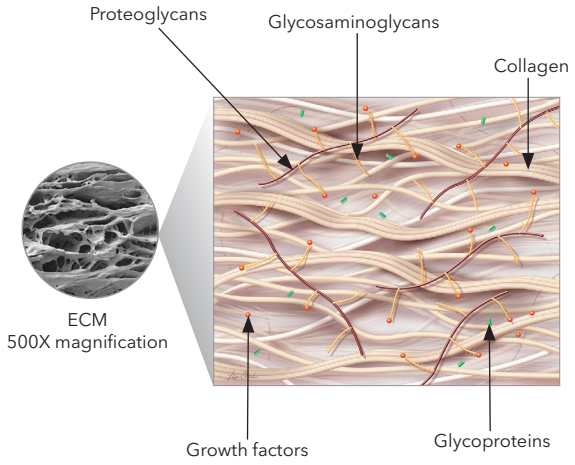
Biology of the Extracellular Matrix (ECM)

The extracellular matrix (ECM) is a fundamental component of biological tissues and is composed of an intricate network of complex protein and carbohydrate-based macromolecules that are organized in a tissue-specific manner (Figure 1).

Figure 1: Extracellular matrix components



Components of the ECM interconnect with each other to form a stable scaffold structure that contributes to the mechanical properties of tissues, provides a reservoir for growth factors and cytokines, and directly interacts with, and controls, many fundamental cell functions, including cell migration and blood vessel formation.[1]

Major structural ECM components

Collagens are formed by three polypeptide chains that wrap around each other to form a triple helical structure. There are at least 28 different types of collagens that can be separated into fibril-forming, network-forming, and fibril-associated forms.[2] In mature dermis, the most common fibril-forming collagen is collagen type I; in early phases of wound healing, collagen type III prevails. The composition of the fibril-forming collagenous backbone dictates tissue architecture, shape, and organization,[1] including that of dermis. Network-forming collagens, such as collagen type IV in the basement membrane of skin, are essential to maintaining normal epidermis function and restoring wound closure following injury.[3]

Proteoglycans are macromolecules containing a core protein with one or more covalently bound **glycosaminoglycan** (GAG) chains.[4] GAGs are linear, anionic polysaccharides made of repeating disaccharide units. There are four groups of GAGs: hyaluronic acid, keratan sulfate, chondroitin/dermatan sulfate, and heparan sulfate, including heparin. The highly negatively charged GAG chains allow the proteoglycans to retain water, providing natural lubrication to the ECM.[1] Proteoglycans also interact with **growth factors** and other ECM components to modulate signal transduction, ECM organization, and skin architecture.[5]

Glycoproteins consist of a large protein core with a polysaccharide chain attached. The laminin family of glycoproteins consists of approximately 20 different variants that assemble into a cross-linked web structure in combination with collagen type IV to form the stable basement membrane in skin.[1,3] Fibronectin is critical for the attachment and migration of cells, functions at many stages of the wound healing process, and acts as a "biological glue" of the ECM. Fibronectin contains binding sites to other fibronectin dimers, collagen, heparin, and cell surface receptors. These interactions between components are essential for normal skin integrity and play various important roles in wound healing after injury.[6-8]

Overview of general ECM functions

Constant Renewal. The ECM is a dynamic structure that is perpetually undergoing remodeling as its components are deposited, modified, or degraded.[1] It responds to external stimuli, such as

mechanical stretch or pressure,[9] and the functions of additional matricellular components, such as growth factors, matrix metalloproteases (MMPs), and cytokines.

Reservoir for bioactive molecules. The ECM serves as a reservoir for growth factors and cytokines. In particular, the fibroblast growth factor family strongly binds to the heparan sulfate chains of heparan sulfate proteoglycan.[10] Transforming growth factor-β, secreted in its latent form, is stored in the ECM attached to its binding protein and remains inactive until activated by MMP-dependent proteolysis.[11] Both of these growth factors are important players in the wound healing process following injury.[12,13]

Providing chemical and physical cues. The ECM directly interacts with the local cells through their surface receptors. Chemical cues provided by ECM components, such as fibronectin, integrin receptors, and growth factors, can trigger distinct cellular responses.[14] Physical properties of the ECM, such as its rigidity, density, porosity, and topography, provide physical cues to the cells that can direct cellular differentiation down different phenotypical paths.[15] These direct ECM/cell interactions, first named "dynamic reciprocity" by Bornstein and colleagues in 1982[16] to describe the effects of the ECM on endothelial cell function, and later elaborated by Bissell and colleagues,[17] explain how the ECM and the cells communicate with each other and respond dynamically to each other to maintain homeostasis.

Summary

The ECM is a dynamic, three-dimensional scaffold composed of an interacting network of collagens, proteoglycans, and glycoproteins. It provides the structural support and the chemical and physical cues that, through direct ECM/cell interactions, regulate cell growth, differentiation, and behavior. Cells produce, secrete, deposit, and remodel ECM to mediate ECM composition. The ECM, in turn, provides a favorable local environment that influences cell characteristics and activities.[1] This feedback mechanism is critical for rapid and appropriate cellular responses to surrounding environmental changes and to the process of wound healing following injury.

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