Constructive tissue remodeling in tissue repair

Biologic grafts made from natural tissues, when processed correctly for clinical use, have unique properties that are not found in synthetic materials, bioresorbable materials, or highly processed and cross-linked graft materials.

These unique properties allow the naturally occurring biologic graft to completely integrate with the recipient's tissues and cells to ultimately form a vascularized, highly organized tissue structure that resembles the native tissue structure and architecture.[1,2]

Dynamic reciprocity

More than just allowing tissue repair to occur, these unique biomaterials directly interact with the recipient in a process known as "dynamic reciprocity" to orchestrate the complex process of tissue remodeling. Dynamic reciprocity is the bidirectional interaction between the acellular part of the body, known as extracellular matrix (ECM), and the body's cells.[3] In a natural environment void of injury, the ECM and the cells communicate with each other and respond dynamically to each other to maintain homeostasis. After injury occurs and the ECM is damaged, a biologic graft can be implanted to restore the matrix structure and allow dynamic reciprocity to begin anew, ultimately achieving tissue restoration via the process of constructive tissue remodeling.[4]

Tissue repair vs. remodeling

Tissue remodeling is more than just another phrase for wound healing or for tissue repair. 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 and collagen deposition occurs; and **remodeling**, where the newly formed tissue matures and collagen strength increases to meet the demands of the body.[5] Wound healing, or tissue repair, results in the formation of scar tissue, which is known to be less strong than native tissue and can therefore be more susceptible to reinjury.[6]

Unlike the tissue-repair process that occurs in the absence of a biologic graft material, the constructive tissue remodeling process that can be directed by the correct ECM graft leads to a more natural healing process in the recipient that is characterized by the deposition of organized connective tissue, rather than just chaotic scar.[7] The correct ECM graft is characterized by an open matrix structure, to allow for rapid cellular ingrowth. It is also characterized by the presence of structural collagens and non-collagen ECM components (such as growth factors, glycoproteins, proteoglycans, and glycosaminoglycans), which act to facilitate the renewal of natural dynamic reciprocity.[8] When tissue homeostasis is disrupted, the biologic graft plays the role of the recipient's natural ECM and works to bridge the recipient's cells across the wound to ultimately restore a homeostatic environment. The restoration of homeostasis following injury in the presence of a biologic graft occurs through the constructive process of tissue remodeling.

Phases of tissue remodeling

Tissue remodeling is a process of tissue restoration that improves upon the scar tissue outcome typically achieved by tissue repair. It can be divided into three separate phases: **cell recruitment, tissue renewal, tissue reinforcement**.

During **cell recruitment**, the remodeling process starts when the body's inflammatory and progenitor cells populate the biologic graft and release

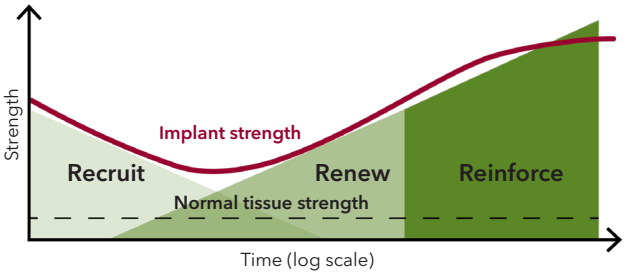
cytokines and growth factors that bind to the graft and recruit collagen-secreting fibroblasts.[8,9] In this phase, the graft primarily acts as a scaffold material to support the population of the open ECM structure by the patient's own cells.

As remodeling progresses, the patient's macrophages and fibroblasts in the newly populated matrix work together with matrix-bound signaling proteins to **renew the tissue** through the complementary processes of phagocytosis, collagen deposition, and angiogenesis (blood vessel formation). In this phase, the biologic graft is gradually replaced by the patient's own tissue and cells.[8,9]

Over the medium to long term, the resident fibroblasts secrete cytokines and growth factors to signal **reinforcement** of the deposited tissue through the processes of additional collagen deposition and maturation, resulting in a strong, repaired tissue.[1,2,10,11] In this phase, the biologic graft is no longer needed as the patient's own collagen has gradually matured into a stable structure that has long-term strength but is entirely the patient's own (Figure 1).[1,2,11] The resulting tissue structure is mature, organized and strong, and can withstand (and is even driven by) the natural physiological forces that it encounters.[12]

A biologic graft with the correct composition and three-dimensional architecture directs the patient's body to replace itself—to completely remodel—rather than to heal through a tissue-repair process that results in chaotic, weak, and ineffective scar tissue formation.[1,2] By providing the correct matrix to help the body restore itself, the graft provides both an essential temporary structure and the local tissue instructions to lead the patient to achieve a natural repair.

Figure 1: Biodesign graft remodeling



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