# Specialized pro-resolving endogenous lipid mediators and resolution of the inflammatory process

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## Abstract

Inflammation is an essential protective response against injury or infection. Physiological inflammation eliminates the pathogen, promotes tissue repair and healing. An exaggerated, out of control inflammation, however, can become pathological. Inflammation can generate secondary cell damage, inflame the vessels (endothelitis), activate coagulation processes. Among these pathogenetic factors (cell damage, inflammation, endothelitis, coagulopathies), self-amplification mechanisms can be created, spreading beyond the initial site, up to Multiple Organ Failure (MOF) and host death. If the inflammation does not resolve in a physiological way, the remodeling of the tissues can be maladaptive and lead to the onset of chronic inflammatory degenerative diseases. Diseases such as sepsis, burns, polytrauma, severe forms of influenza or COVID-19, are characterized by a condition of hyperinflammation, associated with a condition of immunosuppression. The initial events triggered by the pathogen (cell damage, interferon response in the case of viruses) ignite the inflammation by activating the inflammasome, the transcription factor NFkB, the release of pro-inflammatory eicosanoids (Prostaglandins, Leukotrienes, Thromboxanes) by neutrophils and macrophages. Hence, the cells of the innate immune system produce pro-inflammatory cytokines. Indeed, the ''eicosanoid storm'' precedes the ''cytokine storm''. Eicosanoids are a group of potent endogenous lipid mediators derived from omega-6 fatty acids Arachidonic Acid (AA). Eicosanoids include a group of molecules with pro-inflammatory (Prostaglandins, Leukotriens) and pro-coagulant (Thromboxanes) action. In addition, Arachidonic Acid (AA) is the source of Lipoxins (LXs). Lipoxins belong to a group of molecules collectively referred to as specialized pro-solving mediators (SPMs) which also include molecules derived from ω-3 eicosapentaenoic acid (EPA): Resolvins (ReV-E sieres) and ω-3 docohexanoic (DHA): Resolvins D-series (ReV D-series); Protectins (PTs); Maresins (MaRs). SPMs are important for the resolution phase of inflammation to take place properly. Their deficiency could be involved in both acute uncontrolled inflammation and chronic inflammation. The active regulation of the acute inflammatory process, integrating the precursors of Specialized Pro-resolving Mediators (SPMs), such as ω-6 and ω-3 in balanced ratio, or the SPMs themselves, could be a complementary therapeutic approach useful for taming the ``storm of cytokines '' which characterizes exaggerated forms of inflammation. ω-3 and ω-6 are part of already widely used, readily available, inexpensive and safe supplements. Resolvins have already been included in clinical trials for various other inflammatory diseases (eye diseases, periodontal diseases).

**Keywords**: Inflammation; Cytokine Storm; ω-3; ω-6; SPMs; Resolvins;

## Inflammation resolution

Uncontrolled inflammation, named ‘’cytokine storm’’, is a common pathogenetic mechanism for severe diseases that may require hospitalization in the ICU and are burdened with high mortality rates, such as sepsis, ARDS and multi-organ failure (MOF) [4,5,13,21,35,37]. In these pathologies an exaggerated, out of control inflammation, called " cytokine storm " occurs, associated with a condition of immunosuppression (Mehta, 2020) and a condition of hypercoagulability of the blood (Jose, 2020). Some self-amplification mechanisms of these pathogenetic factors (hyperinflammation, immunosuppression, hypercoagulability/thrombophilia) can lead to the overflow of pathogenic factors beyond the site of infection, causing multiple organ failure (MOF) and death of the host. An example of the self-amplification mechanisms that, in a severe form of COVID-19 disease, can trigger uncontrolled inflammation is shown in **Figure 1.**

