GROWTH FACTOR PRODUCTION

EGF
- Submandibular salivary glands
- Kidney
- Others

HGF
- Liver
- Spleen
- Kidney
- Lung
- Other organs

IGF-I
- Liver
- Lung
- Kidney
- Heart
- Muscle
- Other organs

FIGURE 17-5

Production of epidermal growth factor (EGF), insulin-like growth factor (IGF-I), and hepatocyte growth factor (HGF) by various tissues. EGF, IGF-I, and HGF have all been demonstrated to improve outcomes in various animal models of acute renal failure (ARF). All three growth-promoting factors are produced in the kidneys and in a variety of other organs. The local production is probably most important for recovery from an acute renal insult. The influence of production in other organs in the setting of ARF has yet to be determined. This chapter deals primarily with local production and actions of EGF, IGF-I, and HGF.

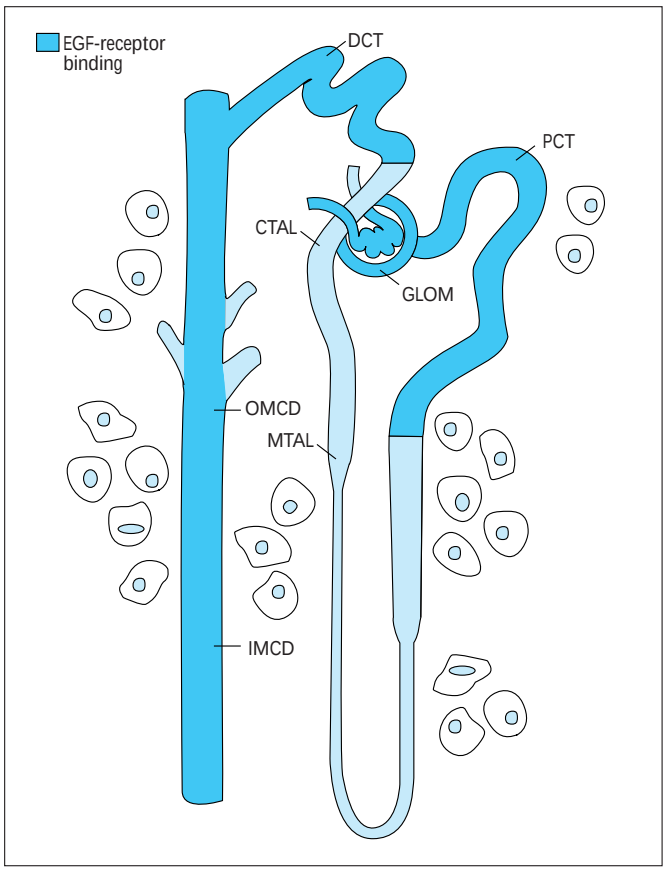

FIGURE 17-6

Receptor binding for epidermal growth factor (EGF). EGF binding in kidney under basal conditions is extensive. The most significant specific binding occurs in the proximal convoluted (PCT) and proximal straight tubules. There is also significant EGF binding in the glomeruli (GLOM), distal convoluted tubules (DCT), and the entire collecting duct (OMCD, IMCD). After an ischemic renal insult, EGF receptor numbers increase. This change in the renal EGF system may be responsible for the beneficial effect of exogenously administered EGF is the setting of acute renal failure. CTAL—cortical thick ascending loop.

