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Review Article

Specialized pro-resolving mediators - Key players in resolution

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ABSTRACT

Inflammation is an essential biologic response observed across species with particular importance to human health and disease. The primary objective of the inflammatory response is to eliminate the initial cause of inflammation and restore tissue homeostasis. Effective resolution of inflammation is essential for maintaining health; this process is active and marked by a shift from the production of classic lipid mediators like prostaglandins and leukotrienes to the synthesis of specialized pro-resolving mediators (SPMs). These include arachidonic acid-derived lipoxins, aspirin-triggered lipoxins, eicosapentaenoic acid-derived resolvins of the E-series, docosahexaenoic acid-derived resolvins of the D-series, as well as protectins and maresins. Understanding the biosynthesis, mechanisms of action, and therapeutic potential of SPMs is crucial for developing strategies to manage inflammatory diseases and improve health outcomes. This article reviews the current knowledge of SPMs, and their roles in inflammation resolution.

1. Introduction

Inflammation is an essential mechanism in human health and diseases. Roman scientist Cornelius Celsus in the 1st century defined the clinical signs of inflammation. Initially, four cardinal signs of inflammation were identified; rubor et tumor cum calore et dolore (redness, swelling with heat and pain) in 1858. In 1958, Virchow on cellular basis of inflammation as a pathologic condition, added a new cardinal sign, functio laesa (loss of origin/tissue function).[1,2]

The primary goal of the inflammatory response is to detect and eliminate functions that interfere with homeostasis. A typical inflammatory response consists of 4 components. Inflammatory inducers, detecting sensors, downstream mediators, and the target tissues.[3,4] Resolution of inflammation is an active process and this process is normally maintained by endogenous mediators – Specialized pro-resolving mediators.(SPMs).[5–7] (Figure 1)

These are a group of fatty acids, an essential part of the cell membrane and act as metabolic fluid for mammalian tissue. They also function as signalling molecules. Omega -6 fatty acid (Linoleic acid-LA) and omega -3 fatty acid (Linolenic acid-ALA) are essential fatty acids that cannot be biosynthesized by humans/ other animals. LA and ALA undergo sequential desaturation reaction and transform into their higher form which are in their unsaturated form. Arachidonic acid (A.A) is formed from LA and EPA (eicosapentaenoic acid), and DHA (docosahexaenoic acid) from ALA.[8,9]

The pro-resolving lipid mediators include Lipoxins, Protectins, Resolvins and Maresins. Lipoxins (LXs) and aspirin triggered lipoxins (ATLs) are formed from arachidonic acid which mainly decrease inflammation and assist resolution. Omega-3 FA is the source of resolvins, maresins and protectins.[8] (Figure 2)

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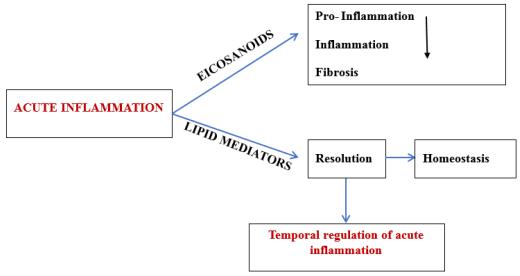

Figure 1: Resolution of natural inflammation

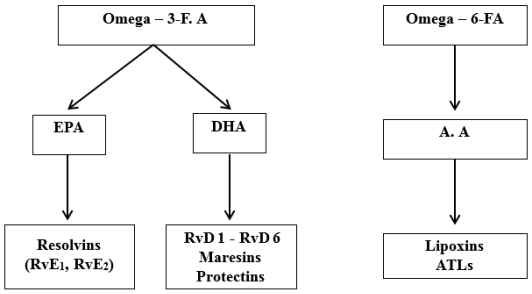

Figure 2: Biosynthesis of lipid mediators

2. Discussion

2.1. Lipoxins

They are natural pro-resolving mediators derived from endogenous F.A. They have strong dual actions, i.e. anti-inflammatory and resolution actions. The first identified lipoxins are lipoxin A4 and B4.[10,11]