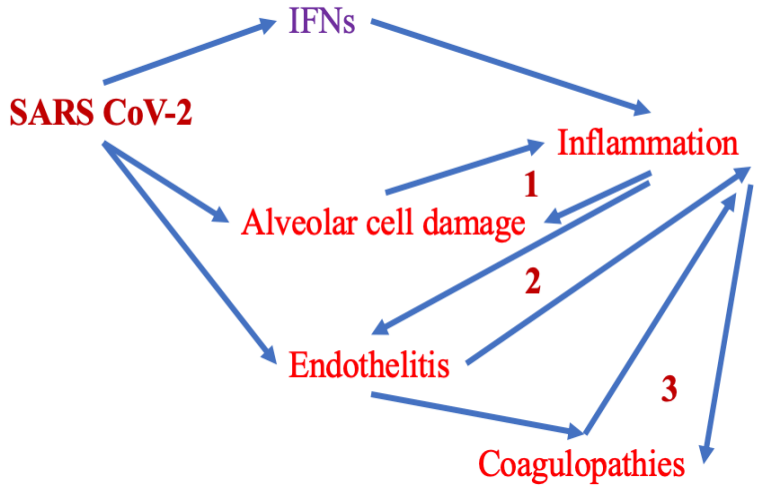


**Figure 1.** The first line of defense against viruses is represented by the interferon response (IFNs I and III). Interferons trigger **inflammation**The SARS CoV-2 virus, thanks to the membrane receptor ACE2, can parasitize the alveolar cells of the lung and endothelial cells. Tissue damage due to the direct action of the SARS CoV-2 virus activates the inflammasome and the inflammation transcription factor NfkB, supporting inflammation. Activated endothelial cells (endothelitis) support inflammation and promote coagulation disorders (thrombosis and disseminated intravascular coagulation) which, in turn, support inflammation. In turn, the inflammation damages the pulmonary alveolar cells and contributes to the aggravation of endothelitis and coagulation disorders (thrombosis and disseminated intravascular coagulation). At least 3 mechanisms of self-amplification of inflammation are created (in the figure numbered from 1 to 3) which can cause pro-inflammatory cytokines to overflow into the systemic circulation (cytokine storm). The anti-inflammatory therapies tested up to now have been directed against the inflammation effectors (tocilizumab: anti IL-6 receptor or Anakinra: anti Il-1 receptor) with a real risk of causing immunosuppression. A series of endogenous molecules, derived from omega-3 eicosanoids (resolvins, maresins, protectins), on the other hand, are able to limit the triggering of inflammation, without the risk of creating immunosuppression (favoring the elimination of cellular debris and dead cells by macrophages) and counteract coagulation disorders. The anti-inflammatory anti-COX-2 drugs block the production of pro-inflammatory eicosanoids but also of these precious molecules that extinguish inflammation [21].

The resolution of inflammation is an active phenomenon [28,31,34] that occurs when the class switching of the lipid mediators of inflammation occurs in favor of lipoxins, Resolvins, Protectins and Maresins [11,17,19,32].

At the cellular level, the resolution phase requires the cessation of neutrophil recruitment and the recruitment and differentiation of macrophages, which clear apoptotic cells and tissue debris to restore tissue homeostasis [3]. **Figure 2.**

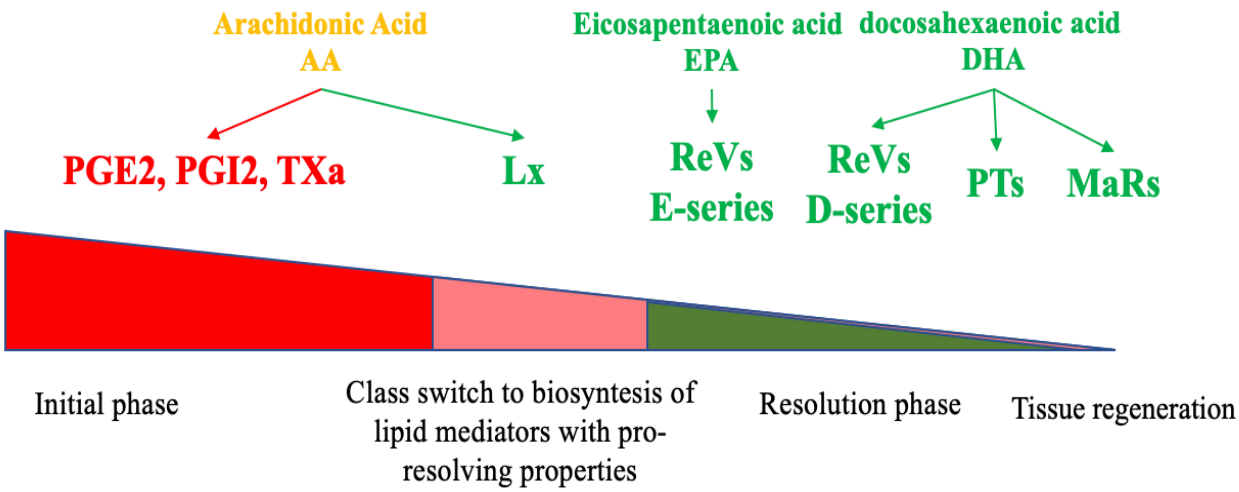


**Figure 2.** The endogenous specialized pro-resolving mediators (SPMs) control key actions of resolution, including leukocyte trafficking, Macrophage reprogramming and Macrophage efferocytosis.

