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Resolvin Infectious Inflammation by Targeting the Host Response

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Severe sepsis remains a major public health problem associated with poor clinical outcomes and substantial health care expenditures. Although the number of sepsis cases in the United States exceeds 750,000 per year and sepsis is associated with an estimated mortality rate of 20–30%, there is a lack of effective treatments.¹ There is also an urgent need to develop new therapeutic strategies due to the rise of antibiotic resistant bacteria.² Therapies that inhibit the activation phase of the acute inflammatory response to infection (e.g., corticosteroids, NSAIDs, anti-TNF α) have repeatedly failed to improve patient outcomes in severe sepsis. In contrast, strategies that promote endogenous factors that actively resolve the acute inflammatory response have not been rigorously explored since the key mediators that regulate this process have remained enigmatic. In this regard, Dalli and colleagues³ discovered a new group of host protective lipids termed 13-series resolvins (RvTs) that are formed during the very early phase of inflammation, promote bacterial phagocytosis, and augment host recovery from systemic infection by accelerating resolution of the acute inflammatory response.

It is well-established that endogenous bioactive lipids derived from ω -6 (arachidonic acid, linoleic acid) and ω -3 (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]) fatty acids via cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 monooxygenase metabolism are key regulators of acute and chronic inflammation. Previous work from Serhan and colleagues has conclusively shown that EPA- and DHA-derived lipids called specialized pro-resolving mediators (SPMs), including the resolvins, protectins and maresins, increase 4–12 hours after infection, regulate resolution of the host inflammatory response and enhance bacterial clearance.⁴ The key mediators that orchestrate the earliest phase of this process, however, had not been previously elucidated. In light of the integral role of neutrophil adherence to the vascular endothelium as a critical early event in the innate immune response to invading pathogens, Dalli and colleagues isolated lipid fractions from neutrophil-endothelial cell co-cultures and demonstrated that these fractions enhanced survival in a mouse model of lethal *E. coli* infection. In order to identify the bioactive molecule(s) within these fractions, the authors employed a metabolipidomics approach. In

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addition to previously characterized eicosanoids and SPMs, the authors discovered four new molecules (RvT1, RvT2, RvT3 and RvT4) that were rapidly formed (within 4 hours) during the initial phase of inflammation in mice infected with *E. coli*. Moreover, RvT concentrations in peripheral blood were acutely increased following exercise (a self-resolving inflammatory state) in healthy volunteers, and were significantly higher in human sepsis patients when compared to healthy volunteers. These data indicate that RvT biosynthesis occurs in a coordinated fashion in connection with acute activation of the immune response (Figure 1).

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The authors also demonstrated that RvT biosynthesis is a two-step transcellular process that requires neutrophil-endothelial cell interactions. First, docosapentaenoic acid (DPA), the intermediate metabolite in the conversion of EPA to DHA, is metabolized by endothelial COX-2 to form 13-hydroxydocosapentaenoic acid (13-HDPA). Second, following transcellular trafficking to adjacent neutrophils, 13-HDPA is metabolized by 5-LOX to form the RvTs. The authors proceeded to elucidate the bioactivities of RvTs in infectious inflammation through integration of *in vitro* and *in vivo* experiments. At picomolar concentrations, which are physiologically relevant, administration of RvTs dose-dependently promoted bacterial phagocytosis and increased production of reactive oxygen species in isolated human neutrophils and macrophages, enhanced efferocytosis of apoptotic neutrophils, and blocked macrophage inflammasome activation (reduced caspase-1 and IL-1 β). In a mouse model of lethal *E. coli* infection, systemic administration of RvTs increased bacterial phagocytosis, limited neutrophil recruitment to the site of inflammation, and mitigated inflammasome activation. In addition, RvTs mitigated systemic inflammation (reduced platelet-leukocyte aggregation and levels of pro-inflammatory prostaglandins involved in the eicosanoid storm), protected against hypothermia, and prolonged survival. Importantly, the RvTs did not exert direct bactericidal or bacteriostatic actions. Systemic administration of atorvastatin, which increased RvT biosynthesis by *S*-nitrosylation-mediated activation of endothelial COX-2, also significantly accelerated the resolution of infection and promoted survival in mice inoculated with *E. coli*. These effects were reversed by co-administration of the COX-2 inhibitor celecoxib and were augmented by co-administration of RvTs, demonstrating that the antiinflammatory and protective effects of atorvastatin are due, at least in part, to increased RvT biosynthesis.

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In summary, Dalli and colleagues discovered a novel group of endogenous lipid mediators (RvTs) that promote the host protective response in infectious inflammation. This work lays a critical foundation for the development of new therapeutic strategies that accelerate recovery from acute infection by targeting the host immune response rather than the bacterial pathogen. The discovery of bioactive lipids that target the resolution phase of the acute inflammatory response is particularly exciting and warrants further investigation as a novel therapeutic strategy. This study also identified a novel mechanism for the pleiotropic effects of statins that mitigate inflammation and promote endothelial function, as well as a potential deleterious effect of COX-2 inhibitors in acute infectious inflammation. Although statin administration in human patients with sepsis has produced disappointing results in recent clinical trials,⁵ discovery of these new bioactive lipids could reopen the door to statin trials in targeted subsets of the population predisposed to impaired RvT biosynthesis. Indeed, application of precision medicine approaches to this clinical problem using

biomarkers of RvT biosynthesis (e.g., genetic polymorphisms in fatty acid elongase-2 [*ELOVL2*], COX-2 [*PTGS2*], and 5-LOX [*ALOX5*]) offers enormous potential to identify subsets of the population who are at risk for poor outcomes and who have an enriched potential to benefit from therapeutic approaches that target this novel pathway.

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Figure 1. Transcellular Biosynthesis and Actions of RvTs

The 13-series resolvins (RvTs) are derived from docosapentaenoic acid (DPA, 22:5, n-3), which is the intermediate metabolite in the fatty acid elongase-2 mediated conversion of eicosapentaenoic acid (EPA 20:5, n-3) to docosahexaenoic acid (DHA, 22:6, n-3). In endothelial cells, cyclooxygenase-2 (COX-2) metabolizes DPA to the intermediate metabolite 13-hydroxydocosapentaenoic acid (13-HDPA), which undergoes transcellular trafficking to adjacent neutrophils and subsequent metabolism by 5-lipoxygenase (5-LOX) to form the four distinct RvT products (RvT1, RvT2, RvT3 and RvT4). Atorvastatin enhances RvT biosynthesis via S-nitrosylation of endothelial COX-2, whereas the COX-2 inhibitor celecoxib suppresses endothelial 13-HDPA biosynthesis. Once formed, RvTs have a myriad of potent autocrine and paracrine effects that promote resolution of infectious inflammation. They promote bacterial phagocytosis in macrophages and neutrophils, and increase production of reactive oxygen species (ROS), block activation of inflammasome components (caspase-1, IL-1β) and attenuate production of pro-inflammatory eicosanoids (LTB₄, PGD₂, PGE₂, TxB₂, PGF_{2α}) in macrophages.