Resolvins resolve to heal mucosal wounds

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Surfaces lined by single or multiple layers of epithelial cells, termed mucosal surfaces, function as selectively permeable barriers that partition the host from the outside world. Given their proximity to microbes and microbial antigens, intestinal epithelial cells (IECs) have evolved mechanisms to maintain barrier function and to aid in promoting rapid and full resolution from inflammatory insult. In recent years, a role for IECs has been ascribed to the generation of specialized proresolving mediators (SPMs), such a resolvins, in the promotion of inflammatory resolution (1). In PNAS, Quiros et al. (2) provide compelling evidence that resolvin E1 (RvE1) coordinates the resolution of inflammation by actively promoting wound healing.

Acute inflammation provides a productive and well-coordinated response to injury. Active inflammation involves the local generation of cytokines, chemokines, and proinflammatory lipids (prostaglandins and leukotrienes) that recruit inflammatory cells and increase vascular permeability. While inflammation provides an essential function, resolution processes are central to the avoidance of chronic inflammation that has been implicated in the pathogenesis of a wide range of diseases including metabolic disorders, mucosal diseases, cardiovascular disease, and even cancer. Indeed, resolution is a critical aspect of a productive inflammatory response (1), and it is now appreciated that this resolution response is an equally active process that is biochemically triggered in a controlled and coordinated fashion. Resolution is a biosynthetically active process that is initiated by SPMs, including resolvins, maresins, and protectins derived from omega-3 polyunsaturated fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), where D-series resolvins are derived from DHA and E-series resolvins are derived from EPA (3). RvE1 was first identified in a murine model of a resolving exudate and was initially characterized as a potent (nanomolar) inhibitor of neutrophil transmigration (4). Resolvins, including RvE1, are made by transcellular biosynthesis involving the interactions of two or more cell types, each contributing an enzymatic byproduct (5). As shown in Fig. 1, epithelial cell cyclooxygenase-2 (COX-2) generates 18*R*-hydroxyeicosapentaenoic acid (18*R*-HEPE) intermediates from dietary omega-3 fatty acids and polymorphonuclear-expressed 5-lipoxygenase (5-LO) generates resolvins such as RvE1. Such locally generated resolvins are then made available to activate surface-expressed ChemR23 receptor, which in turn has been shown to activate a number of antimicrobial and proresolving pathways within the mucosa (6).

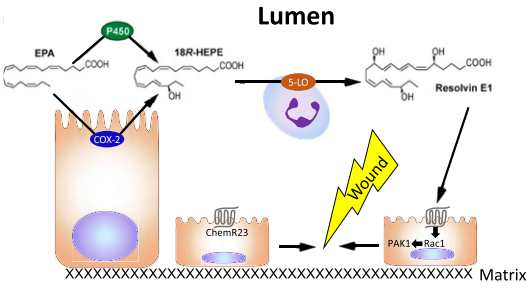

Fig. 1. RvE1 promotes mucosal wound healing. Wounds generated at sites of active mucosal inflammation promote the biosynthesis of RvE1. As shown here, dietary omega-3 fatty acids such as EPA utilize epithelial COX-2 to generate 18*R*-HEPE intermediates that are subsequently converted to RvE1 through neutrophil-expressed 5-LO. Resulting RvE1 is then made available to apical ChemR23 receptors that signal through Rac1 and PAK1 to amplify adhesion and cell migration along the matrix bed to promote wound healing.

Using a miniature colonoscope-based wound-healing approach in mice, Quiros et al. (2) identified the prominent induction of RvE1 biosynthesis in wounded colon tissue. Using a targeted lipidomic approach, they determined that over of period of 4 d RvE1 levels peaked by day 2 and normalized by day 4. Other resolvin classes (e.g., RvE2 and RvE3) did not change in colonic biopsies, suggesting that conditions within the mucosa favor the generation and metabolic

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stabilization of RvE1. A critical feature of productive wound healing involves cell adhesion and migration. Using a proximity ligation assay, Quiros et al. (2) demonstrated that RvE1 activates one of the dominant components controlling cell adhesion and migration, namely the guanosine triphosphatase Rac1 (7, 8). It is through the fine-tuning of Rac1 activity by upstream cell-surface receptors that regulate the cycling Rac1–guanosine diphosphate (inactive) to Rac1–guanosine triphosphate (active) and subsequent downstream signaling to the actin cytoskeleton, protein kinases (e.g., mitogen-activated protein kinase and p21-activated kinase), as well as various transcription factors (nuclear factor κB, signal transducers and activators of transcription, and Wnt/β-catenin). Presumably through binding to the surface G protein-coupled receptor ChemR23 [well-documented expression on IECs (9, 10)], RvE1 promotes cell adhesion and wounded epithelial cell migration (Fig. 1). Rac1 activation promotes lamellipodia formation by driving branched actin polymerization at the leading edge. Following activation, Rac1 associates with downstream effectors such as insulin receptor tyrosine kinase substrate p53 (IRSp53), which further promotes Rac1 binding to WASP-family verprolin-homologous (WAVE) proteins that bridge binding to and activation of the actin nucleating protein, actin-related protein 2/3 (Arp2/3) protein complex. It is through this complex that branched actin polymerization is enhanced within the lamellipodia (8). It is also notable that Rac1 also regulates the expression of a number of matrix metalloproteases, which can contribute to proteolytic degradation of the extracellular matrix (7). The specific molecular details of RvE1 coupling to cell migration await further studies.

As alluded to above, RvE1 represents only one class of a growing family of SPMs. It remains unclear whether other SPMs might also promote mucosal wound healing. Some work has been done in corneal wound-healing models, particularly with the D-series resolvins. These studies have revealed that RvD1 and RvD6 promote corneal wound closure through different mechanisms (11, 12). Likewise, it was shown that RvD2 promotes dermal wound healing by preventing secondary thrombosis formation (13).

SPMs have evolved to be synthesized locally and act locally within tissue sites (14). For this reason, strategies to lengthen their half-life and stability in tissues would be welcome. Quiros et al. (2) accomplished this through encapsulating RvE1 into polymeric polyethylene glycol–poly lactic acid–co-glycolic acid nanoparticles (NPs). Coupled with a collagen IV peptide decoration to promote matrix adhesion, this NP formulation provided sustained and directed release at the site of injury. Using this same miniaturized colonoscope (along with some heroic dexterity), they were able to deliver RvE1 NPs within the wound bed. This targeted maneuver increased wound healing by ∼20% over that of RvE1 alone. Such results hold promise that luminal delivery of a proresolving/wound healing agent might benefit patients with active inflammation. This is an area of active research interest (15). Given the anatomy and the size of the intestine, significant challenges remain. In other more accessible organs (e.g., the skin), nanoparticles in many forms for topical administration are being developed as wound-healing agents and antimicrobial therapies (16). It may be possible to utilize characteristics of the inflamed microenvironment to deliver nanoparticles such as those Quiros et al. (2) describe. For example, ongoing work suggests that targeting of NPs can occur through pH- or reactive oxygen species-dependent targeting (15). Likewise, some success has been shown using ligand-receptor-mediated targeting. It is notable that expression of the RvE1 receptor ChemR23 is polarized to the apical (i.e., luminal) aspect of the epithelium (17), giving it better potential as a topical agent in the intestine. Whether treatment with resolvins might drive wound healing in patients with mucosal disease is anxiously anticipated by many.

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