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Technical Spotlight
From
Cook Biotech Inc.

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 three utilize collagen as a structural scaffold. Bone utilizes 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.

The ECM is comprised of more than collagen. In addition to collagens, the ECM is composed of non-fibrillar support structures called proteoglycans and glycoproteins. These structures are composed of a protein component and a carbohydrate component and play several varied roles in the ECM. They serve such diverse roles as maintaining hydration, absorbing shock, controlling matrix density, and regulating how cells interact with each other.

The carbohydrate portion of a proteoglycan is called a glycosaminoglycan. Glycosaminoglycans play important roles in wound repair, in restoring blood flow to an area of ischemic tissue, or in minimizing scar formation following injury. They also act as attachment molecules for proteins in the ECM known as growth factors. Like many of the components in the ECM, growth factors are able to directly influence the growth and activities of cells.

The ECM is made by the cells resident within it. The cells are able to directly interact with, and are influenced by, its structure. New interactions between the ECM and cells are continuously being discovered, but all seem to involve cell-surface receptors for molecules that are found in the space surrounding the cells. Because ECM molecules can also interact with each other, signals from the cells can be transferred through the ECM to areas further away. Thus, the ECM can exert a physical force on the cell and supply feedback which is important in controlling tissue structure and function.

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This bulletin contains:

Special points of interest:

- *Acellular biomaterials are composed entirely of extracellular matrix components. These structures were deposited by cells.*
- *Fibroblast cells that made the ECM can be removed during processing. The ECM structure, devoid of cells, is retained and utilized in tissue engineering applications.*
- *The ECM components that are retained support an environment that is friendly to the host cells when used for tissue engineering purposes.*

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 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: The 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 chain-link fences or interact with the fibrillar collagens to form fibrils of tightly-regulated diameter. In basement membranes, the non-fibrillar 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 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: As their name implies, 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.

GLOSSARY OF EXTRACELLULAR MATRIX TERMINOLOGY

Acellular: Containing no viable cells.

Allogeneic: Literally, the same species.

Angiogenesis: The formation of new blood vessels from pre-existing capillaries.

Basement membrane: The dense connective tissue ECM upon which cells reside and grow; the structure underlying the cells that form the inner lining of a blood vessel.

Chondrocyte: The cell type responsible for producing cartilage.

Cytokine: A class of small protein structures present extracellularly that are secreted by cells.

Endothelial Cell: The cell type that lines the inner surface of all blood vessels and comprises the entirety of capillaries.

Extracellular Matrix (ECM): The material produced by, and supporting, cells that contributes to the structure of an organ. Common examples of ECM are bone, cartilage, and basement membrane.

Fibrillar: Forming a fibril; long linear protein structures that contribute to the structure of the ECM.

Fibroblast: A cell type responsible for secreting many components of the ECM. This is the cell type responsible for making most all of the ECM.

Glycoprotein: Component of the ECM that contains both protein and carbohydrate components. The majority of glycoproteins are large structures that play roles in matrix structure. Example: Fibronectin.

Glycosaminoglycan: A linear carbohydrate chain found in the ECM. The carbohydrate component of a proteoglycan. Example: Heparin.

Growth Factor: Small protein structures of the ECM that are collectively responsible for the health, growth, and actions of cells. Example: Vascular Endothelial Growth Factor (VEGF).

Heterogeneic: Literally, different species. Also xenogeneic.

Heterotypic: Different in kind, arrangement, or form. Comprised of more than one type.

Homeostasis: Relatively stable state of equilibrium, or a tendency toward such a state, between the different but interdependent components of an organism.

Ischemic: Deprived of oxygen. Tissues that lose their oxygen supply quickly die.

Microvessels: Small blood vessels; capillaries.

Protein: A biological molecule important to sustaining life. Proteins are sequences of amino acids.

Proteoglycan: Component of the ECM that contains both protein and carbohydrate components. The carbohydrate portion is called a glycosaminoglycan. Proteoglycans serve many diverse functions in the ECM depending on the nature of their protein core and glycosaminoglycan carbohydrate chain. Example: Decorin.

Regeneration: The biological process through which an organism reproduces or reconstitutes some or all of a lost or injured part.

Remodeling: Reorganization of an existing structure.

Repair: The collective processes of tissue breakdown, reconstruction, and reorganization taking place following injury.

Scaffold: A supporting framework or "backbone".

Scar: Healing that results in the deposition of hard, inelastic, fibrous tissue.

Submucosa: The ECM connective tissue layer that lies directly under the mucosa of the gastrointestinal and genitourinary tracts and consists of cellular secretion products but few cells.

Tissue: An aggregate of cells, together with their ECM, that forms a functional structure.

Xenogeneic: Literally, across species. Also, heterogeneic.

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