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Basic Structure and Organization of the Extracellular Matrix

Acellular biomaterials are often composed of extracellular matrix (ECM). The ECM is the material found around cells. Until recently, this material was often referred to as "ground substance." The ECM has received increasing attention over the last decade due to its importance in cell to cell signaling, wound repair, cell adhesion and tissue function.

Examples of ECM are bone, cartilage, submucosa, and basement membrane. All four utilize collagen as a structural scaffold. Bone and submucosa utilize primarily type I collagen, cartilage utilizes primarily type II collagen, while basement membrane utilizes primarily type IV collagen. Collagen I and collagen II form long fibrillar arrays, while type IV collagen forms a mesh-type structure reminiscent of a chain-link fence.

Components of the Extracellular Matrix

The ECM consists of all the molecules in a tissue except for the cells. The major components of the ECM are:

- *Fibrillar collagens*
- *Non-fibrillar collagens*
- *Glycoproteins*
- *Proteoglycans*
- *Glycosaminoglycans*
- *Growth factors*

The ECM is made by the cells that are resident within it. Each type of ECM protein interacts with the cells and with each other to form a highly complex communication network where cells are instructed how to act. When the ECM is processed for use in tissue engineering, the cells are extracted from the surrounding matrix, leading to a structure that is friendly for clinical use.

Basic Functions of the ECM Proteins

While each specific ECM component is thought to provide specific instructions for the cells surrounding it, the classes of ECM proteins mentioned above have characteristic functions.

Fibrillar collagens: Fibrillar collagens act as the main structural scaffold of most types of ECM because they self-aggregate into long cable-like structures that form the basis for tissue strength and stability. The most common types of fibrillar collagens are Type I, Type II, Type III, and Type V.

Non-fibrillar collagens: Non-fibrillar collagens are a class of protein molecules that are similar in composition to the fibrillar collagens, but do not form cable-like structures. Instead, they form mesh-like structures reminiscent of chainlink fences or interact with the fibrillar collagens to form fibrils of tightly-regulated diameter. In basement membranes, the nonfibrillar collagen IV provides the mesh-like structure that gives microvessels their stability.

Glycoproteins: Glycoproteins act as the main non-collagenous support structure for the ECM because they possess attachment sites for cells as well as for a variety of other ECM proteins. Many glycoproteins are important in providing structure and stability to small blood vessels. Fibronectin, in particular, has been shown to be a major player in ECM structure and organization.

Proteoglycans: Proteoglycans serve a variety of functions in the ECM that are often dependent on the type of carbohydrate side chain (glycosaminoglycan) attached to the protein core. Many proteoglycans are released by the cells into the ECM and are regulators of matrix density (such as decorin). Other proteoglycans, such as perlecan, remain attached to the outer surface of cells and act as binding sites for growth factors.

Glycosaminoglycans: Glycosaminoglycans are linear, carbohydrate chains that are often found attached to the core protein of proteoglycans, but can also freely associate with a variety of other ECM structures. Two glycosaminoglycans, heparin and hyaluronic acid, are very important to healing. Hyaluronic acid is thought to help regulate matrix density and inhibit scar formation during the healing process. Heparin regulates the function of several growth factors and assists in the formation of new blood vessels (angiogenesis) following injury.

Growth Factors: Growth factors are small protein structures that control cell growth, differentiation, and ECM deposition by the cells. Growth factors are also responsible for initiating wound healing, regulating blood vessel formation, and maintaining tissue homeostasis, among other activities.

For more information on ECM proteins, see: Kreis T, Vale R, Eds. Guidebook to the Extracellular Matrix, Anchor, and Adhesion Proteins. Oxford University Press: Oxford, UK 1999.

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