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Biomaterials-based in situ tissue engineering

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Biomaterials for in situ tissue engineering

Materials suitable for in situ tissue engineering (TE) include those that are either synthetic or naturally occurring in composition. However, such materials must possess the following two properties: be degradable, and elicit either a minimal pro-inflammatory response or an anti-inflammatory, immunomodulatory response. The formation of new, site-appropriate tissue that at least partially restores structure and function to the injured or missing anatomy implies circumvention of the default mammalian response to injury which is inflammation and scar tissue formation. Biomaterial-based strategies to meet these minimum requirements include modulation of surface ultrastructure, functionalization of surfaces with immunomodulatory (not immunosuppressive) molecules, and manipulation of material properties such as pore size and stiffness to influence cell behavior, among others. Such strategies typically apply to synthetic polymer materials that otherwise invariably elicit a pro-inflammatory response.

A fundamental concept of in situ TE involves the induction of in vivo biologic processes that are directed toward the formation of functional tissues that are structurally and functionally appropriate for the intended anatomic site and clinical application. The anatomic location of in situ biomaterial placement may be at the anatomical site where the tissue is needed, or alternatively, in an orthotopic location for later transplantation to the site of need. The advantage of the former strategy is that the developed neurovascular supply of the engineered tissue is secured and need not be interrupted, whereas the latter strategy requires transplantation of the neotissue to an alternative anatomic location and compromise of any developed neurovascular component.

In situ TE is a dynamic process during which the cell component, whether it be of host origin as a result of biomaterial infiltration or it is delivered with the biomaterial scaffold, must proliferate, self-assemble, and perhaps differentiate before reaching a steady state. Therefore, the structural and mechanical properties will change over time. The physical characteristics of the biomaterial during the remodeling phase need only to be adequate to sustain the mechanical requirements of the tissue such that continuity and integrity of the construct is maintained. The characteristics of the remodeled (engineered) biomaterial after months and years are more important than those at the time of implantation. Implied but not explicitly stated in this approach is the fact that mechanical properties of the engineered tissue will change over time and will be influenced by the mechanical loads present in the surrounding microenvironment.

Perhaps the greatest advantage of the in situ approach is elimination of the need to recapitulate the microenvironment that plays such a critical role in tissue development. In contrast to ex vivo approaches to tissue engineering that depend upon recapitulation of the necessary biochemical and biophysical cues within a bioreactor to provide for cell survival, migration, proliferation, and differentiation needed to create a functional tissue or organ, an in situ approach capitalizes upon the natural presence of these factors. Although bioreactors are technologically very sophisticated and can simultaneously control many biochemical factors and variables such as cyclic stretch, pulsatile flow, and electrostimulation, a prerequisite understanding of the temporal and spatial delivery of these factors is necessary for the desired outcome. At the present time, such an understanding does not sufficiently exist. For example, although the liver is arguably the most regenerative tissue/organ in the body, it is still not possible to maintain long term in-vitro culture of primary hepatocytes. Stated differently, technologic capabilities supercede the present understanding of the biology of tissue and organ development. Utilizing the body as an in situ bioreactor not only provides the appropriate combination of homeostatic and developmental cues, but does so in a relatively simple, scalable, and cost-effective manner.

The comparatively less burdensome regulatory requirements of an in situ tissue engineering approach

represents an additional attractive feature. Ex vivo approaches invariably involve more than "minimal manipulation" of cells, thus imposing numerous costly regulations with respect to manufacturing, sterility, shipping, and shelf life. When cells or tissues are combined with biomaterials for therapeutic applications, device regulations are added to the regulatory requirements. While ex vivo engineered constructs will typically be designated as biologics, materials-based constructs for in situ use without cells are usually regulated as devices, decreasing the needed "activation energy" for these products to reach the patient. If in situ implants do include cells their comparative simplicity and lack of manipulation still gives them a regulatory advantage over more heavily manipulated, fully functional tissue or organs created ex vivo. In almost every scenario, in situ tissue engineering approaches experience faster, cheaper, less labor-intensive clinical translation than their ex vivo counterparts.

