Constructive inflammation in wound healing

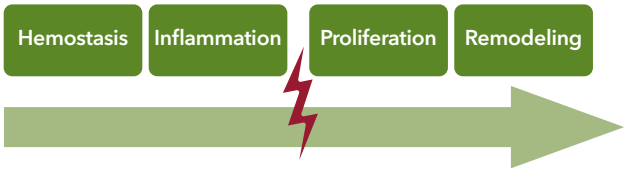
Wound healing is a dynamic process occurring after injury that is characterized by a careful orchestration of events occurring in a well defined order. The stages of wound healing include initial **hemostasis**, characterized by clot formation; **inflammation**, characterized by the deposition of inflammatory and progenitor cells, leading to the formation of granulation tissue; **proliferation**, where resident cells secrete growth factors and cytokines, collagen deposition occurs, and neovascularization begins; and **remodeling**, where the newly formed tissue matures and collagen strength increases to meet the demands of the body.[1]

Inflammation

Inflammation is an essential step in the wound healing process, as it both helps control bleeding and reduce the likelihood of infection. During inflammation, resident macrophages promote the influx of neutrophils. Neutrophils initiate the inflammatory response while secreting chemoattractants that promote the infiltration of additional immune cells like eosinophils, mast cells, and additional macrophages. Bacteria in the wound are phagocytosed, and damaged extracellular matrix (ECM) and dead cells are removed to clean up the area of injury. Growth factors are also released to stimulate angiogenesis (blood vessel formation) and direct the influx of progenitor cells to the area, eventually signaling the fibroblasts to form granulation tissue.[2,3]

In a healthy individual, the stages of wound healing occur in a sequential, yet overlapping order.[2] In patients with severe trauma or multiple comorbidities, however, wound healing often gets stalled in the inflammatory stage and fails to proceed down the ordered path, leading to chronic inflammation and impairment (Figure 1). Chronic inflammation is caused by the hyper and continued influx of immune cells and the overexpression and release of local proteases and enzymes. This leads to continued and repeated breakdown of newly deposited ECM and tissue, preventing the wound from progressing into the proliferation stage.[3]

Figure 1: Wound-healing stages



Chronic wounds fail to progress through the stages of wound healing, often getting stuck in the inflammation stage.

Graft materials following tissue loss

Controlling the inflammatory response and preventing the onset of chronic inflammation in the presence of multiple comorbidities and/or following major trauma are essential to successful wound healing. Because inflammation is partially directed by the ECM environment and the signaling factors contained within it,[4] implanting a naturally occurring graft material that replaces the damaged ECM can be an effective strategy for restoring a normal progression of healing and allowing tissue remodeling to occur.

The key to using a biologic graft material as a replacement for damaged tissue lies in the composition and structure of the graft material itself, largely due to its source and the processing methods used during its manufacture. The patient's immune system needs to accept the graft and the role it plays in tissue restoration, rather than recognizing the graft as foreign and mounting an assault on it, which leads to a rejection response and can create a chronic inflammatory environment.

Foreign-body response due to overprocessing

While synthetic meshes and cross-linked biologic grafts can be engineered to have the adequate mechanical properties to support the primary function of soft tissue reinforcement, these materials have also been shown to have negative effects on inflammation.[5,6] These materials can be highly processed in ways that are not well accepted by the body. They have been shown to be associated with a rejection-type Th1-dominant lymphocyte response; the release of cytokines, such as IL-6, TNF-α, and IFN-γ, that lead to macrophage activation; and the polarization of macrophages into the cytotoxic (M1) phenotype.[5-7] These materials are viewed by the body as foreign, as something that needs to be removed. As a result, the body sets up a response designed to rid the material before returning to the normal progression of healing.

Biodesign in inflammation

In contrast to synthetic materials or cross-linked biologic grafts, Biodesign grafts manufactured from porcine small intestinal submucosa (SIS) not only have adequate mechanical strength for the primary function of soft tissue reinforcement, they have also been shown to be more accepted by the body's immune system and do not lead a rejection response.[8] They do not cause the activation of the complement cascade, nor are they acutely rejected following implant.[8] They are associated with a Th2-dominant lymphocyte response (a response associated with transplant acceptance[9]) that does not adversely affect the patient's ability to overcome viral or bacterial infections.[10,11] They have also been associated with an M2 macrophage phenotype response[5]—a macrophage phenotype that promotes immunoregulation, tissue repair, and constructive tissue remodeling.[12] In a 2020 publication, an *ex vivo* model of peritoneal inflammation demonstrated that Biodesign did not stimulate peritoneal tissue anti-healing gene expression or cytokine production.[13] Taken together, these findings demonstrate that the implantation of Biodesign aids in the successful resolution of the inflammatory stage of wound healing and allows for progression into the proliferation stage, leading to complete tissue remodeling.

References

1. Cañedo-Dorantes L, Cañedo-Ayala M. Skin acute wound healing: A comprehensive review. *Int J Inflam*. 2019;2019:3706315.
2. Lin PH, Sermersheim M, Li H, Lee PHU, Steinberg SM, Ma J. Zinc in wound healing modulation. *Nutrients*. 2017;10(1):16.
3. Muire PJ, Mangum LH, Wenke JC. Time course of immune response and immunomodulation during normal and delayed healing of musculoskeletal wounds. *Front Immunol*. 2020;11:1056.
4. Schultz GS, Davidson JM, Kirsner RS, Bornstein P, Herman IM. Dynamic reciprocity in the wound microenvironment. *Wound Rep Regen*. 2011;19(2):134-148.
5. Badylak SF, Valentin JE, Ravindra AK, McCabe GP, Stewart-Akers AM. Macrophage phenotype as a determinant of biologic scaffold remodeling. *Tissue Eng Part A*. 2008;14(11):1835-1842.
6. Mukherjee S, Darzi S, Paul K, Werkmeister JA, Gargett CE. Mesenchymal stem cell-based bioengineered constructs: foreign body response, cross-talk with macrophages and impact of biomaterial design strategies for pelvic floor disorders. *Interface Focus*. 2019;9(4):20180089.
7. Ge L, Liu L, Wei H, et al. Preparation of a small intestinal submucosa modified polypropylene hybrid mesh via a mussel-inspired polydopamine coating for pelvic reconstruction. *J Biomater Appl*. 2016;30(9):1385-1391.
8. Raeder RH, Badylak SF, Sheehan C, Kallakury B, Metzger DW. Natural anti-galactose alpha1,3 galactose antibodies delay, but do not prevent the acceptance of extracellular matrix xenografts. *Transpl Immunol*. 2002;10(1):15–24.
9. Bach FH, Ferran C, Hechenleitner P, et al. Accommodation of vascularized xenografts: expression of "protective genes" by donor endothelial cells in a host Th2 cytokine environment. *Nat Med*. 1997;3(2):196–204.
10. Allman AJ, McPherson TB, Badylak SF, et al. Xenogeneic extracellular matrix grafts elicit a TH2-restricted immune response. *Transplantation*. 2001;71(11):1631–1640.
11. Allman AJ, McPherson TB, Merrill LC, Badylak SF, Metzger DW. The Th2-restricted immune response to xenogeneic small intestinal submucosa does not influence systemic protective immunity to viral and bacterial pathogens. *Tissue Eng*. 2002;8(1):53–62.
12. Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. *Front Biosci*. 2008;13:453-61.
13. Pengelly S, Carlson GL, Berry JEA, Bell CR, Herrick SE. Regulation of peritoneal inflammatory response to implant material using an ex vivo model system. *J Surg Res*. 2020;247:202-210.