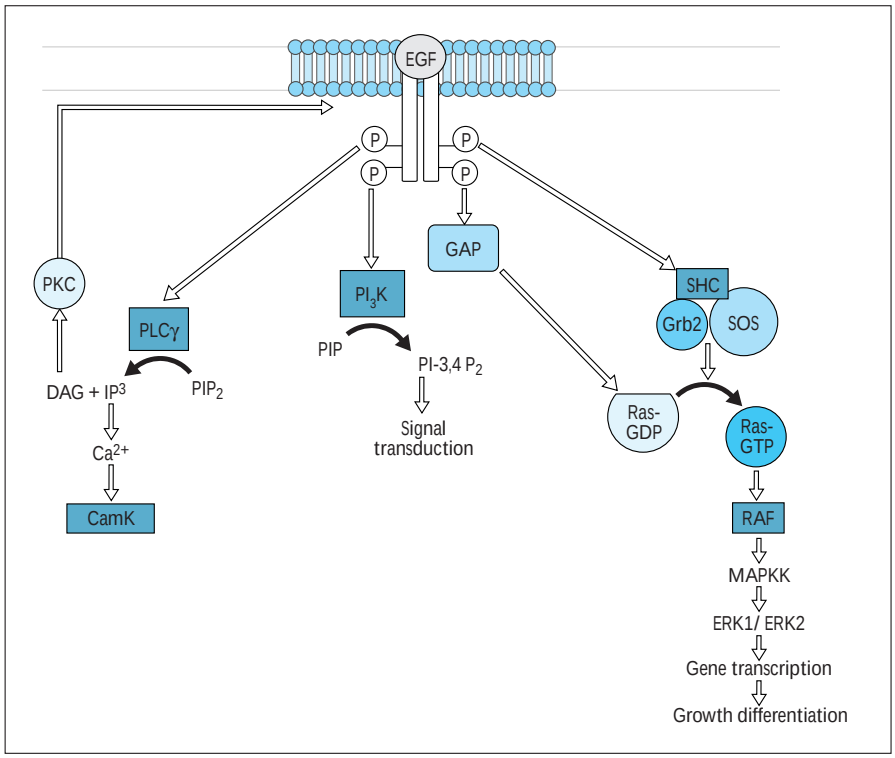

FIGURE 17-7

Epidermal growth factor (EGF)–mediated signal transduction pathways. The EGF receptor triggers the phospholipase C-gamma (PLC-gamma), phosphatidylinositol-3 kinase (PI_3K), and mitogen-activated protein kinase (MAPK) signal transduction pathways described in the text that follows.

Growth factors exert their downstream effects through their plasma membrane–bound protein tyrosine kinase (PTK) receptors. All known PTK receptors are found to have four major domains: 1) a glycosylated extracellular ligand-binding domain; 2) a transmembrane domain that anchors the receptor to the plasma membrane; 3) an intracellular tyrosine kinase domain; and 4) regulatory domains for the PTK activity. Upon ligand binding, the receptors dimerize and autophosphorylate, which leads to a cascade of intracellular events resulting in cellular proliferation, differentiation, and survival.

The tyrosine phosphorylated residues in the cytoplasmic domain of PTK are of utmost importance for its interactions with cytoplasmic proteins involved in EGF–mediated signal transduction pathways. The interactions of cytoplasmic proteins are governed by specific domains termed Src homology type 2 (SH2) and type 3 (SH3) domains. The SH2 domain is a conserved 100–amino acid sequence initially characterized in the PTK-Src and binds to tyrosine phosphorylated motifs in proteins; the SH3 domain binds to their targets through proline-rich sequences. SH2 domains have been found in a multitude of signal transducers and docking proteins such as growth factor receptor–bound protein 2 (Grb2), phophatidylinositol-3 kinase (p85-PI_3K), phospholipase C-gamma (PLC-gamma), guanosine triphosphatase (GTPase)–activating protein of ras (ras-GAP), and signal transducer and activator of transcription 3 (STAT-3).

Upon ligand binding and phosphorylation of PTKs, SH2–domain containing proteins interact with the receptor kinase domain. PLC-gamma on interaction with the PTK, becomes phosphorylated and catalyzes the turnover of phosphatidylinositol (PIP_2) to two other second messengers, inositol triphosphate (IP_3) and diacylglycerol (DAG). DAG activates protein kinase C; IP_3 raises the intracellular calcium (Ca^{2+}) levels by inducing its release from intracellular stores. Ca^{2+} is involved in the activation of the calmodulin-dependent CAM-kinase, which is a serine/threonine kinase.

A more important signal transduction pathway activated by PTKs concerns the ras pathway. The ras cycle is connected to activated receptors via the adapter protein Grb2 and the guanosine diphosphate-guanosine triphosphate exchange factor Sos (son of sevenless). GDP-ras, upon phosphorylation, is converted to its activated form, GTP-ras. The activated ras activates another Ser/Thr kinase called raf-1, which in turn activates another kinase, the mitogen activated protein kinase kinase (MAPKK). MAPKK activates the serine/threonine kinases, and extracellular signal-regulated kinases Erk1 and 2. Activation of Erk1/2 leads to translocation into the nucleus, where it phosphorylates key transcription factors such as Elk-1, and c-myc. Phosphorylated Elk-1 associates with serum response factor (SRF) and activates transcription of c-fos. The protein products of c-fos and c-jun function cooperatively as components of the mammalian transcription factor AP-1. AP-1 binds to specific DNA sequences in putative promoter sequences of target genes and regulates gene transcription. Similarly, c-myc forms a heterodimer with another immediate early gene max and regulates transcription.

The expression of c-fos, c-jun, and Egr-1 is found to be upregulated after ischemic renal injury. Immunohistochemical analysis showed the spatial expression of c-fos and Egr-1 to be in thick ascending limbs, where cells are undergoing minimal proliferation as compared with the S3 segments of the proximal tubules. This may suggest that the expression of immediate early genes after ischemic injury is not associated with cell proliferation.

Several mechanisms control the specificity of RTK signaling: 1) the specific ligand-receptor interaction; 2) the repertoire of substrates and signaling molecules associated with the activated RTK; 3) the existence of tissue-specific signaling molecules; and 4) the apparent strength and persistence of the biochemical signal. Interplay of these factors can determine whether a given ligand-receptor interaction lead to events such as growth, differentiation, scatter or survival.

