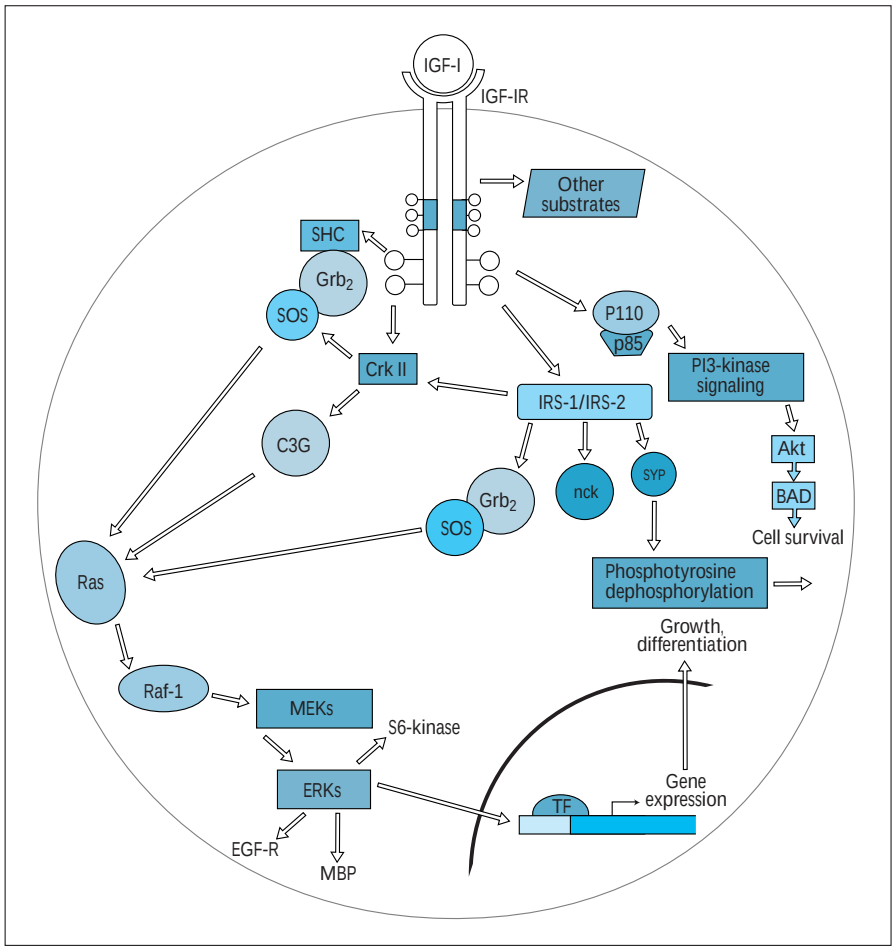

FIGURE 17-10

Diagram of intracellular signaling pathways mediated by the insulin-like growth factor I (IGF-IR) receptor. IGF-IR when bound to IGF-I undergoes autophosphorylation on its tyrosine residues. This enhances its intrinsic tyrosine kinase activity and phosphorylates multiple substrates, including insulin receptor substrate 1 (IRS-1), IRS-2, and Src homology/collagen (SHC). IRS-1 upon phosphorylation associates with the p85 subunit of the PI3-kinase (PI3K) and phosphorylates PI3-kinase. PI3K upon phosphorylation converts phosphoinositide-3 phosphate (PI-3P) into PI-3,4-P2, which in turn activates a serine-thronine kinase Akt (protein kinase B). Activated Akt kinase phosphorylates the proapoptotic factor Bad on a serine residue, resulting in its dissociation from B-cell lymphoma-X (Bcl-X_L) . The released Bcl-X_L is then capable of suppressing cell death pathways that involve the activity of apoptosis protease activating factor (Apaf-1), cytochrome C, and caspases. A number of growth factors, including platelet-derived growth factor (PDGF) and IGF 1 promotes cell survival. Activation of the PI3K cascade is one of the mechanisms by which growth factors mediate cell survival. Phosphorylated IRS-1 also associates with growth factor receptor bound protein 2 (Grb2), which bind son of sevenless (Sos) and activates the ras-raf-mitogen activated protein (ras/raf-MAP) kinase cascade. SHC also binds Grb2/Sos and activates the ras/raf-MAP kinase cascade. Other substrates for IGF-I are phosphotyrosine phosphatases and SH_2 domain containing tyrosine phosphatase (Syp). Figure 17-7 has details on the other signaling pathways in this figure. MBP—myelin basic protein; nck—an adaptor protein composed of SH2 and SH3 domains; TF—transcription factor.

