Therapeutic Applications of Extracellular Matrix

Denise C. Hocking*

Department of Pharmacology and Physiology, University of Rochester School of Medicine and Dentistry, Rochester, New York.

Chronic and hard-to-heal wounds are a tremendous burden on our healthcare system and impair the quality of life for millions of people. An emerging focus of regenerative medicine is the development of natural biomaterials that can stimulate tissue formation or repair by recreating the functional and structural properties of proteins and polysaccharides found within the extracellular matrix (ECM). Promising new developments include the fabrication of novel ECM-based biologics to selectively deliver drugs or growth factors to wounds; new classes of bioactive tissue sealants, scaffolds, and hydrogels; as well as inductive wound dressings derived from decellularized tissues. The advances highlighted in this forum issue provide an exciting glimpse into the growing potential of ECM-based wound therapeutics.

IN ALL VERTEBRATE TISSUES, cells are intimately associated with a complex three-dimensional network of interconnecting proteins and polysaccharides termed the extracellular matrix (ECM).¹ Dynamic interactions between cells and their surrounding ECM regulate most, if not all, cell and tissue functions. In the body, ECMs are assembled and remodeled by cells through a continuous process that is essential to tissue homeostasis. Proteins deposited in the ECM were once thought to serve only as inert scaffolds for cell attachment. It is now known that the interaction of cells with various ECM proteins and glycosaminoglycans occurs through specific cell surface receptors and initiates intracellular signals that regulate many aspects of cell behavior, including cell growth, survival, differentiation, and migration.¹ Several ECM components also regulate intracellular signaling by growth factors and cytokines during inflammation and wound repair, through both direct and indirect mechanisms.² Moreover, the precise com-

position and organization of ECMs contribute to the mechanical and permeability properties of the skin, vasculature, and other organs.³ ECM assembly is a cell-dependent step-wise process that is tightly regulated. Indeed, the cellular mechanisms and structural requirements that control the assembly and turnover of ECMs are complex, multifactorial, and only beginning to be understood.⁴

ECMs vary in biochemical composition and organization in a tissue-specific pattern.⁵ These variations allow for the tremendous structural and functional diversity of ECMs that can be observed throughout the body, ranging from the thin transparent cornea to dense load-bearing bone. ECMs are organized in two general ways: (1) basal laminae, which underlie all epithelial and endothelial layers and are rich in laminins, type IV collagen, and proteoglycans, and (2) interstitial stroma, composed primarily of fibrillar collagens, elastin, proteoglycans, and hyaluronan. In turn, individual ECM components

Denise C. Hocking, PhD

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*Correspondence: Department of Pharmacology and Physiology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Ave., Rochester, NY 14642
(e-mail: denise_hocking@urmc.rochester.edu).

are often broadly grouped into four categories, each of which is reviewed in this forum issue: (1) the structural proteins, including collagens and elastin, which provide tissues with tensile strength and their elastic properties; (2) multidomain adhesive glycoproteins, including fibronectin, vitronectin and laminin, which bind to cells, other ECM components, and modulate growth factor activity; (3) glycosaminoglycans, including hyaluronan and proteoglycans, which allow tissues to withstand compressive forces, contribute to fluid balance, ECM assembly, and intracellular signaling; and (4) matricellular proteins, including thrombospondins, osteopontins, and tenascins, which modulate cell–ECM interactions and regulate inflammation.

Cutaneous wound repair requires complex and coordinated interactions between cells and ECM molecules to restore tissue function and integrity.⁶ Tissue injury initiates a series of temporally and spatially integrated events requiring interactions between various cell types, including inflammatory, connective tissue, vascular, and epithelial cells, and proteins in the surrounding ECM.⁷ The three-dimensional ECM of wounds is composed largely of collagens, glycoproteins, and proteoglycans; ECM synthesis and deposition occur at all stages of wound repair and the exact composition changes as healing progresses. In early stages of wound repair, newly deposited ECM serves to organize cells into functional tissue by providing adhesion sites, migration pathways, and proliferation signals to cells, as well as mechanical stability to newly formed tissues.⁵ Migrating epithelial cells, together with fibroblasts and macrophages previously recruited to the wound, synthesize, deposit, and remodel the ECM to support further cell ingrowth and neovascularization.⁷ Wound healing normally resolves quickly, leaving a thin scar with little fibrosis, and tissue structure and function restored. However, disruptions in this process can lead to nonhealing chronic wounds or, conversely, result in the development of fibrotic scars that compromise tissue and organ function.

Chronic and hard-to-heal wounds are a tremendous burden on our healthcare system and impair the quality of life for millions of people. Chronic wounds are increasingly prevalent, with elderly and diabetic patients at increased risk.⁸ For healthcare professionals, accelerating cutaneous

wound healing has been an elusive goal. As such, a current emphasis in regenerative medicine is the development of ECM-based materials that can stimulate tissue formation or repair by recreating the functional and structural properties of native ECMs.⁹ The focus of this forum issue is to highlight several of the recent advances made in developing wound care products and treatment modalities that are derived from ECM components. In this issue, eight research articles and reviews on this topic were assembled. Promising new developments discussed in these articles include the fabrication of novel ECM-based biologics to selectively deliver antibiotics or growth factors to wounds, as well as the production of a new class of recombinant growth factors that target to specific ECM proteins in the wound bed. Other articles describe new bioactive tissue sealants, scaffolds, and hydrogels, along with degradable bioactive microspheres that can be applied directly to irregularly shaped wounds. Also reviewed are a new group of inductive wound dressings based on natural ECMs derived from decellularized tissues that show considerable promise in accelerating tissue regeneration. Several featured articles also describe the emerging utilization of protein engineering techniques to fabricate semi-synthetic ECM protein fragments that drive specific cell functions by selectively incorporating key functional features of the parent protein into the final product. The advances highlighted in this forum issue provide an exciting glimpse into the emerging potential of ECM-based wound therapeutics.

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ABOUT THE AUTHOR

Denise C. Hocking, PhD, is an Associate Professor of Pharmacology and Physiology and of Biomedical Engineering at the University of Rochester.

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Abbreviation and Acronym

ECM = extracellular matrix