Molecular Signaling

Breakout Session Summary

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BROAD STATEMENT

Tissues and organs consist of specialized living cells arrayed within a complex structural and functional framework generally known as the extracellular matrix (ECM). ECM composition and mechanics are important factors that contribute to the function and characteristics of each organ and tissue, such as the rigidity and tensile strength of bone, the resilience of cartilage, the flexibility and hydrostatic strength of blood vessels, and the elasticity of skin. Also important is the role of the ECM during growth, development, and wound repair, where it serves as a reservoir for soluble signaling molecules and, through its own dynamic composition and mechanics, a source of additional signals to migrating, proliferating, and differentiating cells.

Artificial substitutes for the ECM, called scaffolds, consisting of natural and/or synthetic polymers, have been used successfully alone or in combination with cells and soluble factors to induce tissue formation and promote tissue repair. Cells are also central to many tissue engineering strategies, and significant efforts have been made to identify and propagate pluripotent stem cells, to identify signaling events important for proper differentiation, and to identify ideal microenvironments for maximum cellular function. These efforts have led to a convergence of research in bioengineering, biomaterials, ECM, cell growth and differentiation, and soluble factors that control cell fate.

Recent developments in the multidisciplinary field of tissue engineering have provided a novel set of tissue replacement parts and implementation strategies. Scientific advances in biomaterials, stem cells, growth and differentiation factors, and biomimetic environments have created unique opportunities to fabricate tissues in the laboratory from combinations of engineered ECMs (scaffolds), cells, and biologically active molecules.

Ann. N.Y. Acad. Sci. 961: 164–167 (2002). **© 2002 New York Academy of Sciences.**

VISION

The goals of reparative medicine are to enhance normal tissue regeneration and to engineer artificial tissues for use as replacements for damaged body parts. While significant advances have been made in the development of prosthetic devices that can repair structural defects (e.g., vascular grafts) and even replace complex mechanical behaviors (e.g., artificial joints), the challenge for the future is to develop therapies and devices that restore the normal biochemical functions of living tissues in addition to their structural features. To accomplish this objective, precise design criteria must be established to guide developmental efforts. These criteria must be based on a thorough understanding of the molecular signaling networks, cellular interactions, and biophysical aspects of tissue formation. Such understanding will accelerate our abilities to promote optimal tissue reconstruction and repair.

OBJECTIVES

To facilitate this vision, future research should address areas associated with growth factors (i.e., hormones, cytokines, and other factors that regulate cellular transduction and control cell behaviors), mechanical and stress-induced signaling, ECMs and scaffolds (including cell-to-matrix interactions), cell adhesion receptors and molecules, and temporal (aging) effects. Multidisciplinary and multiorganizational approaches to addressing these research needs are expected to be fruitful.

CHALLENGES

Among the major challenges for tissue engineering are the needs for complex functionality and biochemical stability in laboratory-grown tissues destined for transplantation. Realization of the potential benefits offered by tissue engineering in the development of true human replacement parts will require convergence of molecular signaling principles with research advances in tissue, matrix, growth factor, stem cell, and developmental biology. Specific challenges associated with developing a thorough understanding of molecular signaling and tissue regeneration include the following:

1. Understanding how to manipulate signaling through cell adhesion receptors and molecules to promote the desired endpoints for specific tissue engineering problems. Cell–cell and cell–ECM adhesion receptors and molecules play critical roles in both anchorage and signal transduction. A key feature of receptors is their ability to organize signaling complexes at sites of contact with their extracellular environment. Depending on other aspects of the environment including the nature and organization of the ECM, the presence of growth and differentiation factors, and the presence of mechanical stimuli, these signals can promote or restrain cell proliferation, promote differentiation, trigger matrix remodeling, or promote enhanced tissue organization. The ability to manipulate these variables to control the balance between proliferation and maintenance of the differentiated state for particular cell types is essential for designing effective cellular replacement therapies.

2. Establishing continuous molecular bridges between cell physiology, signal transduction, and gene expression. For a cell to respond to its environment, divide, migrate, or differentiate, signals from the extracellular compartment need to be sensed, reach the nucleus, and then trigger expression or repression of specific factors. Understanding of this information transmission process is currently incomplete. For example, while it is common to know which ligand/receptor interaction will activate a specific kinase pathway, specific insights into the transcriptional events and target genes that will eventually be involved are not known. Also, although numerous nuclear factors are known to control expression of specific genes (e.g., cell differentiation programs), very few signaling cascades have been defined as controlling their activity. Filling these gaps by establishing continuous molecular bridges is key to understanding cell transduction and differentiation.

3. Understanding the impact and mechanisms of growth factor signaling in complex systems where multiple biochemical and physical stimuli modify intracellular signaling and biological responses. Although much insight has been gained from studies of growth factor signaling using simple, well-characterized cultured cell models, studies involving more complex systems are necessary. The acquisition of high-resolution, three-dimensional extracellular matrix component/protein complex structures and the discovery of specificity among ECM components that impart high-affinity protein binding are currently at the forefront of research in this area. Information resulting from related research will facilitate the development of complex artificial scaffolds for tissue regeneration, repair , and replacement.

4. Translating knowledge of molecular events and molecules known to be important during embryonic development to the understanding of adult physiology and physiopathology. It is unlikely that these genetic programs involve totally different sets of regulatory genes. In fact, a small but growing number of genes have been shown to fulfill roles after as well as before birth. A systematic analysis of expression patterns and functions of developmental "master genes" in postnatal and aging models could provide useful information to define novel pathways and strategies for therapeutic intervention and regenerative repair.

5. Understanding how cells sense mechanical forces and integrate them with signals from other tissue control elements (e.g., growth factors and ECM). Cells in tissues constantly experience mechanical stimuli. Even cells in static culture experience the effects of gravity. Stimuli such as shear-stress, fluid-flow, compression, stretch, etc. not only alter the organization and distribution of structural elements and organelles within cells, but also become transduced into biochemical input that modulates intra- and intercellular signaling networks and in turn, gene expression. Understanding the importance of mechanical stresses and microarchitecture in cell signaling is important for the design of medical devices (i.e., for promoting wound healing) as well as the engineering and manufacture of artificial replacement tissue.

6. Fundamental research on cell response to three-dimensional, nonrigid extracellular matrices. Most work with cells *in vitro* has involved culture on two-dimensional rigid substrates. For many cell types, this is not a biologically relevant environment. Studies with three-dimensional matrices have shown that cells behave

very differently under such conditions. Mechanisms by which signals from the ECM, neighboring cells, and growth/differentiation factors synergize to regulate cell growth and survival, affect commitment to tissue-specific differentiation programs, and regulate tissue remodeling need to be evaluated at the molecular level with regard to the more relevant three-dimensional microenvironments. Increased knowledge of the impact of three-dimensional microenvironments at the molecular level will expedite and improve tissue engineering strategies and biomaterials design.

ACKNOWLEDGMENTS

The Molecular Signaling Breakout Session was coordinated by Dr. Richard Swaja, NIBIB, NIH, and Ms. Mollie Sourwine, NIBIB, NIH.