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Tissue repair
The hidden drama

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Abbreviations: cAMP, 3', 5' cyclic adenosine monophosphate; CDK, cyclin-dependent protein; DNA, deoxyribonucleic acid; ECM, extracellular matrix; EGF, epidermal growth factor; FGF, fibroblast growth factor; GAG, glycosaminoglycan; KGF, keratinocyte growth factor; MAD, mothers against decapentaplegic; MMP, matrix metalloproteinase; IL, interleukin; JAK, janus kinase; OPN, osteopontin; PDGF, platelet-derived growth factor; RB, retinoblastoma; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinases; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

As living beings that encounter every kind of traumatic event from paper cut to myocardial infarction, we must possess ways to heal damaged tissues. While some animals are able to regrow complete body parts following injury (such as the earthworm who grows a new head following bisection), humans are sadly incapable of such feats. Our means of recovery following tissue damage consists largely of repair rather than pure regeneration. Thousands of times in our lives, a meticulously scripted but unseen wound healing drama plays, with cells serving as actors, extracellular matrix as the setting and growth factors as the means of communication. This article briefly reviews the cells involved in tissue repair, their signaling and proliferation mechanisms and the function of the extracellular matrix, then presents the actors and script for the three acts of the tissue repair drama.

Proem

All the world's a stage,
And all the men and women merely players;
They have their exits and their entrances
And one man in his time plays many parts,
His acts being seven ages

Shakespeare
As You Like It
Act 2, scene 7, 139–143

The term "repair," when used in the context of the healing of damaged tissue, is defined as the restoration of tissue architecture and function after an injury. It encompasses two separate processes: regeneration and replacement. Regeneration refers to a type of healing in which new growth completely restores portions of damaged tissue to their normal state. Replacement refers to a type of healing in which severely damaged or non-regenerable tissues are repaired by the laying down of connective tissue, a process commonly referred to as scarring. While a few types of tissue injury (such as minor paper cuts) can sometimes be healed in such a way that no permanent damage remains, most of our tissue repair consists of both regeneration and replacement. Tissue repair may restore some of the original structures of the damaged tissue (such as epithelial layers), but may also result in structural abnormalities that impair organ function (such as the scar formed in the healing of a myocardial infarction).

Whether the healing of a wound proceeds down the regeneration or the replacement pathway (or both) depends, in part, on the type of tissue in which it occurs. Certain tissues of the body are more capable of cellular proliferation (and hence regeneration) than others. In this regard, there are three types of tissues: continuously dividing tissues, quiescent tissues and nondividing tissues. Continuously dividing tissues (also known as labile tissues) are comprised of cells that are constantly proliferating in order to replace dead or sloughed-off cells. Examples of such tissues include epithelia (such as skin, gastrointestinal epithelium and salivary gland tissue) and hematopoietic tissues. These tissues contain pools of stem cells, which have enormous proliferative and self-renewing ability, and which give rise to more than one type of cell. Replicating asymmetrically, each stem cell gives rise to one daughter cell that differentiates and matures and another daughter cell that remains undifferentiated and capable of beginning another self-renewing cycle.

Some tissues, known as quiescent tissues (or stable tissues) are composed of cells that normally exist in a non-dividing state but may enter the cell cycle in response to certain stimuli, such as cell injury. Tissues falling into this category include parenchymal cells of the liver, kidney and pancreas, mesenchymal cells such as fibroblasts and smooth muscle cells, endothelial cells and lymphocytes. It should be noted that the liver, unlike other quiescent tissues, has a relatively robust proliferative capacity. When a lobe

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