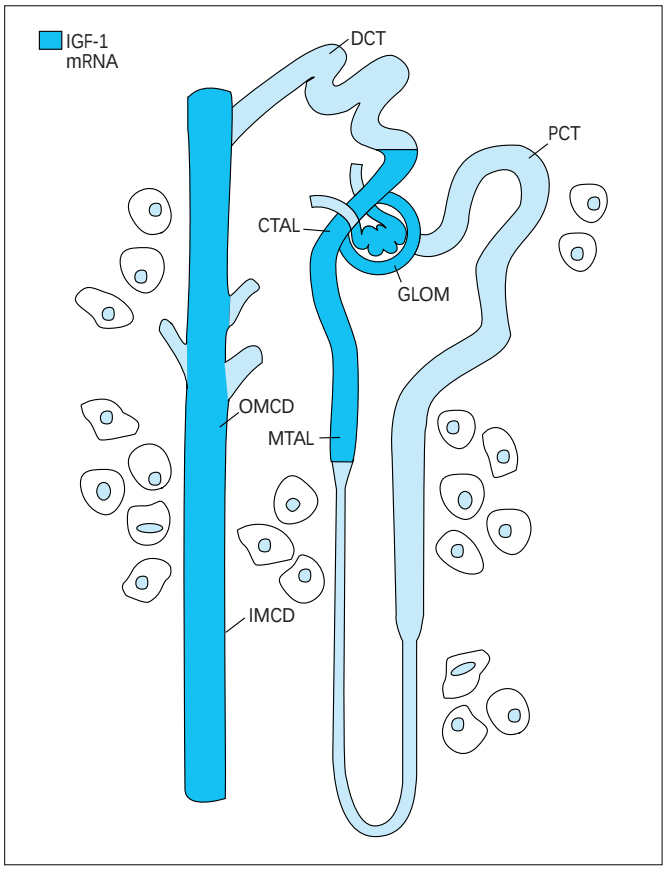

FIGURE 17-8

Expression of mRNA for insulin-like growth factor I (IGF-I). Under basal conditions, a variety of nephron segments can produce IGF-I. Glomeruli (GLOM), medullary and cortical thick ascending limbs (MTAL/CTAL), and collecting ducts (OMCD, IMCD) are all reported to produce IGF-I. Within hours of an acute ischemic renal insult, the expression of IGF-I decreases; however, 2 to 3 days after the insult, when there is intense regeneration, there is an increase in the expression of IGF-I in the regenerative cells. In addition, extratubule cells, predominantly macrophages, express IGF-I in the regenerative period. This suggests that IGF-I works by both autocrine and paracrine mechanisms during the regenerative process. DCT/PCT—distal/proximal convoluted tubule.

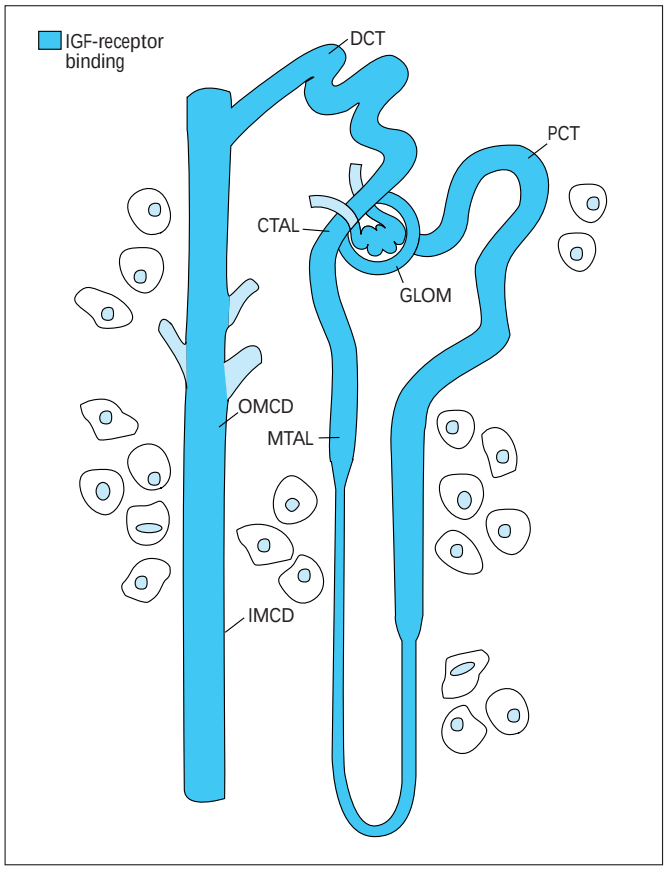

FIGURE 17-9

Receptor binding for insulin-like growth factor I (IGF-I). IGF-I binding sites are conspicuous throughout the normal kidney. Binding is higher in the structures of the inner medulla than in the cortex. After an acute ischemic insult, there is a marked increase in IGF-I binding throughout the kidney. The increase appears to be greatest in the regenerative zones, which include structures of the cortex and outer medulla. These findings suggest an important trophic effect of IGF-I in the setting of acute renal injury. CTAL/MTAL—cortical/medullary thick ascending loop; DCT/PCT—distal/proximal convoluted tubule; GLOM—glomerulus; OMCD/IMCD—outer/inner medullary collecting duct.