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Resolvins, A powerful resolution mediator: Review

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Abstract
Resolvins are endogenous lipid derived mediators generated by the host to regulate resolution of inflammation. They are biosynthesized from dietary fatty acid specifically omega 3 fatty acids. There are two major types of resolvins, E series and D series resolvins. Resolvins control the duration and magnitude of inflammation. They act as anti-inflammatory and proresolution mediators and decrease the tissue accumulation of neutrophils. As resolvins regulate recruitment of neutrophils and macrophages to the inflamed site, they show protective effect in inflammatory diseases like colitis, acute lung inflammation, periodontitis etc. Experiments in animals and humans suggest a new approach for the control of inflammation in these diseases without compromising the host defense.

Keywords: Resolution of inflammation, anti-inflammatory mediators, resolvins

Introduction
Acute inflammation is the protective physiological response that occurs in vascularized tissue to defend the host against pathogen or foreign bodies. The four major outcomes of acute inflammation are progression to chronic inflammation, abscess development, scar formation or resolution that leads to restoration of homeostasis. Loss of resolution can lead to chronic inflammation and therefore complete resolution is essential for maintaining health [1].
Resolution of inflammation was considered as a passive process by declining the levels of pro-inflammatory mediators over time and 'fizzling out' of the acute inflammatory response. In the late 20th century Charles N Serhan mentioned about certain molecules that mediate the resolution of inflammation [2-4]. Now it is considered as an active and highly regulated biochemical process that involves several distinct cellular mechanisms. Cell clearance is critical to resolution and it is mediated by non-phlogistic recruitment of monocytic macrophages, release of neutrophils from the apical surfaces of epithelial cells and phagocytosis of apoptotic cells and microbes (Godson *et al*., 2000; Schwab *et al*., 2007). As the number of leukocytes decreases, pro-inflammatory cytokine levels also decreases and active class switch occurs from generation of pro inflammatory mediators (prostaglandin and leukotriene) to anti-inflammatory mediators. (eg: resolvin, protectin lipoxin and maresin) [5]. These anti-inflammatory mediators are now known as specialized proresolving mediators (SPMs).
In this Review, we provide an update and overview of resolvin that play an important role in resolution of inflammation.

Pro Resolution Mediators
These are endogenous lipid derived mediators generated by the host in response to pathogens to regulate resolution of inflammation. They include resolvin, lipoxin, protectin and maresins [5]. Among these resolvins, maresins and protectins are biosynthesised from omega 3 fatty acid and lipoxins from arachidonic acid which is an endogenous fatty acid. Human milk and fish oil are the dietary source of omega 3 fatty acid. They are abundant in cold water marine fish. Human milk also contains bioactive lipid mediators and they are present at concentrations higher than the plasma level concentration of healthy individuals. Lipoxins are the first identified mediators that inhibit polymorphonuclear neutrophil infiltration and stimulates nonphlogistic recruitment of macrophages [6, 7]. Protectins have anti-inflammatory actions in neural tissues and immune system. They act on glial cells and reduce cytokine expression [8]. They increase the clearance (efferocytosis) of apoptotic neutrophils by macrophages and reduce the neutrophil transmigration [9].

They have protective actions against stroke, animal models of alzheimer's disease and other diseases of neural systems. Maresins are primordial molecules produced by macrophages which stimulate clearance of neutrophils. Resolvins forms the first ''pro-resolution'' pathway and they possess anti-inflammatory and pro-resolution properties.

Resolvins: (Resolution-phase interaction products)

Resolvins are stereospecific lipid mediators that are induced endogenously during the resolution of inflammation. They are derived enzymatically from dietary fatty acid specifically omega 3 fatty acid. The major omega-3 PUFAs are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [10, 11]. Circulating DHA and EPA are found in the normal plasma mostly in their albumin-bound forms. When inflammatory reaction occurs in tissue their local vascular permeability is increased and they can penetrate to other cells like neutrophils or macrophages. Resolvin production involves series of enzymatic conversions namely a transcellular biosynthesis process which involves endothelial cell-neutrophil interactions. The source lipids and intermediates are transcellular transferred to neutrophils and macrophages and resolution mediators are eventually released from them. [12, 13]

Resolvins control the duration and magnitude of inflammation. They act as anti-inflammatory and proresolution mediators. Anti-inflammatory actions include down regulating the recruitment and function of neutrophils and reduction of proinflammatory mediator production and secretion. Proresolving actions are mediated by recruitment of monocytes or macrophages, promoting their non-inflammatory phagocytosis and IL-10 secretion. IL-10 secretion helps to clear exogenous and endogenous pro-inflammatory components.

