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Pro-resolving lipid mediators and diabetic wound healing

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Abstract

Purpose of Review—Defective wound healing is one of the most prominent clinical manifestations of both type 1 and type 2 diabetes. As the global rates of diabetes increase, a detailed understanding of the molecular and cellular defects that give rise to unresolved inflammation and delayed wound healing in diabetes is urgently required. Emerging evidence indicates that timely resolution of inflammation is mediated in part by endogenous pro-resolving lipid mediators, such as resolvins. Here, we review recent advances in the area of resolution and diabetes and highlight the potential of novel pro-resolving strategies for promoting wound healing in diabetes.

Recent Findings—Macrophage dysfunction is a critical underlying feature of altered wound healing in diabetic patients. This is associated with defective clearance of apoptotic cells, increased risk of infection and altered angiogenesis. Diabetes and obesity are associated with chronic inflammation and altered biosynthesis of bioactive lipid mediators that promote the resolution of inflammation. Stimulating resolution with pro-resolving lipid mediators improves metabolic parameters in diabetes, blunts systemic inflammation, restores defective macrophage phagocytosis and accelerates wound healing in animal models of obesity and diabetes.

Summary—Stimulating resolution with pro-resolving lipid mediators may represent a novel strategy for promoting wound healing in diabetes.

Keywords

resolvins; obesity; macrophages; inflammation; resolution

Introduction

Repair of wounds is accomplished by a temporally orchestrated series of events that serve to contain and extinguish invading pathogens, remove dead cells, and rebuild tissue and vascular networks. In normal circumstances, this process proceeds unabated and homeostasis is restored after the insult. However, in diabetes, the wound healing sequelae are dysregulated at multiple levels, giving rise to festering inflammation, unwarranted tissue

damage and in some cases, loss of function. Indeed, diabetics suffer from chronic ulcerations due to peripheral neuropathy, vascular disease and altered immune function, and diabetes remains the number one cause of non-traumatic amputations (1). Several events in the normal wound healing program are disrupted in diabetes, including altered bactericidal actions of granulocytes, extracellular matrix basement membrane thickening and poor tissue perfusion (1). Accordingly, therapeutic management of diabetic wounds is focused primarily on controlling infection and promoting re-vascularization (i.e. angioplasty or bypass grafting) (1). Despite these strategies, the rate of amputation in diabetics with wounds such as chronic foot ulcers remains unacceptably high. Thus, new strategies for promoting wound healing in diabetes are urgently needed.

In healthy tissue, pathogen invasion or tissue injury triggers a prompt inflammatory response that is actively resolved to allow for tissue repair and a return to homeostasis (2, 3). Emerging evidence demonstrates that resolution of inflammation is an active endogenous program regulated in part by specialized pro-resolving lipid mediators, such as resolvins. These mediators are biosynthesized from omega-3 fatty acids; they block excessive leukocyte infiltration into tissues and blunt the production of pro-inflammatory mediators (3). They have distinct pro-resolving actions involving the stimulation of non-inflammatory phagocytosis of microbes and dying cells and the efflux of phagocytes from inflamed tissues. Recent studies suggest that defective resolution of inflammation underlies numerous chronic inflammatory pathologies and that stimulating resolution pathways with pro-resolving lipid mediators could be beneficial in animal models of multiple disease states (2-4). Notably, it has recently been shown that the generation of pro-resolving lipid mediators is altered in diabetes and that restoration of these defects not only resolves inflammation, but also improves metabolic parameters in rodent models of obesity and type 2 diabetes (T2D).

Macrophage dysfunction and altered resolution of inflammation in diabetes

Macrophages are important players in innate immunity and their phenotypic plasticity confers many temporally distinct functions in wound healing (5, 6). As a first line of defense, polymorphonuclear neutrophils (PMN) are recruited to the site of injury to eradicate microbes that are present in injured tissue. Following containment, PMN undergo apoptosis and must be cleared to prevent inadvertent tissue injury due to excessive production of reactive oxygen species (ROS) and other tissue degrading enzymes. The timely clearance of apoptotic PMN is required to prevent secondary necrosis of PMN and their clearance is accomplished primarily by macrophages (7). Thus, clearance of apoptotic PMN by macrophages is a defining feature of timely resolution of inflammation and sets the stage for tissue repair. While macrophages carrying ingested PMN rapidly efflux from the tissue, macrophages also contribute to angiogenesis and tissue repair, by secreting vascular endothelial growth factor (VEGF) and fibrotic cytokines, including transforming growth factor β (TGF- β) (6). Because of these critical functions, macrophages are indispensable to the wound healing program.

