- Promote entry of cells into the cell cycle
- Relieve blocks on cell cycle progression (thus promoting replication)
- Prevent apoptosis
- Enhance biosynthesis of cellular components (nucleic acids, proteins, lipids, carbohydrates) required for a mother cell to give rise to two daughter cells

Although growth factors are characteristically thought of as proteins that stimulate cell proliferation and/or survival, it is important to remember that they can also drive a host of nongrowth activities, including migration, differentiation, and synthetic capacity.

Growth factors are involved in the proliferation of cells at steady state as well as after injury, when irreversibly damaged cells must be replaced. Uncontrolled proliferation can result when the growth factor activity is dysregulated, or when growth factor signaling pathways are altered to become constitutively active. Thus, many growth factor pathway genes are *proto-oncogenes;* gain-of-function mutations in these genes can convert them into oncogenes capable of driving unfettered cell proliferation and tumor formation. Table 1-1 (and the following discussion) summarizes selected growth factors that are involved in two important proliferative processes, tissue repair and tumor development. Although the growth factors described here all involve receptors with intrinsic kinase activity, other growth factors may signal through each of the various pathways shown in Figure 1-11.

Epidermal Growth Factor and Transforming Growth Factor-α. Both of these factors belong to the EGF family and bind to the same receptors, which explains why they share many biologic activities. EGF and TGF-α are produced by macrophages and a variety of epithelial cells, and are mitogenic for hepatocytes, fibroblasts, and a host of epithelial cells. The "EGF receptor family" includes four membrane receptors with intrinsic tyrosine kinase activity; the best-characterized is EGFR1, also known as ERB-B1, or simply EGFR. EGFR1 mutations and/or amplification frequently occur in a number of cancers including those of the lung, head and neck, breast, and brain. The *ERBB2 receptor* (also known as *HER2*) is overexpressed in a subset of breast cancers. Many of these receptors have been successfully targeted by antibodies and small molecule antagonists.

Hepatocyte Growth Factor. Hepatocyte growth factor (HGF; also known as scatter factor) has mitogenic effects on hepatocytes and most epithelial cells, including biliary, pulmonary, renal, mammary,and epidermal. HGF acts as a *morphogen* in embryonic development (i.e., it influences the pattern of tissue differentiation), promotes cell migration (hence its designation as *scatter factor*), and enhances hepatocyte survival. HGF is produced by fibroblasts and most mesenchymal cells, as well as endothelium and nonhepatocyte liver cells. It is synthesized as an inactive precursor (pro-HGF) that is proteolytically activated by serine proteases released at sites of injury. MET is the receptor for HGF, it has intrinsic tyrosine kinase activity and is frequently overexpressed or mutated in tumors, particularly renal and thyroid papillary carcinomas. Consequently, MET inhibitors may be of value for cancer therapy.

Platelet-Derived Growth Factor. Platelet-derived growth factor (PDGF) is a family of several closely related proteins, each consisting of two chains (designated by pairs of letters). Three isoforms of PDGF (AA, AB, and BB) are constitutively active; PDGF-CC and PDGF-DD must be activated by proteolytic cleavage. PDGF is stored in platelet granules and is released on platelet activation. Although originally isolated from platelets (hence the name), it is also produced by many other cells, including activated macrophages, endothelium, smooth muscle cells, and a variety of tumors. All PDGF isoforms exert their effects by binding to two cell surface receptors (PDGFR α and β), both having intrinsic tyrosine kinase activity. PDGF induces fibroblast, endothelial, and smooth muscle cell proliferation and matrix synthesis, and is chemotactic for these cells (and

Table 1-1 Growth Factors Involved in Regeneration and Repair

Growth Factor	Sources	Functions
Epidermal growth factor (EGF)	Activated macrophages, salivary glands, keratinocytes, and many other cells	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration; stimulates formation of granulation tissue
Transforming growth factor-α (TGF-α)	Activated macrophages, keratinocytes, many other cell types	Stimulates proliferation of hepatocytes and many other epithelial cells
Hepatocyte growth factor (HGF) (scatter factor)	Fibroblasts, stromal cells in the liver, endothelial cells	Enhances proliferation of hepatocytes and other epithelial cells; increases cell motility
Vascular endothelial growth factor (VEGF)	Mesenchymal cells	Stimulates proliferation of endothelial cells; increases vascular permeability
Platelet-derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, smooth muscle cells, keratinocytes	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; activates and stimulates proliferation of fibroblasts, endothelial, and other cells; stimulates ECM protein synthesis
Fibroblast growth factors (FGFs), including acidic (FGF-1) and basic (FGF-2)	Macrophages, mast cells, endothelial cells, many other cell types	Chemotactic and mitogenic for fibroblasts; stimulates angiogenesis and ECM protein synthesis
Transforming growth factor-β (TGF-β)	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for leukocytes and fibroblasts; stimulates ECM protein synthesis; suppresses acute inflammation
Keratinocyte growth factor (KGF) (i.e., FGF-7)	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation

ECM, Extracellular membrane.