The first resolvin was identified in exudates collected in the resolution phase of inflamed murine dorsal air pouches [14, 15]. They were identified by physical methods using lipidomic system-based analysis (liquid-chromatography-ultraviolet-mass spectrometry). As they are resolution phase interaction products they are arbitrarily termed as resolvins. These compounds were isolated, retrograde analysis was carried out to identify structures by stereochemistry (Serhan CN 2000 2002, Arita M 2005). Several classes of resolvins were identified according to their source of origin.

Types of Resolvins

1. E-series (from EPA)
2. D-series (from DHA)
3. Aspirin-triggered epimers - Identified for both E and D series resolvins. They are produced by the aspirin acetylated COX-2 pathway [16], when taken along with omega-3 fatty acids in diet. They are more stable and longer acting than the other types.

E-Series Resolvins

Two major E - series resolvins are Resolvin E1 (RvE1) and Resolvin E2 (RvE2). They are derived from eicosapentaenoic acid (EPA). They are generated *in vivo* with EPA and aspirin and were also generated *in vitro* with co-incubation of human endothelial cells and neutrophils.

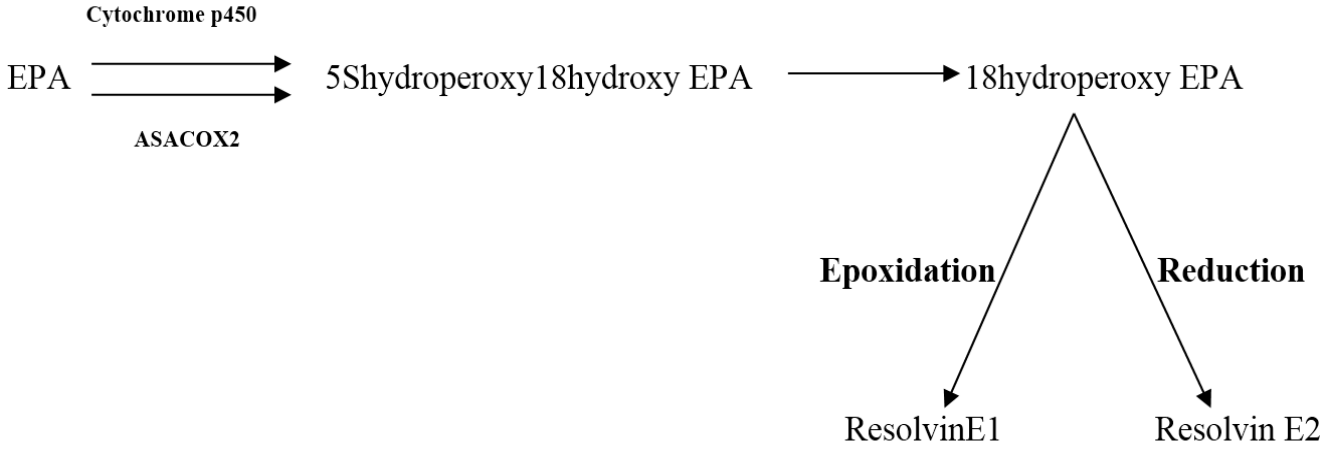

Fig 1

Resolvin E1 &E2 are produced by the vascular endothelium by a series of enzymatic conversions. The cells which finally release resolvins are neutrophils and macrophages. Eicosapentaenoic acid is converted into 18 *R*-hydroperoxy eicosapentaenoic acid and 18S-hydroperoxy eicosapentaenoic acid by either aspirin modified cycloxygenase-2(ASA COX2) or cytochrome P450. 18 hydroperoxy EPA is converted to 5S hydroperoxy 18 hydroxy EPA by 5 lipoxygenase. These intermediates are rapidly taken up by human neutrophils and undergo enzymatic epoxidation to form resolvin E1 and enzymatic reduction to form resolvin E2 [17]. 5-lipoxygenase (5-LOX) pathway is commonly important for all resolvin production and other enzymes are necessary for intermediate-specific oxidations. Both microbial and mammalian cytochrome P450 enzymes can convert EPA into 18-HEPE [14]. So microorganisms at inflamed sites or in the gastrointestinal tract can produce E-series resolvins in humans. RvE1 is spontaneously produced in healthy subjects and their levels are increased in individuals taking aspirin and or EPA [18]. Resolvins are detected in blood in physiologically relevant concentrations after ω-3 supplementation. EPA or aspirin intake can result in increased RvE2 synthesis in amounts greater than RvE1. When given intravenously RvE2 synthesis is equipotent to RvE1 synthesis. When given intraperitoneally it is additive to RvE1 [19].