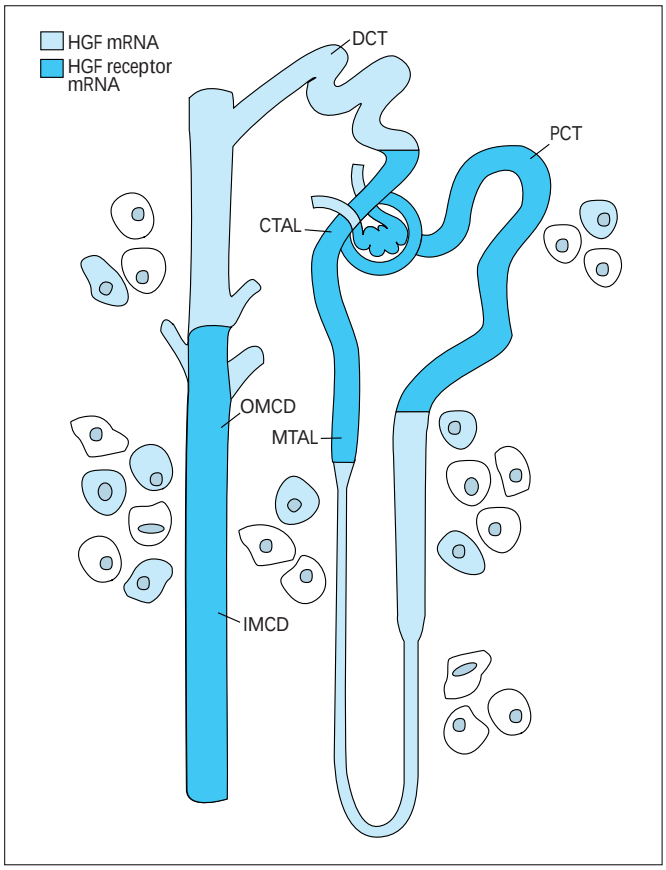

FIGURE 17-11

Expression of hepatocyte growth factor (HGF) mRNA and HGF receptor mRNA in kidney. While the liver is the major source of circulating HGF, the kidney also produces this growth-promoting peptide. Experiments utilizing in situ hybridization, immunohistochemistry, and reverse transcription–polymerase chain reaction (RT-PCR) have demonstrated HGF production by interstitial cells but not by any nephron segment. Presumably, these interstitial cells are macrophages and endothelial cells. Importantly, HGF expression in kidney actually increases within hours of an ischemic or toxic insult. This expression peaks within 6 to 12 hours and is followed a short time later by an increase in HGF bioactivity. HGF thus seems to act as a renotrophic factor, participating in regeneration via a paracrine mechanism; however, its expression is also rapidly induced in spleen and lung in animal models of acute renal injury. Reported levels of circulating HGF in patients with acute renal failure suggest that an endocrine mechanism may also be operational.

The receptor for HGF is the c-met proto-oncogene product. Receptor binding has been demonstrated in kidney in a variety of sites, including the proximal convoluted (PCT) and straight tubules, medullary and cortical thick ascending limbs (MTAL, CTAL), and in the outer and inner medullary collecting ducts (OMCD, IMCD). As with HGF peptide production, expression of c-met mRNA is induced by acute renal injury.

