

Roles of HGF in Wound Healing and Prevention of Skin Aging

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Hepatocyte growth factor (HGF), originally discovered and identified as a powerful mitogen for hepatocytes, has mitogenic, motogenic, and anti-apoptic activities for a variety of cells. HGF has organotrophic roles for regeneration of the liver, kidney, lung, etc. In skin tissues, we previously showed that HGF has mitogenic and motogenic activities for normal human epidermal keratinocytes and melanocytes. We here studied a mechanism of epidermal wound healing by HGF. HGF is produced by normal human skin fibroblasts and HGF production is up-regulated by interleukin-1, platelet-derived growth factor (PDGF), basic fibroblast growth factor, transforming growth factor α and prostaglandins. Using in vitro epidermal wound healing model, we found that HGF but not PDGF stimulated healing of cultured keratinocyte sheet. Importantly, addition of the conditioned medium of PDGF-treated fibroblasts but not non-treated fibroblasts stimulated in vitro epidermal wound healing, indicating that PDGF-treated fibroblasts produce a soluble factor(s) which stimulates epidermal wound healing. The fibroblast-derived soluble factor was identified as HGF. Since PDGF is secreted from activated platelets in wounded skin tissues, the results implicate the presence of a paracrine cascade for epidermal wound healing: PDGF secreted from platelets activates HGF gene expression in dermal fibroblasts, while fibroblast-derived HGF stimulates both migration and cell growth in epidermal keratinocytes, leading to rapid wound healing after skin injury. In addition, HGF can induce growth and migration of dermal endothelial cells, which are essentially involved in wound healing as well. We recently found that HGF potently prevents apoptotic cell death in many types of cells and has therapeutic effects on various fibrotic diseases such as liver cirrhosis, renal fibrosis, and lung fibrosis. Taken together, HGF may well become therapeutic tool for treatment of skin injury and fibrotic skin diseases.