Multiple lines of evidence demonstrate that macrophage dysfunction contributes to chronic, unresolved inflammation in diabetes. In regard to the clearance of apoptotic cells, several

studies have documented that the apoptotic cell burden in diabetic wounds is elevated and tissue necrosis is a defining feature of diabetic foot ulcerations (1, 8). More recently, defects in macrophage phagocytosis were shown to underlie excessive apoptotic cell accumulation in atherosclerotic lesions of diabetic rodents (4). Consistent with the critical role of macrophage-mediated clearance of apoptotic cells, diabetic macrophages display profound defects in their ability to phagocytose both apoptotic cells and bacteria (9-11). This suggests that diabetic defects in wound healing may be related to macrophage dysfunction and therefore could be corrected by improving the phagocytic properties of macrophages.

Macrophages exist in multiple phenotypic states which relate to their function and are driven largely by soluble factors secreted in the microenvironment (5). Classically activated or M1 macrophages have potent microbicidal properties and they secrete pro-inflammatory mediators during the early phases of an acute inflammatory response. This polarization state is stimulated by bacterial lipopolysaccharides (LPS), as well as interferon- γ (IFN- γ), and is associated with an increase in the expression of proteins, such as inducible nitric oxide synthase (iNOS), which play important roles in microbial killing. In contrast, stimulation of macrophages by T helper cell type 2 (Th2) cytokines including interleukin-4 (IL-4) and IL-13, drive macrophage polarization to an alternatively activated or M2 phenotype (5). These M2 macrophages express proteins important for angiogenesis and tissue remodeling, including VEGF and arginase-1 (arg-1). Arginase-1 diverts arginine metabolism to produce the polyamine precursor, urea, as well as ornithine, which contributes to collagen synthesis. While these functionally distinct polarization states serve essential functions, persistent M1 polarization can perpetuate inflammation. Indeed, increased numbers of inflammatory M1 macrophages have been shown to accumulate in adipose tissue of obese-diabetic humans and rodents, as well as in atherosclerotic lesions and diabetic wounds (4, 8, 12). Moreover, macrophages isolated from wounds of diabetic mice secrete more pro-inflammatory mediators, such as tumor necrosis factor α (TNF- α) and IL-6, than those from non-diabetic mice. Regulation of this inflammatory macrophage population by genetic and pharmacologic approaches has demonstrated that this macrophage dysfunction contributes to chronic inflammation and the two primary clinical manifestations of diabetes; delayed wound healing and atherosclerosis (4, 8, 13).

Lipid mediators of resolution

Each phase of the acute inflammatory response is regulated by a multitude of positive and negative regulatory inputs that collectively orchestrate and influence whether the specific phase will proceed, how long it will proceed, and when it will terminate (14). Lipid mediators in particular control distinct phases of the inflammatory response. For instance, the cysteinyl leukotrienes (cysLT) stimulate microvascular permeability while leukotriene B₄ (LTB₄) is a potent PMN chemoattractant (15). In addition, LTB₄ also controls the production of pro-inflammatory cytokines and chemokines, establishing positive feed-forward loops (16). The prostanoids, including prostaglandins E₂ and D₂, as well as prostacyclin and thromboxane, have well documented roles in regulating blood flow, pain sensitization and platelet aggregation (17). Importantly, other eicosanoids, including lipoxin A₄ (LXA₄), negatively regulate PMN trafficking to injured tissues and shut down pro-inflammatory cytokine cascades to signal the early phase of resolution (3).