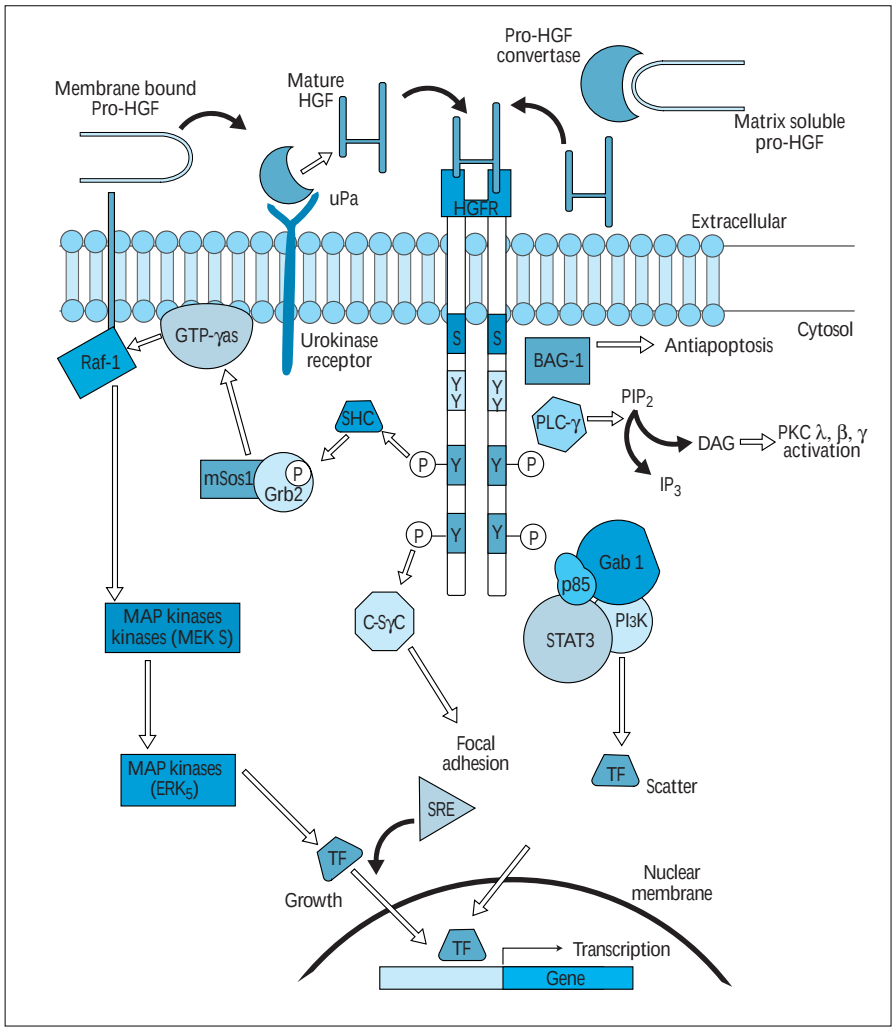

FIGURE 17-12

Model of hepatocyte growth factor (HGF)/c-met signal transduction. In the extracellular space, single-chain precursors of HGF bound to the proteoglycans at the cell surface are converted to the active form by urokinase plasminogen activator (uPA), while the matrix soluble precursor is processed by a serum derived pro-HGF convertase. HGF, upon binding to its receptor c-met, induces its dimerization as well as autophosphorylation of tyrosine residues. The phosphorylated residue binds to various adaptors and signal transducers such as growth factor receptor bound protein-2 (Grb2), p85-PI3 kinase, phospholipase C-gamma (PLC-gamma), signal transducer and activator of transcription-3 (STAT-3) and Src homology/collagen (SHC) via Src homology 2 (SH2) domains and triggers various signal transduction pathways. A common theme among tyrosine kinase receptors is that phosphorylation of different specific tyrosine residues determines which intracellular transducer will bind the receptor and be activated. In the case of HGF receptor, phosphorylation of a single multifunctional site triggers a pleiotropic response involving multiple signal transducers. The synchronous activation of several signaling pathways is essential to conferring the distinct invasive growth ability of the HGF receptor. HGF functions as a scattering (dissociation/motility) factor for epithelial cells, and this ability seems to be mediated through the activation of STAT-3.

Phosphorylation of adhesion complex regulatory proteins such as ZO-1, beta-catenin, and focal adhesion kinase (FAK) may occur via activation of c-src. Another Bcl_2 interacting protein termed BAG-1 mediates the antiapoptotic signal of HGF receptor by a mechanism of receptor association independent from tyrosine residues.

DETERMINANT MECHANISMS FOR OUTCOMES OF ACUTE RENAL FAILURE

Mitogenic	Anabolic
Morphogenic	Alter leukocyte function
Cell migration	Alter inflammatory process
Hemodynamic	Apoptosis
Cytoprotective	Others

FIGURE 17-13

Mechanisms by which growth factors may possibly alter outcomes of acute renal failure (ARF). Epidermal growth factor, insulin-like growth factor, and hepatocyte growth factor (HGF) have all been demonstrated to improve outcomes when administered in the setting of experimental ARF. While the results are the same, the respective mechanisms of actions of each of these growth factors are probably quite different. Many investigators have examined individual growth factors for a variety of properties that may be beneficial in the setting of ARF. This table lists several of the properties examined to date. Suffice it to say that the mechanisms by which the individual growth factors alter the course of experimental ARF is still unknown.