

Mucosal Healing in Intestinal Inflammation

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Mucosal healing in intestinal inflammation and particularly in IBD, as it is defined by the International Organization of IBD (IOIBD), is the absence of all friability and visible ulcers and erosions in all examined segments of the gut mucosa. Mucosal healing, documented via endoscopic scores, combined with clinical remission, has been characterized as deep remission. The term complete remission, which includes histological remission, in addition to mucosal healing and clinical remission, has been suggested as a treatment target in IBD.

intestinal wound healing

probiotics

inflammatory bowel diseases

1. Mucosal Healing in Intestinal Inflammation

Mucosal healing in intestinal inflammation and particularly in IBD, as it is defined by the International Organization of IBD (IOIBD), is the absence of all friability and visible ulcers and erosions in all examined segments of the gut mucosa ^{[1][2]}. Mucosal healing, documented via endoscopic scores, combined with clinical remission, has been characterized as deep remission ^[3]. The term complete remission, which includes histological remission, in addition to mucosal healing and clinical remission, has been suggested as a treatment target in IBD ^[4]. Histological remission is determined by the absence of polymorphonuclear cells in the crypts and lamina propria, the presence of a normal number of eosinophils, and the absence of plasma cells. However, this definition is more appropriate for UC rather than CD, which is characterized by discontinuous and transmural bowel lesions, and it is still obscure whether mucosal healing also implies complete transmural healing ^[4].

Mucosal healing was traditionally assessed by endoscopic examination. In CD, clinicians usually validate endoscopic mucosal healing by examining four different factors—namely, (a) the location of ulcers on the intestinal surface, (b) the location of other inflammatory lesions on the intestinal surface, (c) the presence or absence of ulcers, and finally, (d) the presence of stenotic areas ^[5]. In UC, the assessment of endoscopic mucosal healing is more complicated, as several different factors need to be evaluated, including (a) the presence of erythema, friability, ulcers, and erosions; (b) the absence of vascular pattern; (c) the presence of spontaneous bleeding ^[5].

Recently, deep remission has been defined as clinical remission, followed by mucosal healing and histological remission. In addition, newer markers, such as fecal calprotectin, magnetic resonance enterography, and capsule endoscopy are also used to define clinical remission and mucosal healing ^{[6][7]}. Although the definition of mucosal healing in IBD remains controversial, the IOIBD has proposed a definition of histological remission, the absence of neutrophils in crypts and lamina propria, the absence of basal plasma cells, and the reduction in eosinophils in lamina propria to normal counts ^[4]. Given that CD is a discontinuous and transmural disease, histological remission

in patients with CD is less clearly defined compared with patients with UC, in whom histological healing would indicate complete remission and probably be a better clinical outcome, compared with endoscopic and clinical remission [8]. Transmural healing in CD and histological healing in UC should be considered as markers of the extent of remission, while mucosal healing should be treated as an initial event that suppresses the submucosal inflammation, rather than as a sign of complete suppression of gut inflammation.

Mucosal healing seems to improve the clinical course of patients with IBD, by reducing drug therapy, hospitalization, and surgery [9]. However, whether mucosal healing improves the natural history of the disease and the long-term disease-related morbidity still remains unclear. Various studies have shown that deep remission is associated with increased chances of steroid-free clinical remission and decreased risk of disease relapse in patients with CD, while mucosal healing has been shown to reduce the risk of colorectal carcinoma in patients with UC [10][11]. Although there are not many studies, achieving mucosal healing seems to be cost effective, as it results in reduced hospitalization and surgery and improves the quality of life of patients [12], and it should be recognized as the main target for IBD therapy [13].

The intestinal epithelium absorbs nutrients and water from the gut lumen, it is implicated in the fluid and electrolyte homeostasis, and it has to tolerate the commensal microbiota while at the same time combating the pathogenic bacteria [14]. The regular and coordinated performance of these fundamental functions of the intestinal mucosa is based on the fact that it is a highly regenerative tissue, under normal conditions or after damage [15]. The intestinal epithelium normally is rapidly renewed, as epithelial stem cells in the bottom of crypts give rise to absorptive enterocytes and secretory cells, and when the damage is able to be repaired, several adaptive mechanisms occur. These mechanisms include several events, such as the increase in epithelial proliferation, the decrease in apoptosis, the migration of mesenchymal and immune cells in the wounded surface area, and a well-orchestrated inflammatory response that lead to wound healing and prevents a chronic injury and inflammation [16].