2.1.1. Biosynthesis of lipoxin- 3 main pathways has been identified.[12]

1. In blood vessels- Human platelets do not have the ability to produce lipoxins on their own, but become the major source of lipoxin, when they adhere to PMNs (polymorphonuclear neutrophils), i.e. the formation of lipoxin is initiated by platelet-leukocyte interactions. Initially, there is transcellular conversion of 5-LO (lipoxygenases-LOs) product, LTA4(leukotriene A4). When platelet get adhere, 12-LO converts this LTA4 into lipoxin A4 and B4(LXA4 and LXB4 – positional isomers).
2. Classical pathway- In human mucosal tissue, GI tract, oral cavity, the sequential oxygenation of A.A by 15-LO and 5-LO followed by enzymatic hydrolysis leads to the production of lipoxin A4 and B4, i.e. when epithelial cells get activated, they generate and release 15S-HETE (hydroxy-eicosatetraenoic acids), that is taken up by the PMN and converted to lipoxin with help of 5-LO.

   This all together leads to lipoxin biosynthesis and reduces leukotriene formation. (Figure 3)

   Ecosanoid class switch – during inflammation, when there is PMN infiltration, there is coordinated coincidence of LT and PMN, which is associated with spontaneous resolution of the condition. When human blood PMN is exposed to PGE2(prostaglandins), which triggers eicosanoid class switch by regulating 15-LO. These event block LTs(leukotrienes) formation, thereby regulates leukocytes, PGD2 and HETE .[12] (Figure 3)
3. The synthetic pathway by aspirin is mainly seen in cells that bear COX-2 like vascular endothelial cells, epithelial cells, monocytes and macrophages. When aspirin is administered during inflammation, the stimuli induce COX-2 to generate 15R-HETE, this is rapidly converted to 15-epimeric-LX / aspirin triggered by lipoxins by 5-LO.[13–15] (Figure 4)

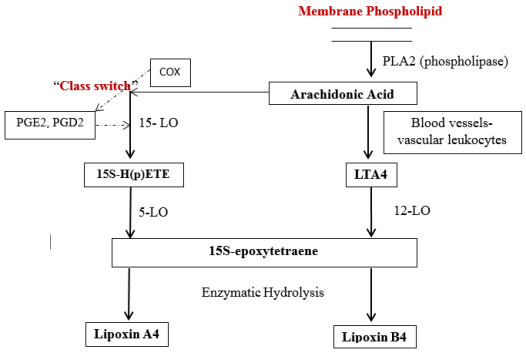

Figure 3: Lipoxin formation by transcellular biosynthesis

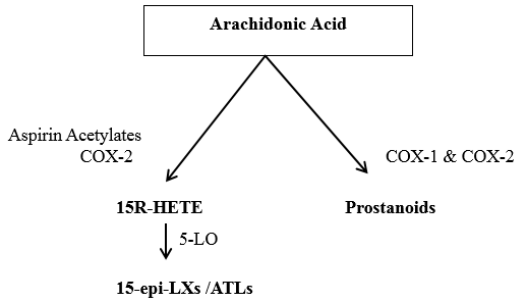

Figure 4: Generation of ATL mediators

2.1.2. Cellular functions of lipoxins

1. Decreases adherence of leukocytes
2. Reduces vascular leakage.
3. Lowers prostaglandin E2 levels in exudates.
4. Reduces the number of apoptotic neutrophils.
5. Inhibit neutrophil recruitments.

6. Attenuates expression of the nuclear factor kappa B gene.
7. Blocks leukocyte adhesion protein-1 and chemotaxis
8. Promotes lymphatic removal of phagocytes
9. Inhibits T- cell adhesion to vascular and salivary epithelium.
10. Enhances microbial phagocytic function.[16]

2.2. *Resolvins*

These are endogenous lipid mediators produced during the resolution phase of acute inflammation from essential fatty acid (EPA – eicosapentaenoic acid & DHA-docosahexaenoic acid). Two series of resolvins are there, E series from EPA and D series from DHA.[17,18]

2.2.1. *Biosynthesis of resolvins*

The first bioactive molecule identified among resolvins is RvE1- Resolvin E1. Vascular endothelial cells initiate the biosynthesis through 2 pathways.