The following sections are organized according to biomaterial origin and composition: synthetic, naturally occurring, and hybrid.

Synthetic biomaterials

Synthetic biomaterials are commonly used in the practice of medicine and are manufactured from a variety of base materials such as stainless steel, polypropylene, silicone, and polyurethanes, among others [1-4]. Synthetic biomaterials can be manufactured with high precision and can be terminally sterilized and packaged by well-recognized and accepted methods. Some synthetic materials are degradable within the human body (e.g., polylactic-glycolic acid) while others are essentially non-degradable (e.g., polypropylene). As stated earlier, one requirement for successful in situ tissue engineering is degradability of the biomaterial component. Without exception, the use of synthetic materials for in situ TE is as a template/scaffold for delivery of tissue-specific cell types and/or bioactive molecules. The synthetic material component of the construct is typically designed to degrade relatively rapidly (weeks to months) during the in situ remodeling phase, leaving behind the delivered cell types plus those host-derived cells that have infiltrated the construct during the course of in situ remodeling. Most commonly, the cell plus scaffold construct requires an in vitro step in which the seeded cells are given an opportunity to adhere to and attach to the synthetic material, and reach a homeostatic state prior to in vivo implantation.

One of the advantages of the use of synthetic materials for in-situ TE is the ability to "custom" manufacture the scaffold to perfectly accommodate the target anatomy of the individual patient. However, a disadvantage of synthetic materials is the inevitable proinflammatory response which promotes deposition of scar tissue and interferes with site-appropriate cell self-assembly. The rate of biomaterial degradation is a critical determinant of outcome. The longer the (foreign) material is present, the greater the impact of the associated inflammatory reaction on the downstream outcome. As stated above, the material and mechanical properties of the TE construct must be adequate to temporarily fulfill the function of the missing or injured tissue during the remodeling phase.

One example of synthetic materials utilized for in situ tissue engineering is the use of resorbable electrospun poly(ε-caprolactone) grafts as small-diameter blood vessels. These tubular scaffolds were filled with fibrin gel and monocyte chemoattractant protein 1 and implanted into rat abdominal aortas. After 3 months in situ, these grafts contained a medial layer with smooth muscle cells, an intimal layer with elastin fibers, and confluent endothelium [5]. A second example involves polyglycolic acid molded into the shape of a 3-year-old child's auricle. Multiple synthetic scaffolds were seeded with bovine chondrocytes and implanted subcutaneously into athymic mice, creating cartilaginous tissue resembling the complex structure of a child's auricle [6]. Taken one step further in a separate study, cartilaginous masses were generated in the lower abdomen of four patients using autologous auricular chondrocytes, which were subsequently sculpted into an ear framework and implanted into the normal anatomic position of the ear [7]. Other examples include tissue engineered tracheas made of polyglycolic acid [8,9], poly-lactic-glycolic acid [10], and polyester-urethane [11], various 3D-printed bioscaffolds such as bone [12], aortic valves [13], liver [14], skeletal muscle [15], a customized heart printed from specific patient data [16].

Naturally occurring materials

Materials composed of the secreted products of cells, including the extracellular matrix (ECM) or individual components of ECM such as collagen, are considered to be naturally occurring materials. For example, ECM bioscaffold materials composed of urinary bladder matrix (UBM) and small intestinal submucosa (SIS) are manufactured by the decellularization of their source tissue. These materials often retain sufficient bioactivity to promote positive remodeling effects such as recruitment/differentiation of endogenous stem/progenitor cells and modulation of host immune response when implanted in vivo. In one example of in situ tissue engineering, 13 patients were treated for volumetric muscle loss with sheets of porcine-derived ECM harvested from either urinary bladder, small intestine, or dermis. These ECM sheets were placed in contact with adjacent native healthy tissue and secured under tension with absorbable monofilament sutures for subsequent in situ remodeling. Compared with pre-operative performance, by 6 months after ECM implantation