Receptors

Bioactive eicosanoids, such as prostaglandin, leukotriene and lipoxins, transduce their signals by their interactions with specific receptors. Similarly RvE1 also regulate their action through specific G protein coupled receptors. Chemokine like receptor 1 and BLT1 receptor are the two receptors for RvE1.Chemokine like receptor 1 or chemR23 is a G protein coupled receptor on monocytes and dendritic cells [20, 21].

BLT1 is a leukotriene receptor on neutrophils [22]. RvE1 antagonizes BLT1 receptor and activates chemR23 receptor. Antagonistic action on BLT1 leads to suppression of neutrophil infiltration and intracellular signaling which decreases the production of pro inflammatory cytokines including TNF alpha. ChemR23 activation leads to the phagocytic clearance of apoptotic neutrophils. Previously ChemR23 was identified as a receptor for chemerin which transduces anti-inflammatory signals [20].

The RvE2 receptor is not molecularly characterized. RvE2 stops zymosan-induced neutrophil infiltration and shows potent anti-inflammatory action in murine peritonitis [19]. RvE2 plays a resolving role similar to that of RvE1 [23].

Metabolic Actions

RvE1 decreases tissue accumulation of neutrophil by blocking its trans endothelial migration and by increasing the clearance of neutrophils from mucosal epithelial cells [24]. It also stimulates the phagocytosis of apoptotic neutrophils. As compared to dexamethasone or aspirin only a small amount of RvE1 is required to reduce the leukocyte infiltration by 50–70% [25]. RVE1 is active at concentrations as low as 1 NM. RvE1 attenuates pro inflammatory signaling and inhibits the cytokine release and migration of dendritic cell. Because of its action on neutrophil, dendritic cell and leukocytes, RvE1 has a protective effect in diseases like peritonitis, colitis, asthma and acute lung inflammation. It has been proven that RvE1 is a potent modulator of L-selectin, and they selectively disrupt thromboxane-mediated platelet aggregation. They also regulate normal physiological process like wound healing [26].

Metabolic Inactivation

RvE1 inactivation pathways include enzymatic NAD+ dependent dehydrogenation and results in the production of 18-oxo-RvE1. Additional metabolic products like 10, 11-dihydro-RvE1 and 20-carboxy-RvE1 are also identified [27]. RvE1 inactivation pathways are region specific, species, tissue, and cell-type specific and thus different metabolites are generated. All these metabolites are generated in the lung. When compared with RVE1, their metabolic product shows decreased bioactivity *in vivo*. Metabolic inactivation of these resolution mediators provides cell-localized control for restoration of homeostasis.

19-(p-fluorophenoxy)-RvE1 is a synthetic analog of RVE1 which resist rapid metabolic inactivation. It retains its biological activity and reduces neutrophil infiltration and cytokine/chemokine production *in vivo*. Topical application of RvE1 analogs RX-10008 and RX-10045 reduces the choroidal neovascularization of retina after laser induced injury [28]

D-Series Resolvins

They are derived from docosahexaenoic acid (DHA) and it is a substrate for 17S and 17R groups of resolvins. There are 4 series of resolvins, which includes D1, D2, D3, and D4 [16]. DHA is mainly present in human brain, synapses and retina.

Biosynthesis

D-series resolvins were first identified from resolving exudates of mice which were given DHA and aspirin. Retrograde analysis was done to determine the structure, route of synthesis and origin of these compounds. Both aspirin-triggered RvD1 (AT-RvD1) and RvD1 are derived from DHA. This involvs a series of biosynthetic pathway initiated by aspirin-acetylated COX-2 or 15 LOX pathways, which produce an epoxide containing intermediate. Leukocyte 5-LOX acts on these intermediates to produce D series resolvins. In the absence of aspirin DHA is converted to 17s hydroperoxy DHA by 15 lipoxygenase and in the presence of aspirin, DHA is converted to 17R-hydroperoxy DHA (17R-HDHA) by aspirin acetylated COX2 [17]. Here oxygenation at carbon-13 changes to the carbon-17 position with an R configuration. These are produced in response to aspirin treatment in exudates and in brain.