1. Aspirin modified COX-2 coverts EPA into 18R-hydroperoxy-eicosapentaenoic acid (18R-HPEPE) and 18S-hydroperoxy-eicosapentaenoic acid (18S-HPEPE). Aspirin impacts the formation of Resolvin E1 by acetylating COX-2 in vascular endothelial cells, that stereo selectively generate 18R-HPEPE. This is taken up by human monocytes and metabolized to RvE1 and RvE2 by leukocytes 5-LO. (Figure 5)
2. Resolvin D is formed from DHA. The LOX product 17S-hydroxy-DHA (17S-HDHA) which is rapidly transformed by the LOX activity in human PMNs into 2 epoxides intermediate. This open to form a bioactive product – 17S resolving series (RvD series).[19,20] (Figure 6)

2.2.2. *Functions of resolvin E1*[6,17,21]

1. Inhibits neutrophil infiltration
2. Modulates chemokine/cytokine synthesis
3. Promotes healing of inflamed tissues and bone regeneration
4. Enhances phagocytosis
5. Activates lymphatic removal of phagocytes
6. Attenuates systemic production of c- reactive protein and interleukin-1
7. Reduces eosinophil and lymphocyte recruitment
8. Regulates adipokines.
9. Decreases inflammatory actions of COX-2
10. Attenuates expression of the nuclear factor kappa-B gene
11. Reduces the monocytes concentration
12. Increases CD55 expression on epithelial cell and PMN cell clearance
13. Rescues impaired phagocytosis in LAP patient macrophages
14. Prevents rejection of allografts
15. Activates anti-apoptotic signals.

2.2.3. *Functions of resolvin D1*[22,23]

1. Inhibits neutrophil recruitment
2. Anti-hyperalgesic properties
3. Shortens resolution interval
4. Reduces oxidative stress-mediated inflammation
5. Attenuates agonist pain molecules
6. Induces macrophage phagocytosis
7. Stimulates M2 macrophage phenotype
8. Temporally regulates micro RNAs
9. Reduces cytokines in broncho alveolar lavage fluid
10. Ameliorates insulin sensitivity
11. Enhances microbial clearance
12. Reduces level of prostaglandins and leukotrienes.

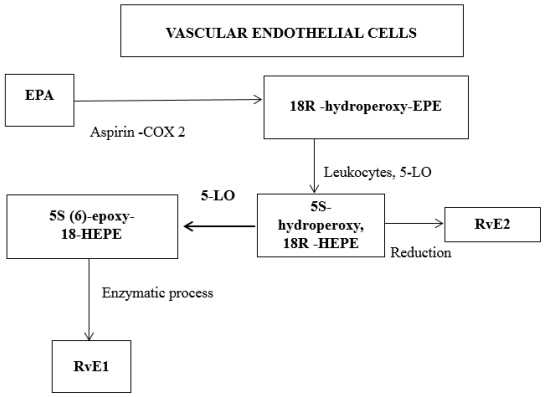

Figure 5: E-series resolvin biosynthesis

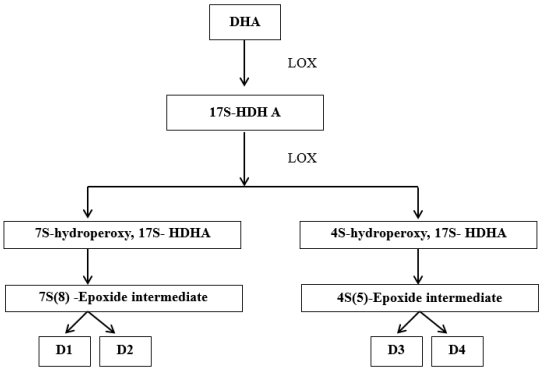

Figure 6: D-series resolvin biosynthesis

2.3. *Protectins*

Endogenous lipid mediators, also called as neuroprotectins, account for the protective actions observed in neural tissues and within the immune system.

