the enzymes from the family of lipoxygenases (LOX-5, LOX-12, LOX-15) and cyclooxygenases (COX-2 or ASA-COX2; the latter is the enzyme acetylated with the aid of acetylsalicylic acid, a common aspirin) as well as monooxygenases from the family of cytochrome P450, sequentially catalyse changes of initial substrates (AA, EPA, DHA, DPA) to lipid compounds with anti-inflammatory potential. Biosynthesis of anti-inflammatory lipid mediators requires therefore interaction of various types of cells, which transfers semi-finished products for further processing to each other and spontaneous non-enzymatic reactions (e.g. epoxidation or hydrolysis). Detailed description of biosynthesis and inactivation, pharmacological properties and mechanisms of action of particular mediators can be found in other articles of the author [29, 31] as well as in many recently published original and review articles [2, 3, 5, 35, 36, 37, 39, 41].

Among the mentioned anti-inflammatory mediators derived from omega-3 and omega-6 PUFAs, a number of compounds preceded with an abbreviation 'AT' (AT-lipoxins, AT-resolvins) originating from, i.e., can be found. The abbreviation AT means 'aspirin-triggered' – dependent on aspirin (acetylsalicylic acid); it aims at emphasizing the fact that AT-mediators were produced by COX-2 acetylated with the aid of aspirin, i.e. ASA-COX2. It should be mentioned that acetylation of COX-2 deprives the enzyme capacity to catalyze transformation of e.g. AA into pro-inflammatory compounds (i.a. prostaglandins and leukotrienes), and simultaneously opens the way for new metabolic pathways, as the

Table 1: Anti-inflammatory and pro-inflammatory action of derivatives of omega-3 PUFA: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and of omega-6 PUFA: arachidonic acid (AA) and docosapentaenoic acid (DPA- ω6)

Agent	Omega-6 mediators originating from Arachidonic acid	← Physiologic action	→ Physiologic action	Omega-3 mediators originating from EPA and DHA
Prostaglandins	PGD_2, PGE_2 PGF_2, PGI_2	pro-arythmic	anti-arythmic	PGD_3, PGE_3 PGF_3, PGI_3
Thromboxane	TXA_2, TXB_2	activator of platelets constraction of vessels	inhibitor of platelets dilation of vessels	TXA_3, TXB_3
Leukotrienes	LTA_4, LTB_4, LTC_4, LTD_4, LTE_4	pro-inflammatory	anti-inflammatory	LTA_5, LTB_5, LTC_5, LTD_5, LTE_5
Derivatives of Epoxyeicosatriene	5,6-EET, 8,9-EET 11,12-EET, 14,15-EET	inflammatory		
Derivatives of Hydroxyeicosatetraenoate	5-HETE, 12-HETE 15-HETE			
Lipoxins	LXA_4, LXB_4	anti-inflammatory		
Resolvins			anti-inflammatory	RvE1, RvE2 RvD1, -2, -3, -4
Neuroprotectin			anti-inflammatory	NPD1
Marezin			anti-inflammatory	MaR1
Derivatives of DPA-ω6	17-HDPA-ω6 10,17-HDPA-ω6	anti-inflammatory		

acetylated enzyme acquires new catalytic properties concentrated on the changes of PUFAs to anti-inflammatory mediators [2, 18, 43].

Table 1 shows anti-inflammatory lipid mediators as well as other biologically important inflammatory mediators derived from omega-3 and omega-6 fatty acids together with their physiological activities.

Figure 4 is the specification of a diagram shown in Fig. 1 and contains suggested answers to still unsolved issue of resolution of acute inflammatory process. Of the two manners of resolution of inflammation shown in Fig. 1, i.e. the passive one (as a result of a decrease of activity and/or elimination of pro-inflammatory agents) or active one (resulting from activation and action of 'agonistic' anti-inflammatory proresolving factors), the second manner seems to be more likely to occur in the light of current knowledge.