Following inflammation and injury, the intestinal mucosa undergoes a healing process through complex mechanisms of epithelial restitution, proliferation, and differentiation, and a network of cellular communication of epithelial, mesenchymal, and immune cells, such as macrophages, granulocytes, and lymphocytes [17][18]. This process leads to the recruitment of immune cells and the release of different cytokines that coordinate the trafficking of immune cells with complex interactions with different cellular components via the induction of particular cell signaling pathways [19]. Thus, the wound healing of the intestinal mucosa is a function that participates in the inhibition of the inflammatory response, which results in the damage restoration and contributes to the suppression of inflammation.

The process of intestinal wound healing consists of three successive cellular phases: restitution, proliferation, and differentiation of the epithelium, surrounding the wounded area. However, these steps overlap with each other, and many cellular elements and soluble mediators are involved in more than one phase [20]. The initial response, following intestinal inflammation and mucosal damage, is characterized by a type 1 immune response and the production of pro-inflammatory cytokines. In contrast, the mucosal healing process is a type 2 immune response with increased anti-inflammatory cytokines production that governs tissue regeneration and homeostasis [21]. The

first step, termed epithelial restitution, involves epithelial cells migration into the damaged area, forming structures to extend into the denuded mucosa and close the wound. The most important regulator of restitution is transforming growth factor β (TGF- β) that is produced by epithelial cells, myofibroblasts, regulatory T cells, dendritic cells, and macrophages in the gut mucosa [22][23]. Activation of TGF- β enhances restitution by upregulating a number of mediators such as matrix metalloproteinases [24] and vascular endothelial growth factor [25], which promote epithelial cell migration and amino acids such as histidine and arginine that mediate restitution via interaction with Smad signaling [26]. This phase seems to be independent of cell proliferation.

The next phase, proliferation, is mediated by growth factors, including epidermal growth factor, fibroblast growth factor, and keratinocyte growth factor [27][28], and by cytokines such as IL-6, IL-28, IL-33, and IL-22 [29][30][31][32] that increase the number of epithelial cells in order to recover the damaged mucosa and promote immune homeostasis [20]. TLR2 has been found to suppress apoptosis of epithelial cells and promote wound healing by regulating epithelial connexin-43 and trefoil factor 3 expression [33][34]. Another study has shown that interferon- γ induces ligand intercellular adhesion molecule-1 expression in neutrophils and neutrophil binding resulting in increased epithelial cell proliferation, and wound repair [35]. The last phase of differentiation follows the normal process in which intestinal stem cells, located in the crypts, differentiate into secretory to absorptive cell types of progenitors that renew the cellular population of the gut epithelium [36]. This final step of mucosal healing that implicates differentiation and maturation is crucial for the maintenance of the mucosal barrier function [19].

2. Immune Cells and Soluble Mediators in Mucosal Healing

This sequential process of mucosal healing involves a number of immune and stromal cells of the gut mucosa, communicating and interacting through the secretion of cytokines, growth factors, and conventional gut peptides that are involved in inflamed and restoration processes [13][37]. Neutrophils are the first leukocytes that migrate to sites of mucosal injury, promoting inflammation, in response to the chemokines-rich milieu [38][39]. These cells respond to proinflammatory cytokines by attracting inflammatory monocytes and promoting further inflammation and impairment of the mucosal injury [40]. However, their antimicrobial properties through phagocytosis, production of reactive oxygen species, regulation of the local microenvironment through oxygen metabolism, and the formation of neutrophil extracellular traps (NETs) are essential for wound healing [41][42][43]. Reactive oxygen species generated from neutrophils were found to orchestrate signaling events in epithelial cells contributing to intestinal repair [44]. Depletion of neutrophils or blocking neutrophil invasion in the inflamed gut mucosa, in experimental models of colitis, resulted in aggravation of colitis and impaired restoration of epithelial integrity [45][46].

Despite intestinal mucosa being a large macrophage pool [47], circulating monocytes are rapidly recruited to injured or inflamed areas, increasing the number of tissue macrophages in intestinal inflammation that differentiate into inflammatory M1-like or wound repairing M2-like macrophages [48][49]. Alterations in macrophage differentiation and functionality might contribute to increased susceptibility to IBD [50][51]. Aberrant M1/M2 macrophage polarization and the presence of intestinal Toll-like receptor-responsive macrophages are implicated in the severity and progression of IBD [52][53]. However, due to their heterogeneity, they are implicated in all phases of initiation and restoration of inflammation, including wound repair. Depletion of macrophages in experimental models resulted in

increased injury and delayed regeneration and healing, indicating that are necessary for proper epithelial regeneration [54][55]. In addition, macrophages could promote wound repair through the production of cytokines [56], such as IL-10, which possess anti-inflammatory and homeostatic properties [57], and IL-23, an important mediator of wound healing [58]. Another study demonstrated that liver and lymph node sinusoidal endothelial cell C-type lectin (LSECtin)-dependent apoptotic cell clearance by macrophages promotes resolution of inflammation and intestinal regeneration in a model of colitis via the activation of mammalian target of rapamycin (mTOR) [59].

