The What, Where, and How of Resolvins

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Received 24 November 2011 / Accepted 27 April 2012

Abstract. Complete resolution of an acute inflammatory response and its return to homeostasis are essential for healthy tissue. Once thought to be a passive process, the resolution of inflammation is now shown to involve active biochemical programmes, which enable inflamed tissues to return to homeostasis. The recently uncovered families of endogenous mediators are now gaining attention. This new genus of mediator possesses pro-resolving, anti-inflammatory, and antibiotic as well as host-directed antimicrobial actions. Therefore it seems to promise a novel approach for the treatment of inflammation associated diseases, based on endogenous agonists of resolution. The following review therefore focuses on the basics of resolvins, covering their generation pathway and activity.

Keywords: Antibiotic, Antiinflammatory, Antimicrobial, Inflammatory response, Resolvins.

INTRODUCTION

Inflammation is the first response of the immune system to infection or injury, but excessive or inappropriate inflammatory responses contribute to a range of acute and chronic human diseases. One such inflammatory condition is periodontal disease. This is a local inflammatory disease initiated by bacteria, characterized by neutrophil-mediated tissue injury followed by development of a chronic immune lesion, that eventually result in tissue and tooth loss. The ideal outcome, or resolution, in such an inflammatory condition, is a highly coordinated active process, involving specialized pro-resolving mediators, found in the resolution phase, actively stimulating the tissue to regain homeostasis. Traditionally, it was argued that the gradual catabolism of pro-inflammatory cytokines was enough to turn off inflammation (Marino and Joris, 2004). It was also suggested that the shift from an acute physiological response to a chronic pathological inflammatory response was the result of an excess of pro-inflammatory cytokines. New research suggests that interference with the resolution of inflammation may result from defects in the production of endogenous pro-inflammation resolving compounds (Serhan, 2007). New evidence from various laboratory studies indicates that the return from inflammation to the ‘normal’ or healthy state is not merely a passive termination of inflammation but rather an actively regulated programme of resolution (Serhan, 2007). This event is accompanied by lipid mediator class-switching from pro-inflammatory prostaglandins (PGs) and leukotrienes (LT) to the biosynthesis of anti-inflammatory mediators, such as lipoxins (LXs) (Levy et al., 2001), as well as the appearance of new families of pro-resolving mediators biosynthesized in exudates from omega-3 polyunsaturated fatty acid (PUFA) precursors (Serhan, 2000; Serhan, 2002; Hong et al., 2003).

In this regard, anti-inflammation and pro-resolution pharmacopeia is of utmost interest (Patrono and Baigent, 2009). Aspirin (acetylsalicylic acid), as an example, is known to dampen pro-inflammatory signals and more recently has been demonstrated to jump-start resolution of acute inflammation (Serhan, 2007). Since the early 20 th century, omega-3 fatty acids (PUFA) were also shown to possess beneficial roles in health and organ function (Burr and Burr, 1929). At high concentrations in vitro, omega-3 PUFAs decrease the production of pro-inflammatory prostaglandins, cytokines, and reactive oxygen species are known to play critical roles in inflammatory diseases (James et al., 2003). Clinically relevant anti-inflammatory properties have been reported with high doses of omega-3 fatty acids in periodontal disease (Hamazaki, 2006). Resolvins and protectins are, thus, distinct chemical families that now join the lipoxins (Serhan, 2005).

To date, the prevention of gum disease has been limited to successful oral hygiene and regular professional care. However, despite these preventive actions, in susceptible individuals with a high inflammatory response, plaque control is not enough to prevent disease. This has opened a new era for some other treatment modalities. Lipid-based mediators such as lipoxins, resolvins, and protectins play important roles in re-establishing tissue health. Rather than only tar-
targeting the inhibition of inflammatory mediators, researchers are now also focusing on the use of agents that stimulate mechanisms within the body for resolving inflammation (Serhan, 2008).

What is resolution of inflammation?

Acute inflammation is often characterized by the rapid influx of blood granulocytes, typically neutrophils, into the injured tissues followed by monocytes that mature into inflammatory macrophages that subsequently proliferate and thereby affect the functions of resident tissue macrophages. Resolution of inflammation can occur if granulocytes are eliminated and the tissue mononuclear cell population returns to normal pre-inflammation numbers and phenotype (Gallin, 1999).