Receptors

G protein-coupled receptor 32 and lipoxin A4 receptor (ALX)/formyl peptide receptor 2 are the receptors for D series resolvins. Human ALX is found on neutrophils, monocytes, macrophages, T cells and intestinal epithelial cells. CB2 receptor is a recently found receptor expressed on platelets and polymorphonuclear neutrophils. Activation of CB2 receptor leads decrease in neutrophil chemotaxis by the inhibition of P selectin expression [29]. It has not been proven whether RvDs and their epimers share the same receptor site. A recent study shows that AT RvD1 activates the same G protein coupled receptor as RvDs.

Metabolic Actions

D-series resolvins reduce the inflammation by decreasing platelet leukocyte adhesion. Accumulations of neutrophils are decreased in tissue by blocking its trans endothelial migration and by increasing the phagocytosis of neutrophils by macrophages. Both resolvin D1 and its aspirin-triggered forms are strong regulators of human and mouse neutrophils [16]. 17S and 17R resolvins block TNF-induced transcripts for interleukin-1β (IL-1β) in microglial cells. Interleukin-1β is rapidly expressed in response to neuronal injury. Aspirin-triggered resolvin shows both anti-inflammatory and pro-resolution properties.

Metabolic Inactivation

RvD1 is converted to novel 8-oxo- and 17-oxo- RvD1. 17-oxo-RvD1 shows dramatically reduced bioactivity. 8-oxo-RvD1 shows retained activity in peritonitis treatment. AT-RvD1 resists rapid inactivation and it is likely to be longer acting *in vivo* [30].

Clinical Applications

As resolvins regulate recruitment of neutrophils and macrophages to the inflamed site, they show protective effective in inflammatory diseases like colitis, acute lung inflammation, periodontitis etc. Animal studies were done to see the clinical effect of these resolution mediators in the treatment of above said diseases.

Effect of Resolvins on Pain

Resolvins are naturally occurring molecules which can boost the innate resolution pathways and NSAIDs are synthetic molecules which cause disruption of the natural signaling flow. So the safety concern is less for resolvins when compared to NSAIDs. The nociceptor nerve terminal is the pain receptor present in the tissue. In inflammation these receptors are stimulated by bradykinin, endotoxins, prostaglandin etc. If inflammation is not resolved, it causes continuous stimulation of nociceptors, which results in chronic pain and its aggravation. Resolvins are mainly effective in reducing inflammatory pain. They have direct action on sensory neuronal pathways. As neuronal components have GPR receptors, they can modify sensory ion channel functions like detecting environmental damage inputs [31].

Powerful analgesic effect of RvE1 at very small quantities was demonstrated in animal models. Peripheral and central neural hypotheses are the two differential mechanism involved in analgesic effect [31]. When RvE1 is injected intraplantar it prevents neutrophil infiltration and paw edema. It also reduces the expression of pro-inflammatory cytokines and chemokines in carrageenan-inflamed paw tissues, which can result in resolution of inflammation. Sensory ion channels such as TRPV1 and TRPA1 are the two important peripheral analgesic targets. They detect damage signals in normal and inflammatory conditions. When RvE1 acts on TRPV1receptor it blocks the spontaneous pain and heat pain mediated by the receptor [32]. RvD2 inhibit both TRPV1 and TRPA1. RvD1 shows accurate specificity to subtypes like TRPA1, TRPV3, and TRPV4. Other receptors like TRPV1, TRPV2, and TRPM8 shows resistance to RvD1 function. The inhibitory action of AT-RvD1 is specific to TRPV3.

When give intrathecally, RvE1 and RvD1 reduces inflammatory pain, heat and mechanical hypersensitivity. It also reduces neuropathic pain due to its inhibitory action on microglial activation. Analgesic effect depends on the GPR signaling cascade. Resolvins acts either through peripheral or central neural mechanism and produce beneficiary result only in pathological pain management [31]. Resolvins have postoperative analgesic effects in pain models.

Resolvins and Systemic Diseases

In allergic airway inflammation, RvE1 promotes the function of natural killer cells. They suppress the production of pro-inflammatory IL-23 and IL-6 and thus down regulate T helper-17 cells. In a murine model, treatment with RvE1 diminishes neutrophil accumulation in aspirational pneumonia and promotes Escherichia coli clearance in the lung [33]. RvE1 decreases leukocyte infiltration in colitis [12, 34]. RvE1 suppresses the lesion and level of angiogenesis in herpes simplex virus induced stromal keratitis [35]. RvE1 prevent neovascularization in retinopathy in a murine model.