The resolving lipid mediators stimulate the resolution of inflammation by interrupting the recruitment of neutrophils, promoting the efferocytosis of the apoptotic cells and the clearence of the cellular debris (which would maintain inflammation) by macrophages, increasing the phagocytosis of microbes, against regulating and sequestrating pro-inflammatory cytokines, down regulating prostanoids [6,7,10,27]. Classically-activated M1 macrophage populations initially are predominant but are later replaced by an alternatively activated M2 phenotype which play important roles in the resolution of inflammation and in the process of regeneration [7,12]. Pro-resolving macrophages and apoptotic neutrophils also produce SPM [33].

## Endogenous specialized pro-resolving lipid mediators (SPMs)

In response to pathogen or tissue damage, polyunsaturated fatty acids are released from membrane phospholipids to be converted to specialized mediators [15]. Within minutes, arachidonic acid-derived eicosanoids facilitate the recruitment of neutrophils to the site of infection [8,30].
PGE2 and PGI2 regulate blood flow; LTC4 and LTD4 regulate vascular permeability. LTB4 acts as a chemotactic factor for neutrophils [1,18,25,26].
Pro-inflammatory eicosanoids, together with pro-inflammatory cytokines, chemokines and complement factors (C5a and C3b), induce the accumulation of neutrophils at the infection site that engulf and kill pathogens [9,22].
In the resolution phase arachidonic acid metabolism switches from the production of leukotrienes to the production of the mediator pro-resolving lipoxins [17].
Lipid Mediators are derived from ω-3 (fish oil) and ω-6 (vegetable) polyunsaturated fatty acids. ω-6s generates prostaglandins (PG), leukotrienes (LT), thromboxanes (Tx) and lipxins (Lx). The resolvins originate from ω-3 which include eicosapentaenoic acid (EPA) and docohexanoic (DHA). The resolvins are mediators for resolving inflammation and include the E series resolvins, derived from the EPA and the D series resolvins, derived from DHA [2]. **Figure 3.** PUFA are present in various dietary sources, such as fish oil (ω-3 PUFA) and vegetable oil (ω-6 PUFA).