Resolution of inflammation or its catabasis (pertaining to the decline of a diseased state) (Bannenberg et al., 2005), is the reduction or removal of leukocytes and debris from inflamed sites, enabling the return to homeostasis. Rather than being a passive process, resolution is now considered to be an active biochemical and metabolic process (Bannenberg et al., 2005; Serhan, 2004). The resolution process is rapidly initiated after acute challenges by cellular pathways that actively biosynthesize mediators, such as the lipoxins, resolvins and protectins (Serhan, 2000; Serhan, 2001).

Resolution by precise definition is not the same as endogenous anti-inflammation. For example, a pro-resolving small molecule can, in addition to serving as an agonist of anti-inflammation, also promote the uptake and clearance of apoptotic neutrophils from the site of inflammation by macrophages (Maderna and Godson, 2005; Serhan and Savill, 2005).

The resolution phase can be defined at the histological level as the interval from maximum neutrophilic infiltration to the point when they are lost from the tissue. Concomitantly, mononuclear cells are then introduced in a non-phlogistic fashion and play a key role in tissue repair (Majno and Joris, 2004; Cotran et al., 1999). These cellular terms and temporal relationships had enabled us to define the precise changes in leukocytes’ traffic and biochemical pathways activated in exudates, as well as to determine the impact of various endogenous mediators, exogenous compounds, and potential drugs within the resolution phase (Bannenberg et al., 2005; Damazo et al., 2006).
What are resolvins?

The first public exposure for resolvins was at the 11th international conference on Advances in Prostaglandin and Leukotriene Research, Italy, 2000 where the discovery of resolvins was reported. After that, during the 87th General Session of the International Association for Dental Research, scientists from Boston University further disclosed biologically active products of omega-3 fatty acids with the therapeutic potential to resolve periodontal inflammation (Serhan, 2000).

The term ‘resolvins’ or ‘resolution-phase interaction products’ was coined by Professor Charles Serhan and colleagues because these compounds were first encountered in resolving inflammatory exudates. These novel mediators were endogenous agonists controlling inflammation via stimulation of resolution. These novel endogenous anti-inflammatory and pro-resolving mediators also provide the biotemplates to produce stable analogs and mimetics (Serhan et al., 1995). Together with the lipoxins they constitute a pharmacologic genus of pro-resolving and anti-inflammatory molecules. Figure 1 clearly depicts the families of lipid autocoids (adapted from Serhan, 2006).

How resolvins were discovered

Acetylation of cyclooxygenase (COX-2) by aspirin transforms its enzyme activity from a cyclooxygenase to a 15-lipoxygenase–like (15-LOX–like) enzyme, synthesizing the precursors of pre-resolving mediator instead of PGH2 from arachidonic acid (Holtzman, 1992). Also, aspirin blocks the platelet activation by inhibiting cyclooxygenase-1 (COX-1)–dependent thromboxane formation, and triggers the formation of epimeric forms of naturally occurring lipid mediators (e.g. 15-epi-lipoxin A4) (Claria and Serhan, 1995). These properties of aspirin inspired the idea that aspirin promotes the formation of lipid mediators from omega-3 PUFAs. To examine this possibility, mice were given injections of sterile air to create air pouches, followed by intrapouch injections of tumor necrosis factor alpha (TNF-α) with omega-3 PUFAs and aspirin (Serhan, 2000; Serhan et al., 2002). The inflammatory exudates formed in the air pouches contained several previously unrecognized products derived from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These newly identified products were named resolvins because they were originally identified from mouse-resolving exudates.
Chemistry and Biology

The omega-3 essential fatty acids are currently the focus of considerable interest among nutritionists. The resolvins are synthesized either from EPA or from DHA.

Figure 2 is adapted from Serhan et al., 2002 and Hong et al., 2003, and shows 18R E-Series resolvins. The basic structure of this potent bioactive product generated from EPA proved to be 5, 12,18R-trihydroxyeicosapentaenoic acid (EPE) (Serhan, 2000). RvE1 possesses an interesting and novel distinct structure consisting of a conjugated diene plus a conjugated diene chromophore present within the same molecule. Both biogenic (Serhan, 2000) and total organic syntheses were achieved and its complete stereochemical assignment was established along with that of several related natural isomers (Claria and Serhan, 1995). RvE1 proved to be 5S, 12R, 18R trihydroxy-6Z, 8E, 10E, 14Z, 16E-eicosapentaenoic acid.