Resolvins (resolution phase interaction products) are a relatively new family of endogenous lipid mediators that are generated from omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (18). Resolvins were first identified by profiling of lipid-based mediators generated during the resolution phase of acute, self-resolving inflammation (19-21). Their biosynthesis corresponds to the phase in which mononuclear phagocytes actively remove apoptotic PMN from inflammatory sites. This pattern suggests that temporal relationships exist between different families of lipid mediators, with each family serving distinct roles during the acute inflammatory response. It is important to note that in addition to resolvins, other pro-resolving mediators generated from EPA and DHA have been identified and include the protectins and maresins (18, 21, 22).

Liquid-chromatography/mass spectrometry (LC/MS/MS)-based methods enabled the structural elucidation of resolvins generated *in vivo*. The resolvins are hydroxylated derivatives of EPA and DHA and therefore it was posited that their formation likely occurs via biosynthetic routes that are similar to the eicosanoids. As with the lipoxin biosynthetic routes, transcellular biosynthesis is key in the formation of resolvins, highlighting both temporal and spatial regulation of their formation. For instance, interactions between different leukocyte subsets, or leukocytes and endothelial or epithelial cells, enables transfer of resolvin biosynthetic precursors from a donor cell to another cell type which completes the resolvin biosynthetic pathway. Indeed, studies in isolated human cells demonstrate that DHA can be converted to 17-hydroperoxydocosahexaenoic acid (17-HpDHA) by 15-lipoxygenase, which is further transformed by activated leukocytes expressing 5-lipoxygenase to distinct regioisomers, including resolvin D1 (RvD1; 7*S*,8*R*,17*S*-trihydroxy-docosa-4*Z*,9*E*,11*E*,13*Z*,15*E*,19*Z*-hexaenoic acid) and resolvin D2 (RvD2; 7*S*,16*R*,17*S*-trihydroxy-docosa-4*Z*,8*E*,10*Z*,12*E*,14*E*,19*Z*-hexaenoic acid). The detailed biosynthetic routes giving rise to resolvins has been recently reviewed (18). Importantly, resolvins are generated in both murine and human cells and were recently identified in cells isolated from rainbow trout, suggesting that these biosynthetic pathways are evolutionarily conserved (3).

Although the endogenous biological actions of resolvins are still being actively investigated, it is clear that they are potent agonists of resolution. Isolated resolvins, including RvE1, RvD1 and RvD2, potently reduce PMN infiltration in murine peritonitis and enhance macrophage phagocytosis of both apoptotic PMN, as well as microbes (18). Administration of resolvins and protectins also markedly enhances the efflux of phagocytes from inflamed tissues and hastens the resolution of acute peritonitis (18, 23). In addition, we have recently shown that resolvins, such as RvD2, enhance survival in polymicrobial sepsis and that this is associated with decreased bacterial burden (24). *In vitro*, resolvins enhance phagocyte-mediated killing of live bacteria, and markedly blunt the production of pro-inflammatory mediators induced by LPS (24-27).

Pro-resolving lipid mediators in diabetic wound healing

Given that many of the features of delayed diabetic wound healing are related to altered resolution of inflammation and the chronic nature of inflammation in diabetes in general, recent studies have begun testing whether defects in pro-resolving lipid mediators contribute to unresolved inflammation in diabetes and importantly, whether stimulating resolution

pathways could promote diabetic wound healing. Recent studies have shown that obesity and systemic insulin resistance in high fat-fed rodents are associated with a decrease the levels of omega-3 fatty acids in the liver, skeletal muscle and adipose tissue (28). To determine whether increasing omega-3 fatty acids could attenuate insulin resistance, mice overexpressing *fat-1* were utilized in high fat feeding studies. Fat-1 is a desaturase enzyme enabling the endogenous conversion of omega-6 to omega-3 fatty acids and overexpression of this enzyme led to an increase in tissue levels of omega-3 fatty acids. In addition, the resolvin biosynthetic pathway marker 17-hydroxydocosahexaenoic acid (17-HDHA), as well as protectin D1 (PD1), was increased in both the skeletal muscle and adipose tissue of these mice. Significantly, metabolic parameters, including hyperinsulinemia and insulin tolerance, were improved in *fat-1* transgenic mice, supporting the notion that lipid mediators could improve insulin resistance (28). Similarly, feeding obese-diabetic mice a diet rich in omega-3 fatty acids increases the production of 17-HDHA, RvD1 and PD1 in adipose tissue and is associated with an improvement of metabolic parameters (29).

