Mediators of Resolution in Inflammation: Exploring Avenues

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Abstracts: Timely resolution of an acute inflammatory response is essential for healthy tissues. Specialized chemical mediators derived from essential fatty acids are identified that actively promote resolution of inflammation via novel pro-resolving and anti-inflammatory cascades. In this review, we summarize potent role of the lipoxins ,resolvins along with other chemical mediators that are enzymatically generated and identified in the resolving inflammatory exudates.[Aruna G NJIRM 2015; 6(1):89-92]

Key Words: Inflammation, lipoxins, resolvins.

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Introduction: Acute inflammation is an indispensable host response to foreign challenges or tissue injury. In healthy conditions, inflammatory processes are self-limiting and self-resolving, suggesting the existence of endogenous mechanisms for the control of inflammation and resolution. In the process of resolution the endogenous pro resolving mediators play a vital role in restoring homeostatic conditions.

Resolution at the histologic level was thought as a passive process however, it is becoming clear that this well-orchestrated phenomenon is an active process involving biochemical circuits that biosynthesize local mediators within resolution phase[1-3]. Resolution by precise definition is not the same as endogenous anti-inflammation. For example, a proresolving small molecule can, in addition to serving as an agonist of anti-inflammation, also promotes the uptake and clearance of apoptotic neutrophills from the site of inflammation by macrophages[4].Because of the importance of this type of trafficking these proresolving mediators can be referred as local "go" and "stop" signals or "checkpoint regulators"[5] .

This entire event is accompanied by class switchingfrom pro-inflammatory prostaglandins (PGs) and leukotrienes(LT) to the biosynthesis of anti-inflammatorymediators, such as lipoxins (LXs) [6] ,along with the appearance of new families of pro-resolving mediatorsbiosynthesized from ω-3 polyunsaturated fattyacid (PUFA) precursors[7].

Production of Lipoxins and Aspirin-Trigerred Lipoxins: Lxs and their 15 epimers, aspirin triggered lipoxins (ATL), are eicosanoids derived from sequential lipoxygenase (LO) metabolism of arachidonic acid.

Two major routes of LX biosynthesis in human cell types have been established. One pathway involves peripheral blood platelet-leukocyte interactions. Human platelets do not produce LX on their own but become a major source of LX when platelet-polymorphonuclear neutrophills (PMN) adhesion occurs. This is mediated by 5-LO and 12-LO enzymes[8].

The second biosynthetic route is initiated at the mucosal surfaces by 15-LO that inserts molecular oxygen into arachidonic acid (AA) at the carbon 15 position to produce 15*S*-hydroxyleicosatetraenoic acid (15*S*HETE); this latter metabolite is rapidly taken up by PMNs and is converted subsequently via 5-LO to LXs.

Aspirin being a non-steroidal anti-inflammatory drug (NSAID) acetylates the cyclooxygenase (COX) -2 enzymes inhibit the further production of prostanoids while inducing the synthesis of 15R-hydroxyleicosatetraenoic acid (15RHETE).This process, in association with 5-LO forms 15-epi LX or ATLs.

Table 1: Actions of LXs and ATLs based on Cell Type [9].