Figure 3 is adapted from Serhan et al., 2002 and Hong et al., 2003) and shows 17R and 17S D-series resolvins from DHA. Human microvascular endothelial cells, when treated with aspirin in hypoxia, release 17RHDHA produced from DHA. Human recombinant COX-2 converts DHA to 13hydro (peroxy)-DHA, which is monitored as 13-hydroxydocosa-hexaenoic acid. With aspirin, these switch to 17R-oxygenation to give a group of AT resolvins (AT-RvD1 to RvD4) that were also found in the brain (Serhan, 2000; Hong et al., 2003).

Using the mediator lipidomics-informatics approach (Hong et al., 2007), and employing tandem LC-PDA-MS-MS, it was exciting to find that neither aspirin nor exogenous DHA was required to monitor the production of these new structures in vivo (Hong et al., 2003; Duffield et al., 2006). The endogenous DHA was converted in vivo to a 17S alcohol containing a series of resolvins via LOX-initiated mechanisms (Hong et al., 2003; Marcheselli et al., 2003). The stereochemistry of both 17R- and 17S-series of resolvin D1 (RvD1 and AT-RvD1) was established and total organic synthesis achieved (Sun et al., 2007). RvD1 proved to be 7S,8R,17-Strihydroxy 4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid, and AT-RvD1 matched 7S,8R,17R-tri- hydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid. Also, the total organic synthesis of resolvin D2 (RvD2) was reported by Rodriguez and Spur (2004), confirming the physical properties of the original compound identified in exudates (Hong et al., 2003).
How resolvins are generated

The switch from synthesis of pro-inflammatory eicosanoids, such as the prostaglandins and the thromboxanes, to the pro-resolving resolvins and protectin D1, occurs via induction of 15-LOX. Disruption of COX-2 or inhibition of LOX enzymes results in a disruption in the normal process of inflammation resolution.

Biosynthetic scheme proposed for E-series resolvins

EPA is oxygenated at the carbon-18 position via the action of aspirin-acetylated COX-2 to form 18R-HEPE, which is subsequently oxygenated to form 5S-hydro (peroxy)-18R-HEPE via 5-LOX activity. The 5S-hydroperoxy group is either converted to a 5,6-epoxide intermediate to form RvE1 or reduced to a 5S-hydroxyl group to form RvE2 (Figure 2) (Serhan et al., 2002; Hong et al., 2003).

Biosynthetic scheme proposed for D-series resolvins

DHA is the substrate for two groups of resolvins produced by different biosynthetic routes, referred to as the 17S and 17R D series resolvins, during the resolution of inflammatory exudates. Endogenous DHA is converted into vivo via lipoygenase-initiated mechanisms to the 15S-hydroxy-containing series of four resolvins, known as resolvins D1 to D4. In the presence of aspirin, the oxygen at carbon position 13 switches to position 17 with an R configuration that is a precursor for the aspirin-triggered 17R D series resolvins (Serhan et al., 2002; Hong et al., 2003).

In the alternative reaction, in the absence of aspirin 15-lipoxygenase generates 17S-hydroxy-DHA as the initial product. This is converted to 7S hydroperoxy,17S-hydroxy-DHA by the action of a 5- lipoxygenase, and thence via epoxy intermediates to resolvin D1 (RvD1 or 7S,8R,17S-trihydroxydocosa-4Z,9E,11E,13Z,15E,19Z-hexaenoic acid) and epimeric resolvin D2 (RvD2 or 7S,16,17Trihydroxydocosa-4Z,8E,10Z,12E,14E,19Z-hexaenoic acid) (Figure 3, adapted from Serhan et al., 2002 and Hong et al., 2003).