Given the possibility that an imbalance between pro-inflammatory and pro-resolving lipid mediators might be contributing to chronic inflammation and metabolic derangements in obesity and diabetes, we and others evaluated whether stimulating resolution with resolvins might confer protection in these conditions. Indeed, we found that administration of RvD1 to obese-diabetic mice improves glucose tolerance and hyperglycemia (30). Importantly, adipose tissue macrophage-mediated inflammation was largely blunted by RvD1 treatment and the ratio of alternatively activated to classically activated macrophages was increased. Similarly, treatment of obese-diabetic mice with RvE1 led to an increase in the expression of insulin sensitizing genes and decreased hepatic steatosis (29).

Recent work from our laboratory has also demonstrated that RvD1 restores defects in phagocytosis by macrophages isolated from obese-diabetic mice, while *in vivo* administration of RvD1 enhances the clearance of PMN from the inflamed peritoneum in diabetic mice (31). Additional studies have shown that a novel DHA-derived mediator, 14*S*, 21*R*-dihydroxydocosahexaenoic acid (14*S*, 21*R*-diHDHA), is generated by macrophages during normal wound healing, suggesting that the formation of this mediator may be important for timely wound repair (32). Interestingly, the formation of 14*S*, 21*R*-diHDHA is decreased in the wounds of obese-diabetic mice and treatment of diabetic wounds with this DHA-derived mediator improves wound closure (33). Mechanistically, 14*S*, 21*R*-diHDHA was found to promote macrophage-dependent production of pro-angiogenic factors, such as VEGF, as well as blunt the production of ROS (33, 34). Angiogenesis was markedly enhanced by 14*S*, 21*R*-diHDHA in diabetic wounds, recapitulating its potent actions in isolated macrophages. These data illustrate that diabetes directly impinges upon the production of reparative pro-resolving lipid mediators important for wound healing, and demonstrate that restoration of these defects improve wound healing in animal models of T2D.

In addition to regulating the pro-resolving role of macrophages, pro-resolving lipid mediators have direct actions on keratinocytes (35). Using an electric cell impedance-sensing system, we found that RvD1 enhanced wound closure in isolated human epidermal keratinocytes. Of interest, we also identified that endogenous microparticles generated

during the resolution of acute inflammation contain pro-resolving lipid mediator precursors (35). We constructed novel humanized nanoparticles containing resolvins to mimic these endogenous delivery systems. These nano pro-resolving medicines enhanced keratinocyte wound healing *in vitro* and were markedly more potent than isolated resolvins. These findings show that this delivery system is capable of influencing keratinocyte wound healing and could serve as the basis for novel biomimicry-based pro-resolving therapeutics. These findings lend further support to the notion that pro-resolving lipid mediators may have multiple roles and cellular targets during the natural process of wound healing and that these pathways could potentially be exploited for treating non-resolving wounds in diabetes.

Conclusion

The endogenous mechanisms regulating the resolution phase of acute inflammation are just beginning to be appreciated and insights into this vital process have helped us in understanding the persistence of inflammation in chronic disease. Among the mediators of resolution, lipid autacoids have emerged as important players that have multiple cellular targets and potent biological actions. Multiple lines of evidence indicate that delayed wound healing in diabetes could arise in part because of altered resolution of inflammation. First, apoptotic cells accumulate in diabetic wounds; second, diabetes induces macrophage dysfunction; third, pro-resolving lipid mediator production is decreased and; stimulation of resolution by pro-resolving lipid mediators enhances wound healing, systemic inflammation and metabolic parameters in diabetes. Collectively, these studies support the possibility that pro-resolving lipid mediators could become a new class of wound healing therapeutics.

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Key points

- Defects in the resolution of inflammation, and macrophage function in particular, might underlie the chronic nature of diabetic wounds.
- Deficiencies in the production of pro-resolving lipid mediators are associated with the development of diabetic wound inflammation, as well as insulin resistance in obesity and diabetes.
- Stimulating resolution with pro-resolving lipid mediators improves metabolic parameters, systemic inflammation and wound healing in diabetes and may represent a novel strategy for treating diabetic wounds.