Growth Factors in Wound Healing

The Present and the Future?

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KEYWORDS

• Wound healing • Growth factors • Transforming growth factor
• Vascular endothelial growth factor • Epidermal growth factor
• Fibroblast growth factor • Platelet-derived growth factor

KEY POINTS

- The complex sequences of molecular and cellular events that are carefully orchestrated during wound healing are difficult to reproduce.
- Administration of growth factors has been shown to promote healing by affecting all phases of wound healing.
- Several growth factors have been studied for the promotion of diabetic wound healing.
- Advances in tissue engineering and regenerative medicine have provided technologies capable of delivering multiple growth factors in a spatially oriented approach.

INTRODUCTION

Growth factors play a vital role in the communication between cells and their microenvironment. By transmitting signals, growth factors regulate development and normal growth by both stimulating and inhibiting processes such as cellular proliferation, differentiation, migration, and adhesion. Initiation of these activities occurs when the growth factor binds to the receptor of target cells, with the level and type of response dictated by its chemical identity, concentration and duration of action. They can be synthesized and secreted by many types of tissues and have been shown to initiate cell division and sustain phases of tissue repair.[1]

In wound healing, growth factors play an essential role because of their unique ability to stimulate continuous mitosis of quiescent cells in vitro. An improved understanding of the individual roles of each growth factor in the wound healing cascade may help

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Clin Podiatr Med Surg 32 (2015) 109–119
http://dx.doi.org/10.1016/j.cpm.2014.09.010 **podiatric.theclinics.com**
0891-8422/15/$ – see front matter

to direct the application of exogenous growth factors in stimulating stagnant wounds.[2] The growing field of biologic wound products aims to accelerate healing by understanding and adjusting this balance of inflammatory mediators.[3]

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GROWTH FACTORS IN WOUND HEALING

Several studies have identified diminishment of specific growth factors involved in the wound healing process through analysis of wound fluid. In 1987, Cromack demonstrated that transforming growth factor (TGF)-β levels increased initially and then gradually declined with wound closure.[4] Cooper and colleagues[5] also demonstrated that chronic wounds have reduced levels of platelet-derived growth factor (PDGF), basic fibroblast growth factor, epidermal growth factor (EGF), and TGF-β compared with acute wounds. Although growth factor levels seem to decrease in the chronic wound, proteinases have been shown to be elevated in chronic wounds, potentially playing a role in delaying wound healing (**Table 1**).[1]

Platelet-Derived Growth Factor

Platelet-derived growth factor was first discovered in 1974, when it was observed that a material released from platelets at the time of wounding was responsible for the growth of many of the cells grown in culture that are serum dependent.[6,7] Normally, PDGF is present sequestered within the α-granule of the platelet and is believed to be released during platelet degranulation at sites of vascular injury.[6–8] Normal human plasma contains undetectable levels of PDGF and Bowen-Pope and colleagues[8] found that that PDGF injected intravenously into baboons was rapidly cleared from plasma with a $t_{1/2}$ of less than 2 minutes. Therefore, local synthesis and secretion are likely responsible for cells to ability to respond, because PDGF not localized to the site of injury would be rapidly cleared from circulation.[6–8]

Table 1
Growth factors in wound healing

Growth Factor	Location	Target Tissue/Biologic Effect
Platelet-derived growth factor	Endothelial cells, platelets, macrophages, fibroblasts	Mitogenic for vascular smooth muscle, fibroblasts
Epidermal growth factor	Almost all body fluids, platelets	Mitogenic for most epithelial tissues, fibroblasts, endothelial cells
Fibroblast growth factor	Fibroblasts, astrocytes, endothelial cells, bone cells, smooth muscle	Mesenchymal and neural tissue mitogen
Transforming growth factor-β	Macrophages, lymphocytes, fibroblasts, bone cells, keratinocytes, platelets	Inhibits replication of most cells in vitro, including keratinocytes, endothelial cells, lymphocytes, and macrophages; may inhibit or stimulate fibroblasts
Vascular endothelial growth factor	Pituitary cells	Mitogenic for endothelial cells, but not keratinocytes, smooth muscle, or fibroblasts