How resolvins act

Experimental evidence indicates that resolvins reduce cellular inflammation by inhibiting the production and transportation of inflammatory cells and chemicals to the sites of inflammation. In general, pro-resolution molecules stimulate and accelerate resolution via mechanisms at the tissue level that are multi-factorial. Specific lipoxins and members of the resolvin and protectin families provide potent signals that selectively stop neutrophil and eosinophil infiltration, stimulate non-phlogistic recruitment of monocytes (that is, without elaborating pro-inflammatory mediators), activate macrophage phagocytosis of microorganisms and apoptotic cells, increase the exit of phagocytes from the inflamed site through the lymphatics, and stimulate the expression of molecules involved in antimicrobial defense (Serhan et al., 2002; Serhan et al., 2007).

Two receptors are known to be involved in the actions of resolvin E1. The GPCR chemokine-like receptor 1 (CMKLR1, also known as ChemR23) attenuates TNF stimulated NF-kB activation in response to resolvin E1 binding, indicating a counter-regulatory action of this ligand–receptor pair. Counter-regulation of TNF signaling was used to identify this GPCR because TNF is a key mediator in the early steps of acute inflammation (Serhan, 2000; Arita et al., 2005). Recently, a second GPCR that interacts with resolvin E1 was identified, the leukotriene B4 receptor (BLT1) (Arita et al., 2007). Resolvin E1 interacts in a stereospecific manner with BLT1 expressed by human neutrophils as a receptor antagonist (Serhan, 2000), attenuating leukotriene B4-dependent pro-inflammatory signals via BLT1 (Arita et al., 2007).

The function of resolvins

Given the notion that these mediators are generated endogenously during defined intervals within the acute inflammatory response (Serhan, 2000), the view emerges that they may not necessarily serve solely to block and/or inhibit inflammation, but may also activate resolution within the inflammatory exudate and thus promote the return to homeostasis (Serhan, 2004).

The inflammation gets investigated through various steps. One traditional view argued that pro-inflammatory mediator catabolism was sufficient for inflammation to switch off and the response subsequently just “fizzled out” (Cotran et al., 1999). This is only part of the process at the tissue level, as polymorphonuclear leukocyte (PMN) or eosinophils, if left unchecked, could do untold harm to an already inflamed site and must be disposed of in a controlled and effective manner. Thus, next in the sequence of events is cell clearance. The exit routes available to inflammatory leukocytes include systemic recirculation (less well described) or local death followed by their phagocytosis by recruited monocyte-derived macrophages. Once phagocytosis is complete, macrophages exit the inflamed site by lymphatic drainage, and there is evidence that a small population may die locally by apoptosis. If all of these pathways are strictly followed, then acute inflammation will resolve without causing excessive tissue damage and give little opportunity for the development of acute, ongoing inflammation and its associated complications. The last but equally essential aspect in the quest for tissue resolution and homeostasis is that the parenchymal or stromal cells that hosted the inflammatory event revert back to a non-inflammatory phenotype (Filer et al., 2006). Most current therapies target immune cells in an attempt to inhibit the production of pro-inflammatory chemical mediators. However, an equally important target is the active induction of pro-resolution programmes by stromal cells such as fibroblasts within the inflamed tissues (Serhan, 2004). As with the onset phase of acute inflammation, each of the above steps in the quest for resolution is also highly co-ordinated and under the tight control of what may be called “pro-resolution” factors (Kasuga, 2008).

RvE1 displays potent counter-regulatory and tissue-protective actions in vitro and in vivo. Studies indicate that
circulating omega 3 fatty acids rapidly appear in inflammatory sites which require conversion to resolvins that control excessive neutrophil infiltration, protect organs, and foster resolution.

Resolvins are not antibacterial per se. However, the alteration of microbial flora induced by RvE1 is intriguing. The mechanisms underlying this effect are under investigation, but these data support the hypothesis that in periodontitis the host changes associated with inflammation may be responsible for facilitating the growth of more pathological flora (van Dyke, 2008).

Application of exogenous resolvins at nanomolar concentrations inhibited PMN migration across endothelial cell monolayers (Serhan et al., 2002). Also in vivo, intravenous administration of resolvins in nanogram quantities dramatically reduces PMN infiltration in a murine acute inflammation model (Serhan et al., 2002). Resolvins also regulate macrophage and dendritic cell functions by controlling the production of cytokines and/or by regulating phagocytosis (Scwab et al., 2007; Arita et al., 2006). Tables 1 and 2 illustrate the above described functions of E and D series resolvins respectively (Hiroyuki et al., 2010; Hasturk et al., 2007).