Soluble mediators secreted by T lymphocytes play a crucial role in immune and stromal cell communication and cell trafficking during the wound healing process [60][61]. Activated T helper cells (T_H) produce various cytokines that induce tissue regeneration and healing. T_H17 and T_H22 have been shown to produce IL-22 that ameliorates intestinal inflammation [62] and promotes wound healing, via the increase in innate lymphoid cells (ILC3) and mucus production in the intestinal epithelium [63]. Injury of the intestinal mucosa can induce polarization of naïve T cells to T_H17 cells, via IL-6, TGF- β , and IL-1 β signaling, which further expand and produce IL-17 and IL-22, promoting wound healing [64]. Furthermore, $\gamma\delta$ T cells are recruited in the site of injury via the expression of CCL20 [65], where they promote healing by producing Keratinocyte growth factor (KGF) in the gut mucosa, which maintains the integrity of intestinal epithelium and is also involved in epithelial cell proliferation and differentiation, which is important in tissue repair [66]. In addition, resident $\gamma\delta$ T cells are implicated in wound healing by promoting proliferation and migration of stem cells in the side of injury [67]. Another study has shown that mice lacking $\gamma\delta$ T cells had a reduced ability to repair the gut injury in a model of Dextran Sulfate Sodium (DSS)-induced colitis [68]. However, T lymphocytes mediators' production during inflammation and tissue injury could also worsen the inflammatory process, if not tightly controlled.

Treg cells with a stable expression of Foxp3 were initially considered as the main regulatory T cell population. Over the last years, a heterogeneity of different Treg cell populations has been reported. Suppressor T cells could inhibit the effect of T_H cells via the production of anti-inflammatory and immunomodulatory cytokines [69][70]. Experimental studies from various organs in mice have shown that the depletion of Tregs deteriorates the clinical outcome by increasing the inflammation and inhibiting wound healing [71][72]. There is evidence that Treg-produced fibroblast growth factor (FGF) and IL-17 decrease the accumulation of pro-inflammatory macrophages and are also implicated in gene regulation of intestinal epithelium's repairment [73][74]. Another study has shown that Foxp3⁺Tregs might promote mucosal healing in intestinal inflammation and injury via vascular endothelial growth factor receptor 1 tyrosine kinase (VEGFR1-TK) signaling, as mucosal repair in DSS-induced colitis is impaired in VEGFR1-TK knock-out mice [75]. On the other hand, expansion of regulatory T cells has been reported to maintain mucosal healing in UC [76]. Data from experimental studies have shown that commensal microbiota regulate the generation of regulatory T cells from microbial activated effector T cells [77]. Accumulation of Tregs in the lamina propria of the large and small intestine has been found to be affected by changes in gut microbiota, as it was found impaired in germ-free or antibiotic-treated mice, and fecal transplantation from normal mice increased the number of Tregs [78], while probiotic administration has been found to modulate the functional metabolism of regulatory T cells via the regulation of dysbiosis [79].

Innate lymphoid cells (ILCs), another important cell population of the intestinal mucosa [80], apart from their contribution to IBD, promote resolution of intestinal inflammation and mucosal healing [81]. The ILC3s subset is the main source of IL-22 after induction by IL-23 during intestinal damage, which protects intestinal stem cells from immune-mediated responses and activates them to promote wound repair [82][83]. In addition, the ILCregs subset promotes wound healing via the secretion of IL-10, suppressing activated ILC1s and ILC3s subsets [84]. Recently, another study demonstrated that GPR34 receptor deficiency in the ILC3s subset decreased IL-22 production and tissue repair in colon and skin injury in mice. Expression of GPR34 receptor in ILC3s triggers intestinal mucosa healing, upon recognition of dying neutrophils [85].

The mucosal healing process in intestinal inflammation repairs mucosal integrity and maintains the epithelial barrier with important clinical benefits. Although certain mechanisms and immune cells implicated in the process of wound repair are well studied, the overall picture of the interplay between cellular components and mediators has not been clarified.

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