RvD1 reduces interstitial fibrosis and leukocyte infiltration. It improves the function and morphology of kidney by blocking the Toll-like receptor (TLR)-mediated macrophage activation [36]. In peritonitis, RvD1 regulate microRNA (miRNA) expression. Overexpressed miRNA then up-regulates the IL-10 in macrophages. When diabetic mice are treated with RvD1 disturbed accumulation of apoptotic thymocytes occurs. They promote resolution of peritonitis, wound closure, and macrophage phagocytosis in diabetic mice [37]. Treatment with D series resolvins improved body weight loss, colonic damage and neutrophil infiltration in dextran sulfate sodium induced colitis.

D series resolvins dampens allergic inflammatory responses in airways. They also resolve inflammation induced by oxidative stress and infection. RvD1, RvD5 and neuroprotectin D1 enhance bacterial clearance in inflammatory lesion without releasing pro-inflammatory signals. They control inflammation at many levels, and reduce peritonitis and skin inflammation, protects organs from reperfusion injury and neovascularization. Treatment using these RvDs also improves antibiotic effectiveness for bacterial clearance [31]. RvD2 is protective in a murine model for sepsis, cecal ligation. 100 ng of RvD2 prevents hypothermia, reduces systemic and local bacterial burden and neutrophil infiltration into the peritoneum. Endogenous proresolving mediators display anti-inflammatory, antifibrotic, and anti-infectious actions in several widely used laboratory models of acute inflammation. These results show the practical usefulness of resolvin in infection-mediated diseases.

Resolvins and Periodontitis

Treatment goal of inflammatory disease includes complete healing and regeneration of lost or damaged tissue without scarring. On RvE1 application, periodontal disease development and progression can be prevented. There are no neutrophils or tissue damage at the diseased site. Remarkable absence of osteoclast proliferation is noted and bone remained largely intact. So pre-treatment with RvE1, can reduce inflammation-induced tissue and bone loss in periodontitis. RvE1 reversed the defective phagocytic function of macrophages in localized aggressive periodontitis [38].

Animal study by Hasturk *et al*. 2006, 2007 concluded that therapeutic use of RvE1 cause complete absence of inflammation and can prevent gingivitis and periodontitis. There were no inflammatory changes, bone loss or osteoclast formation. Radiographic assessment revealed reduced bone loss. Treatment with RvE1 can also cause changes in the micro flora. P. gingivalis and Aggregatibacter Actinomycetemcomitans were almost disappeared after treatment with RvE1 and the levels of other organisms reduced to pre-disease levels. As RvE1 has no direct antiseptic properties the exact reason for change in micro flora is unknown. Possibilities are (1) Release of antimicrobial peptides, such as defensins and bactericidal/permeability-increasing protein by resolvin molecules. (2) P. gingivalis is an asaccharolytic organism that requires essential amino acids as a food source which is produced during an inflammatory response from degradation of collagen fragments (Van Dyke 2007). So P. gingivalis won't be able to survive in the biofilm after the resolution of inflammation. (3) Increased bacterial clearance by resolution macrophages. Another study in chemR23 transgenic mice indicates that RvE1 directly impacts bone remodeling by suppressing bone resorption.

None of the resolution agonists has been approved for clinical use and many are in development. In a pilot trial (El-Sharkawy *et al*. 2010) Dietary supplement of omega-3 fatty acid along with the standard periodontal treatment shows reduced pocket depth and increase in clinical attachment, and reductions in inflammatory mediators in saliva.

Future Perspective

The isolation and characterization of resolvin molecules has opened a new therapeutic approach for the management of inflammatory diseases like chronic periodontitis, colitis, acute lung inflammation, inflammatory bowel diseases. Their therapeutic administrations successfully mimic and even greatly promote the resolution mechanism. They can produce resolution of inflammation without side effects as compared to pharmacological anti-inflammatory treatment. Further studies are required to formulate their mimetics so that anti-inflammatory, analgesic, immunomodulatory drugs with less side effects can emerge and these also will restore the homeostasis which we always anticipate.

Conclusion

Resolution of inflammation is an essential mechanism to maintain tissue homeostasis. This will prevent tissue destruction and chronic inflammation. Resolvins are one of the endogenous proresolution lipid mediators that help to retain tissue homeostasis. Experiments in animals and humans suggest a new approach for the control of inflammation in disease without compromising host defense. The potential for treating human disease with resolvins awaits thorough investigation.

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