2.3.1. Biosynthesis

Endogenously produced DHA is converted into triene containing conjugated structure via LOX pathway defines the key feature of the family derived from DHA. LOX product 17S-H(p)DHA undergoes enzymatic epoxidation to 16(17)-epoxide, that is enzymatically converted to 10,17 dihydroxy containing bioactive product- 10R,17S diDHA, NPD1/PD1 – protectins/ neuroprotection.[24,25] (Figure 7)

Human peripheral blood lymphocytes also have the ability to produce protectin D1 with a Th2 phenotype there by reducing TNF-α and interferon γ secretion, and thereby blocking T cell migration and promoting T cell apoptosis.[26]

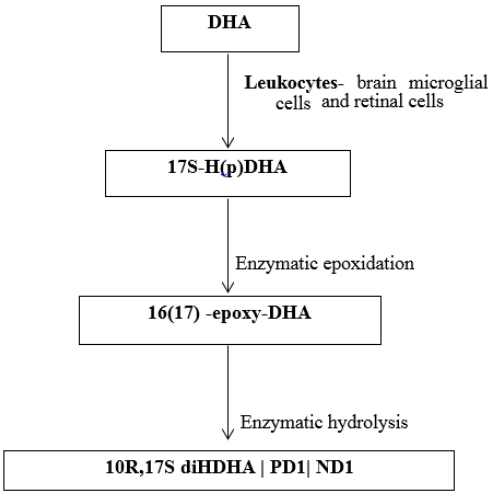

Figure 7: Biosynthesis of protectins

2.3.2. Functions[17,27]

1. Decreases inflammatory actions of COX-2
2. Inhibits neutrophil infiltration
3. Modulates chemokine/cytokine synthesis
4. Regulates T-cell migration
5. Regulates macrophage function
6. Upregulates CCRS expression on apoptotic leukocytes
7. Prevents hepatocyte steatosis
8. Inhibits pain signals
9. Suppresses eosinophil chemotaxis and adhesion.

2.4. Maresins

They are macrophage mediators in resolution of inflammation, primary molecules produced by macrophages with homeostatic function. They are the third largest family of SPMs derived from DHA 20.[6,28]

2.4.1. Biosynthesis

1. It occurs mainly in M2 macrophages and is initiated by human macrophage 12- lipoxygenase (12-LO).
2. Initially, DHA is converted enzymatically into14-hydroxyDHA intermediate. This requires the addition of oxygen atom into DHA at the 14^{th} carbon atom. This give rise to 14S- H(p)DHA, which is further metabolized to 13S, 14S- epoxide maresin, again undergoes enzymatic hydrolysis to form maresin-1.[20] (Figure 8)

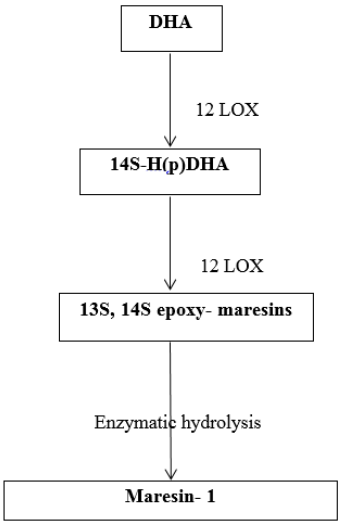

Figure 8: Biosynthesis of maresins

2.4.2. Functions[29]

1. Reduces neutrophil number in exudate
2. Enhances macrophage phagocytic functions
3. Decreases trans endothelial polymorphonuclear cell migration

3. Conclusion

Acute inflammation serves to protect the host and is primarily initiated by neutrophils in response to a challenge. The outcome of inflammation depends on a balance between factors that either amplify the inflammatory response or promote its resolution. Recent insights reveal that the resolution of inflammation is regulated by protective mediators such as lipoxins derived from arachidonic acid, aspirin-triggered lipoxins, E-series resolvins derived from eicosapentaenoic acid, D-series resolvins derived from docosahexaenoic acid, protectins, and maresins.

These lipid mediators interact with G protein-coupled receptors on innate immune cells to facilitate several processes: they halt leukocyte infiltration, restore normal vascular permeability and reduce edema, promote the apoptosis of polymorphonuclear neutrophils, encourage the non-inflammatory infiltration of monocytes/macrophages, and assist macrophages in clearing apoptotic neutrophils, bacteria, and necrotic debris from the affected area. Through

these processes, inflammation resolves effectively, leading to a return to homeostasis.

4. Source of Funding

None.

5. Conflicts of Interest

None.

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