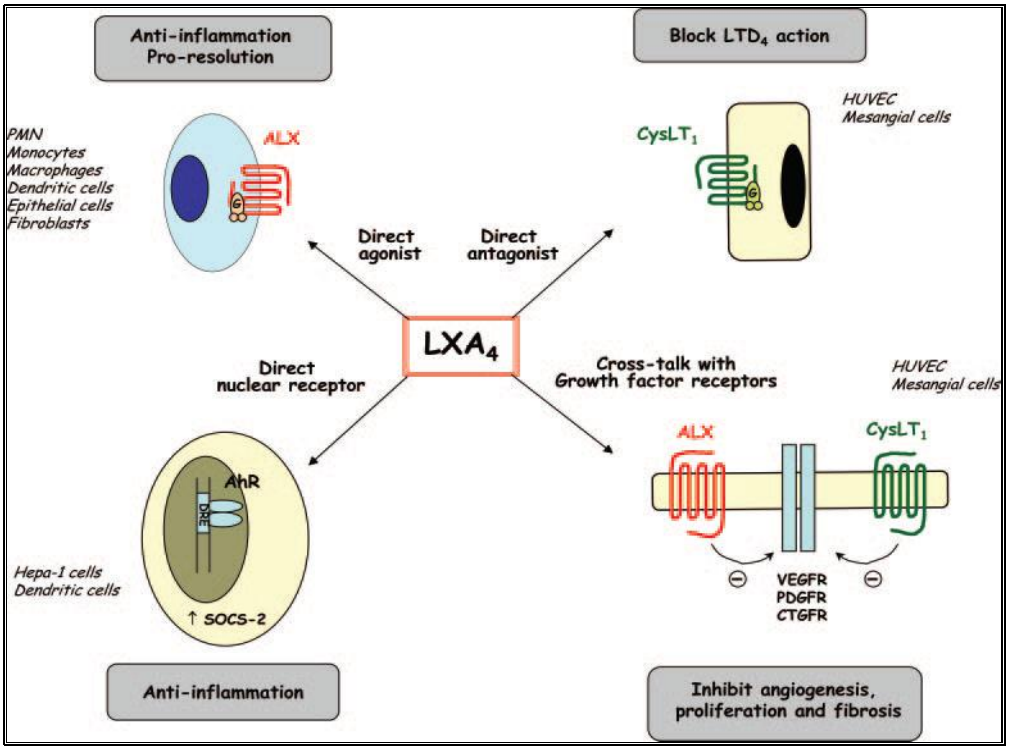
Sl No	Cell type	Functions
	Whole blood	prevent shedding of L-selectin and reduce peroxynitrite generation on PMNs, monocytes, and lymphocytes .
	Neutrophils	Inhibit chemotaxis,

		adherence and transmigration . Inhibit PMN-epithelial and PMN-endothelial cell interactions . Block superoxide anion generation.
	Monocytes	Stimulate chemotaxis and adhesion to laminin without increase in cytotoxicity Inhibit peroxynitrite generation
	Macrophages	Stimulate nonphlogistic phagocytosis of apoptotic PMNs
	Dendritic cells	Block interleukin (IL)-12 production
	Eosinophils	Stop migration/chemotaxis in vivo and inhibit IL-5 generation
	Activated T cells and NK cells	Inhibit TNF-secretion .
	Fibroblasts	Inhibit IL-1 induced IL-6, IL-8, and matrix metalloproteinases (MMP)-3 production

Receptors: To address the sites of action of LXA4, radiolabeled [11, 12-^{3}H] LXA4 was synthesized and characterized[10]. By using this radioligand, the specific LXA4 binding sites were first characterized on human PMNs[11].

The formyl peptide receptors-like-1 (FPRL1) were identified as the receptors for LXs and ATLs which belong to a class of G protein-coupled receptors.This receptor is also known as FPRH1 [formyl peptide receptor homolog-1], FPR2 (formyl peptide receptor- 2) and HM 63(Human monocyte 63 cloned from cDNA library) [12 -13].

The overall action of LXA4 in vivo is likely to be attributed to its interactions with multiple receptors, including [9]
1) direct activation of ALX as a receptor agonist,
2) direct inhibition of cysteinyl-leukotrine (CysLT1) as a receptor antagonist,
3) direct activation of the nuclear receptor,
4) cross-talk with growth factor receptors.



These receptors have been expressed on PMNs, monocytes, activated T cells, enterocytes, synovial fibroblasts and in organs like spleen, lung with lesser amounts in heart, placenta and liver.