### Table 1. E series resolvins in cellular action and periodontal action. Adapted from Seki et al., (2010) and Hasturk et al., (2006).

<table>
<thead>
<tr>
<th>Target Cells</th>
<th>Cellular Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>- Stop LTB4 stimulated transendothelial migration (Serhan., 2000; Tian, 2009)</td>
</tr>
<tr>
<td></td>
<td>- Block fMLP stimulated transepithelial migration (Campbell et al., 2007)</td>
</tr>
<tr>
<td></td>
<td>- Block IL-8 stimulated chemotaxis. (Haas-Stapleton et al., 2007)</td>
</tr>
<tr>
<td></td>
<td>- Enhance phagocytosis, ROS generation and pathogen killing (Haas-Stapleton et al., 2007)</td>
</tr>
<tr>
<td></td>
<td>- Regulate L-Selectin shedding and reduce CD18 expression. (Dona et al., 2008)</td>
</tr>
<tr>
<td></td>
<td>- Inhibit superoxide generation (Hasturk et al., 2006)</td>
</tr>
<tr>
<td>Dendritic Cells</td>
<td>- Inhibit IL-12 production (Arita et al., 2005)</td>
</tr>
<tr>
<td></td>
<td>- Inhibit the release of IL-23, IL-6, and TNF (Haworth et al., 2008)</td>
</tr>
<tr>
<td>Macrophages</td>
<td>- Promote phagocytosis of apoptotic PMNs and zymosan (Schwab et al., 2007)</td>
</tr>
<tr>
<td>Platelets</td>
<td>- Block ADP and U46619-stimulated aggregation (Dona et al., 2008)</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>- Inhibit pro-inflammatory cytokine production and adhesion molecule mRNA expression (Jin et al., 2009)</td>
</tr>
<tr>
<td>Periodontal Action</td>
<td>- Reduce PMN infiltration</td>
</tr>
<tr>
<td></td>
<td>- Prevent connective tissue and bone loss</td>
</tr>
<tr>
<td></td>
<td>- Promote healing of diseased tissues</td>
</tr>
<tr>
<td></td>
<td>- Regenerate lost soft tissues and bone</td>
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</tbody>
</table>

### Table 2. D series Resolvins in Cellular action. Adapted from Seki et al., (2010).

<table>
<thead>
<tr>
<th>Target cells</th>
<th>Cellular action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil</td>
<td>- Stop LTB4 and fMLP stimulated transendothelial migration (Jin et al., 2009).</td>
</tr>
<tr>
<td></td>
<td>- Block IL-8 and PAF stimulated chemotaxis (Spite et al., 2009).</td>
</tr>
<tr>
<td>Macrophage</td>
<td>- Inhibit superoxide and ROS generation (Spite et al., 2009).</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>- Inhibit pro-inflammatory cytokine production and adhesion molecule mRNA expression. (Jin et al., 2009).</td>
</tr>
<tr>
<td></td>
<td>- Stimulate production of prostacyclin and nitric oxide. (Spite et al., 2009).</td>
</tr>
</tbody>
</table>

### Pharmaceutical and clinical development - copies of resolvins

RvE1 is a local acting autacoid that has proved to display pro-resolving activity when treatments were given either by topical, intra venous, or intra peroneal administration (Bannenberg et al., 2005; Arita et al., 2006).

Resolvyx Pharmaceuticals is investigating a series of resolin E1 analogs, including the eicosapentaenoic acid (EPA)-derived RX-10005 (RX-05) and RX-1001, for the potential treatment of acute and chronic inflammatory diseases including colitis, periodontitis, arthritis, asthma and dry eye disease.

**About RX-10001** The resolin known as RX-10001 is a naturally occurring, small molecule lipid mediator. It acts to protect healthy tissue during an inflammatory response to an environmental insult and to resolve inflammation once the environmental insult has passed. In pre-clinical tests, RX-10001 has shown to be active with a very high potency across a range of inflammatory disease models, including asthma, colitis, rheumatoid arthritis, atherosclerosis, dry eye and retinopathy, active by oral, intravenous and subcutaneous routes of administration. Resolvyx Pharmaceuticals, Inc., a resolin therapeutics company, has announced that it has initiated the first human clinical trial evaluating RX-10001 in a phase I clinical trial in healthy volunteers.