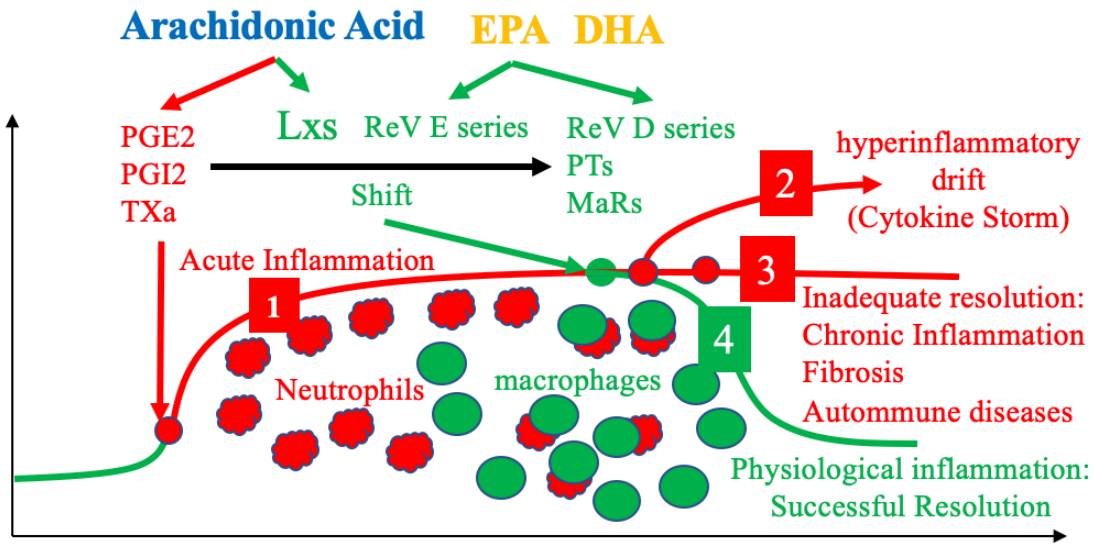


**Figure 3. Possible trajectories of lipid mediators, immune cells and the inflammatory process.** 1: acute inflammation; In response to pathogen or tissue damage, polyunsaturated fatty acids are released from membrane phospholipids to be converted to lipid mediators (PGE2, PGI1, TXa), derived from Arachidonic Acid. Pro-inflammatory eicosanoids, together with pro-inflammatory cytokines, chemokines and complement factors (C5a and C3b), induce the accumulation of neutrophils at the acute inflammation site. 2: hyperinflammatory drift; Some self-amplification mechanisms of these pathogenetic factors (hyperinflammation, immunosuppression, hypercoagulability/thrombophilia) can lead to the overflow of pathogenic factors beyond the site of infection, causing multiple organ failure (MOF) and death of the host. 3: Inadeguate resolution; If the inflammation does not resolve physiologically, it can persist and can lead to chronic inflammatory diseases, fibrosis, autoimmune diseases. 4: Physiological Inflammation (Successfull resolution). The resolution of inflammation is an active phenomenon that occurs when the class switching of the lipid mediators of inflammation occurs in favor of Lipoxins, Resolvins, Protectins and Maresins. At the cellular level, the resolution phase requires the cessation of neutrophil recruitment and the recruitment and differentiation of macrophages, which clear apoptotic cells and tissue debris to restore tissue homeostasis.

ω-6 fatty acids (arachidonic acids) are the precursors of PGs, LTs and LXs. Resolvins derived from ω-3 fatty acids (EPA and DHA) are termed resolvins E (RvE) and resolvins D (RvD) series, respectively [23]. To date, six members of this family has been identified (ReV D1-6). Resolvins are biosynthesized from ω-3 polyunsaturated fatty acids (PUFA) by specific enzymes including lipoxygenase (LOX) [23].

## Conclusions

Inflammation is an essential protective response against injury or infection. Physiological inflammation eliminates the pathogens, promotes tissue repair and healing. Diseases such as sepsis, burns, polytrauma, severe forms of influenza or COVID-19, are characterized by a condition of hyperinflammation, out of control, associated with a condition of immunosuppression. If the inflammation does not resolve in a physiological way, the remodeling of the tissues can be maladaptive and lead to the onset of chronic inflammatory degenerative diseases. The resolution of inflammation is an active phenomenon that occurs when the class switching of the lipid mediators of inflammation occurs in favor of Lipoxins, Resolvins, Protectins and Maresins. At the cellular level, the resolution phase requires the cessation of neutrophil recruitment and the recruitment and differentiation of macrophages, which clear apoptotic cells and tissue debris to restore tissue homeostasis. The resolving lipid mediators stimulate the resolution of inflammation by interrupting the recruitment of neutrophils, promoting the efferocytosis of the apoptotic cells and the clearence of the cellular debris (which would maintain inflammation) by macrophages, increasing the phagocytosis of microbes, against regulating and sequestrating pro-inflammatory cytokines, down regulating prostanoids.

The active regulation of the acute inflammatory process, integrating the precursors of Specialized Pro-resolving Mediators (SPMs), such as ω-6 and ω-3 in balanced ratio, or the SPMs themselves, could be a complementary therapeutic approach useful for taming the `` storm of cytokines '' which characterizes exaggerated forms of inflammation. ω-3 and ω-6 are part of already widely used, readily available, inexpensive and safe supplements. Resolvins have already been included in clinical trials for various other inflammatory diseases (eye diseases, periodontal diseases).

**Abbreviations**

AA: arachidonic acid

DHA: docosahexaenoic acid

EPA: eicosapentaenoic acid

LTs: Leukotriens

LXs: Lipoxins

MaRs: Maresins

PGs: Prostaglandins

PTs: Protectins

ReV E: Resolvin E

ReV D: Resolvin D

SPMs: specialized pro-resolving mediators

TXa: Thromboxanes

**Declaration of interests:**

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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