Analogs of Lipoxins: A main limitation for *in vivo* studies with native lipoxins is represented by their short half-life, since they undergo rapid metabolic inactivation hence a number of stable analogs have been synthesized in recent years, mainly focusing on the A series of lipoxins. Among these were 15*R/S*-methyl-lipoxin A4 and 16-phenoxy-lipoxin A4. These analogs retained receptor-binding affinity and full biological activity in assays of neutrophil transmigration across intestinal epithelial cells[14].
More recently,aromatic, pyridin, and benzo analogs have been obtained with enhanced anti-inflammatory properties[15 -16].

Negative Side of COX Inhibitors On LXs: Although the COX inhibitors reduce inflammation surprisingly, they have deleterious effect on resolution. They block the resolution by increasing the dwell time of exudates, i.e., the time interval at which PMNs remain at the site and the corresponding reduction in lipid mediators that are required for restoring homeostasis[17.] This chronic low grade inflammation possibly explains the potential serious consequences of chronic use of COX-2 antagonists.

Other Proresolution Mediators: Decades of reports have highlighted the essential roles of omega 3 poly unsaturated fatty acids (PUFA) in preventing diseases hence, elucidating the molecular mechanisms of Eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) which is an important challenge for molecular and translational medicine. Resolvins ,Protectins and Marecins are newer compounds identified in the resolution of inflammation [18].

Resolvins: Resolvins (resolution-phase interaction products) are endogenous compounds made from omega -3 fatty acids EPA and DHA; they are termed E series resolvins and D series resolvins respectively. Aspirin triggered Resolvins are also produced by COX-2 pathway in the presence of aspirin[19] . D series resolvins are referred to as 17 R series which again consists of four variants D-1, D-2, D-3 and D-4. E series are called 18 R series consisting of E-1 and E-2 .[20]

Actions: Resolvins reduce the PMN tranendothelial migration, dendritic cell migration and IL- 12 production .They block the production of proinflammatory mediators and regulate the trafficking of inflammatory cells to the site of inflammation.

Receptors for Resolvins: Receptors involved in the RvE1 bioactions are the GPCR. An orphan receptor, denoted earlier as ChemR23 was found to attenuate nuclear factor in response to RvE1. Recently a second receptor leukotrine B_4 receptor (BLT1) was also identified as a receptor for RvE1[17].

Protectins: Protectins are also generated from DHA via a separate new pathway distinguished by 22-carbon atoms with six double bonds, three in conjugated triene structure. The name “protectins” stems from observed anti-inflammatory and protective actions in neural tissues and hence they are reffered to as neuroprotectins.

Maresins : Maresins are newly described macrophage-derived mediators of inflammation resolution. The term Maresins is coined from Macrophage mediator in resolving **in**flammation and was found to possess potent anti-inflammatory and proresolving properties similar to RvE1.Maresins are derived from essential omega-3 fatty acids by a new 14-lipoxygenase pathway that may be linked to homeostasis, inflammation resolution, wound healing, and cancer. These new compounds isolated from macrophages showed distinct and separate actions on PMNs compared with mononuclear cells, such as those recently identified for multifunctional mediators. They not only enhance the removal of apoptotic and necrotic cells at sites of inflammation but also restrict the unwanted tissue injury damage and oxidative stress that can accompany inflammation and infection[21].

Conclusion: The use of systematic, temporal and differential analyses using combined cell trafficking, lipid mediator lipidomics informatics

and proteomic analysis have uncovered a wide array of proresolution mediators. Additionally, they open new avenues to design “resolution targeted” based therapies where aberrant uncontrolled inflammation are components of disease pathophysiology and these agonists of proresolution are likely to have a promising future. With the advent of nanomedicine, nano-proresolving molecules (NPRMS) are being investigated as they possess potent beneficial bioaction reducing toxicity and offer a new therapeutic approach.Our current understanding of the pharmacological profile for these proresolution mediators suggests potential utility in diseases with significant unmet clinical needs however, further research will inevitably expand our knowledge of the actions and therapeutic potential of these mediators.

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