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VIEWPOINT

Growth Factors and Wound Repair

From a phenomenologic infancy in the 1950's and 60's, growth factorology has developed into a mature science which in turn has spawned an industry. Growth factor research was nurtured by tissue culture techniques which provided convenient assays for factor activities, by increasingly sophisticated protein biochemistry which provided methods for isolation, purification, and sequencing of active peptides, and more recently by molecular biology which provided methods for DNA sequencing, cloning, and protein expression of genetic recombinant material. It is the production of milligram quantities of genetic recombinant material that has fathered the growth factor industry. While tissue culture technology, protein biochemistry, and molecular biology gave the essential nutrients for the growth of this science, cell biology and experimental pathology have provided an excellent environment for maturation. Thus growth factor actions can be examined in the microcosm of a cell and in the macrocosm of tissues, organs, and the whole animal. It is within the latter context that the April Keystone Symposia Conference on wound repair was designed. Wound repair, in fact, can provide a relatively small temporal, spatial window in which to study the effects of growth factors on tissues. Since growth factors are a subset of cytokines, many previous and subsequent statements regarding growth factors can be extended to cytokines in general.

Although wound repair may be confined to a small space and time, complexities still abound. Wound repair is not a simple linear process where growth factors released by phylogistic events trigger parenchymal cell growth but rather an integration of contextual interactions between growth factors, cells, and extracellular matrix (ECM).

In a straightforward sequential model, growth factors released from plasma or platelets would stimulate cells to migrate and proliferate into the wound. Although these events do occur, the repair process is clearly more complex. For example, growth factors can originate from one cell type, such as the macrophage, and stimulate a second cell type, such as a fibroblast, through a paracrine pathway. Alternatively growth factors may arise from a responsive cell type through a autocrine pathway. For example transforming growth factor-α (TGF-α) is produced by epidermal cells and stimulates these cells to proliferate. Moreover, transformed fibroblasts have been observed to produce and respond to platelet-derived growth factor (PDGF) without secreting the factor, suggesting that the cytokine was an active ligand inside the cell that made it. Since cells regulate growth factors at the level of transcription, translation, and posttranslational modification and since growth factors can induce or inhibit cell production of the same growth factor and other growth factors, a tight biologic feedback loop can be established either between cells or within a cell.

In addition growth factors may alter cells so that subsequently the cells respond differently to further growth factor stimulation. Growth factor receptor down regulation is a simple example of this. More complexity arises when one considers that growth factors may induce cells to produce new ECM which may directly interact with growth factors or may modify the ability of cells to respond to growth factors. For example, heparan sulfate proteoglycan binds fibroblast growth factor (FGF) and IL-3, and decorin binds transforming growth factor-beta (TGF-β). These proteoglycans may, in fact, act as reservoirs for growth factors which are then released during subsequent cell interactions with the matrix. In contrast, collagen appears to suppress fibroblast responsiveness to PDGF and TGF-β, and heparan sulfate suppresses mitogenic responsiveness of certain epithelial cells.

In addition to interactive feedback loops, general contextual situations such as cell age and nutrient state, cell population density, and the presence of other growth factors or growth inhibitors in the milieu may also greatly affect cellular response to growth factors.

Although it is hypothesized that these complex, environmentally modified interactions be-

tween growth factors, cells, and ECM can be integrated into a progressive chain of biological events that culminate in wound repair, the existence of such events in vivo remains to be proven. Nevertheless data are currently being accumulated to elucidate the appearance of growth factors and their receptors during wound repair using immunohistochemistry with specific antibody probes and in situ hybridization with specific RNA or DNA probes. Even though these studies provide no information about function, mapping the presence of growth factors and their receptors at specific stages of wound repair will facilitate future investigations of function.

The first information about growth factor function in tissue repair came from the application of recombinant growth factors on normal wounds and nonhealing ulcers. Future experiments using genetic manipulation may provide more insight into the biologic function of growth factors during healing processes. In both arenas we stand to learn much about the rich tapestry of events in wound repair including the various patterns of growth factor activities. In the process of gaining this knowledge, growth factor acceleration of normal wound repair and nonhealing ulcers may become a reality.

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