A necessary condition for generation of proresolving mediators is the presence in the area of inflammation of cells capable of expressing specific enzymes (LOX, COX) and capable of interacting with each other in order to proceed with transcellular biosynthesis of such compounds. If such situation arises, it points at a far advanced specificity of biosynthesis of lipoxins, resolvins, protectins, maresins and oxylipins derived from DPA-omega-6 (Fig. 4). Such situation determines also some delay in initiating defensive mechanisms, whose task is to actively finish inflammatory reaction via catabasis – resolution phase of inflammatory reaction.

The dynamic aspect of generating *in vivo* anti-inflammatory proresolving mediators was a subject of meaningful study in the past years and it is essential to recall the most important results showing the generation of such compounds within the inflammatory reaction. Studies conducted on mice with induced peritonitis through intraperitoneal injection of zymosan revealed the increase of DHA, EPA and AA concentration with peak level after 2 h (DHA) and 4 h (EPA, AA) from inducing the inflammation. Generation of protectin D1 (PD1) derived from DHA occurred biphasely with two peaks after 2 h and 24 h and increased concentration observed after 24 h was slowly reducing after 24-72 h, still not reaching the basic (initial) level in the investigated period of time [2].

The same study has revealed that intraperitoneal injection of proresolving mediators derived from AA (15-epi-LXA_4), EPA (RvE1) and DHA (PD1) in dose of 300 ng (5 minutes before zymosan administration) rapidly and effectively reduced 'pro-inflammatory' migration of leukocytes and macrophages as well as generation of pro-inflammatory chemokines/cytokines in catabasis phase [2]. Further studies conducted *in vivo* on mice treated with omega-3 PUFA tagged with deuterium (d_5) confirmed rapid (during 2 h) translocation of d_5-EPA and d_5-DHA to the area of inflammation, displaying a correlation of anti-inflammatory effect with the generation of proresolving mediators and a correlation between the occurrence of anti-inflammatory effect with the presence of the same mediators, and not their precursors [11].

A progression of acute inflammation to the chronic one is associated – according to current knowledge – with insufficient production and/or ineffective action of proresolving mediators. The rightness of such concept may be supported with the fact that exogenous administration of metabolically stable lipoxins and AT-lipoxin analogues increases the rate of healing of inflammatory lesions both *in vitro* and *in vivo* conditions [14, 34, 35-37, 41]. Such tests show that agonist drug may be an effective anti-inflammatory agent, which mimics the actions of endogenously generated proresolving mediators, and hence strengthen physiological mechanisms.

In recent years numerous studies in several laboratories were aimed at synthesizing various metabolically stable analogues of both lipoxins and resolvins [3, 35]. Lipoxin analogues are currently being tested as drugs in human organism. The tests generally included derivatives mainly of AT-LXA4 (15-epi-LXA4) – the structures generally being more resistant to metabolism and inactivation in vivo. These compounds are known as ATLa1 and ATLa2 that is 15 R/S-methyl-LXA4 and 15-epi-16-(p-fluoro)phenoxy-LXA4 respectively (the latter one occurs as methyl ester being a pro-drug). Other promising lipoxin analogues are 3-oxo-15-epi-16-(p-fluoro)-phenoxy-LXA4 (ZK-994), o-[9, 12]-benzo-omega6-epi-LXA4 and 16-phenoxy-LXA4. Moreover, resolvin analogues series E and D such as19-(p-fluorophenoxy)-RvE1 and 17-(R/S)-methyl RvD1 (both in the form of carboxymethyl ester) are currently undergoing advanced and promising pre-clinical studies and preliminary clinical trials [3, 14, 35, 36, 41, 47].

Intensive researches are in progress, they bring closer the day, which may turn into a breakthrough in the therapy of acute and chronic inflammations [3, 47]. In the latter group many diseases conditioned by the presence of chronic inflammatory process with typical course and defined as a para-inflammation may be placed. They all are difficult to treat and constitute serious medial concern. Will metabolically stable analogues of proresolving anti-inflammatory mediators meet a challenge? The time will show.

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