### Resolvins and their therapeutic value (in periodontitis)
Regeneration of lost periodontal tissues is considered to be one of the most challenging aspects of periodontal therapy. Our current understanding of the role of the host immune-inflammatory response in periodontal diseases forms the basis of new therapeutic approaches. Many studies have been carried out to evaluate the efficacy of systemic administration of omega-3 polyunsaturated fatty acids as an adjunct treatment to routine periodontal therapy. The findings suggest that the combination therapy demonstrated successful reduction of gingival inflammation, reduction of pocket depth and attachment level gain, accompanied by a trend for modulation of the cytokine profile in gingival crevicular fluid (Elkhouli, 2011).

Improved outcomes are attributed to the primary metabolites of omega-3 fish oils, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In a 5-year longitudinal study of subjects 70 years of age at baseline, an inverse independent relationship was found between dietary DHA intake and periodontal disease events, after controlling for confounding factors. People with low DHA intake had an approximately 1.5 times higher incidence rate of periodontal disease progression (Iwasaki et al., 2010).

Topical application of 4 mg resolvin E1 per tooth every other day for 6 weeks in cases of periodontitis was shown to reduce PMN infiltration, and stop inflammation-induced tissue and bone loss (Hasturk et al., 2006).

The effect of dietary supplementation was evaluated by El-Sharkey et al. (2010) in a double blind clinical study of parallel design. The control groups were treated with scaling and root planing (SRP) or a placebo while the test group received SRP followed by dietary supplementation of fish oil (900mg EPA1DHA) and 81mg aspirin daily. Results showed a significant reduction in pocket depth and attachment gain after 3 and 6 months in the test group compared with baseline and control group. In addition, supplementation with omega-31 aspirin resulted in a significant shift in the frequency of pockets. The aim of this study was to evaluate the efficacy of systemic administration of omega-3 polyunsaturated fatty acids plus low-dose aspirin as an adjunctive treatment to regenerative therapy of furcation (bone loss) defects.

Resolvsins in the future

It is clear that future care of trauma and surgical patients, as well those with periodontal diseases, will rely heavily on clinicians having a detailed map and fundamental appreciation of the temporal relationships involved in the resolution of local acute inflammation and tissue injury at the cellular, molecular, organ, and systemic levels. Novel lipid mediator pathways are very attractive for new therapeutic interventions because they: rely on small molecules (<500 MW); are amenable to total organic synthesis; and can be manufactured with currently available pharmaceutical facilities (Serhan et al., 2002, Navia and Peattie, 1993).

It is too early to speculate on the intended use as a periodontal therapeutic. It is doubtful that an inflammation modulating agent will ever completely replace some form of mechanical therapy aimed at the control of the biofilm; even if the veracity of the hypothesis that inflammation impacts upon the composition of the biofilm is proven, the biofilm will still be there. Reduction of the mass of the biofilm as a means of reducing the inflammatory burden remains a viable approach. The use of these molecules may be an interesting preventative approach that will protect against the acquisition or overgrowth of intrinsically pathogenic bacteria (Maurizio et al., 2011).

Resolvins offer an entirely novel biological approach to treating significant inflammatory diseases, with a decreased potential for immuno-suppression. Resolvins are potential candidates for drugs to treat a broad range of acute and chronic diseases caused by a failure to resolve the inflammatory response and restore immune homeostasis. Such diseases include autoimmune diseases (like Crohn’s disease, psoriasis and rheumatoid arthritis), allergic diseases (like asthma) and chronic inflammatory diseases. Resolvins offer an entirely novel biological approach to treating significant inflammatory diseases, with a decreased potential for immuno-suppression.

CONCLUSION

The resolution of inflammation can now be regarded as an integral component of the programme of acute inflammation. The new families of EPA- and DHA-derived chemical mediators, namely the resolvins, qualify as ‘resolution agonists’, in this new arena of immunomodulation and tissue protection. Thus, agonists of inflammatory resolution are likely to have a promising future in drug development for inflammatory diseases and regenerative medicine.

REFERENCES


to regulate inflammation. *Journal of Immunology* 178: 3912–3917.


Resolvins uncovered...


