

Importance of Growth Factors

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Most growth factors are polypeptides that bind to specific cell surface receptors and considered as hormone-like modulators of cell proliferation and differentiation in different cell types [1]. Most of these receptors exhibit protein-tyrosine kinase activity located in their cytoplasmic domain of the subunit structure [1]. The regulation of cell proliferation are affected by the cellular and molecular actions of growth factors [2]. Unlike hormones in general, growth factors may have other biological activities in addition to the stimulation of cell proliferation [3]. In addition to the stimulation of cell growth, some growth factors can trigger cellular differentiation, enhance cell survival, initiate cell migration and stimulate the secretion of tissue specific hormones from differentiated cell types [1]. Examples of growth factors include the epidermal growth factor (EGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), transforming growth factor (TGF), nerve growth factor (NGF) and fibroblast growth factor (FGF). Hepatocyte growth factor (HGF) is a growth factor produced in mesenchymal cell [4], whereas vascular endothelial growth factor (VEGF) is an endothelial cell mitogen that has potent permeability [5]. Some cytokines are considered as growth factors such as the hemopoietic cytokines, which form a family of glycosylated extracellular proteins and regulate the production and functional activity of hemopoietic cells [6]. Also, T cell growth factor (TCGF) or interleukin 2 (IL-2) is required for the proliferation of mature T cells [7-11].

Tumor necrosis factor- α (TNF- α) is a potent proinflammatory cytokine and important mediator of inflammatory tissue damage [12]. Many experimental studies and clinical observations support a role for TNF in the pathogenesis of acute and chronic renal disease. However, TNF may mediate both proinflammatory as well as immunosuppressive effects, particularly in chronic kidney diseases and systemic autoimmunity. Blockade of TNF in human rheumatoid arthritis or Crohn's disease led to the development of autoantibodies, lupus-like syndrome, and glomerulonephritis in some patients. Also, there is an evidence of distinct roles for TNF receptors in mediating local inflammatory injury in the kidney and systemic immune-regulatory functions [13]. On the other hand, TNF- β is a cytokine that is activated by interleukin-10 (IL-10) [14].

Although different growth factors cause different responses in a given cell, there are many overlapping responses as well. In 3T3 cells (mouse endothelial fibroblasts), insulin, IGF-1, EGF and PDGF all stimulate the phosphorylation of the ribosomal protein S6 whereas PDGF leads only to a reorganization of the active filaments [15-19]. Transforming growth factor (TGF), an important fibrogenic and immunomodulatory factor, may also function either as a pro- or as an anti-inflammatory cytokine [20].

EGF receptor (EGFR), as a model of growth factor receptors is three domains subunit composed of extracellular, transmembrane and intracellular or kinase domains (Figure 1). It is transactivated by some heterologous ligands in response to the interaction with multiple receptors and the activity of intracellular kinases [21]. Overexpression

or activation of EGFR is associated with metastasis, poor prognosis and resistance to chemotherapy [22]. In addition, EGFR is over expressed or activated by autocrine or paracrine growth factor loops in epithelial malignancies [23]. TGF β -1 is a multifunctional cytokine involved in the regulation of growth and differentiation of both normal and transformed cells (Figure 2). It has been reported that TGF β -1 mRNA and its protein were overexpressed in hepatocellular carcinoma tissues [24]. A significant higher serum level of EGF and TGF- β 1 was recently found in patients with hepatocellular carcinoma compared to their level in patients with chronic hepatitis C infection and control subjects. The levels of phosphorylated EGFR in hepatocellular carcinoma and chronic hepatitis C patients show a highly significant difference between patients [25]. Accordingly, EGF and its phosphorylated form can be used as sensitive biomarkers for the diagnosis and prognosis of these diseases. In conclusion, various growth factors are involved in different biological processes, some of which are of clinical importance in disease.

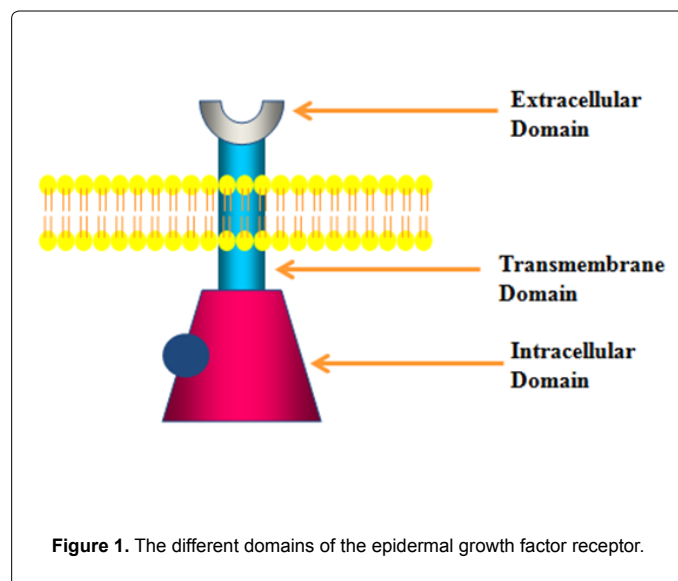


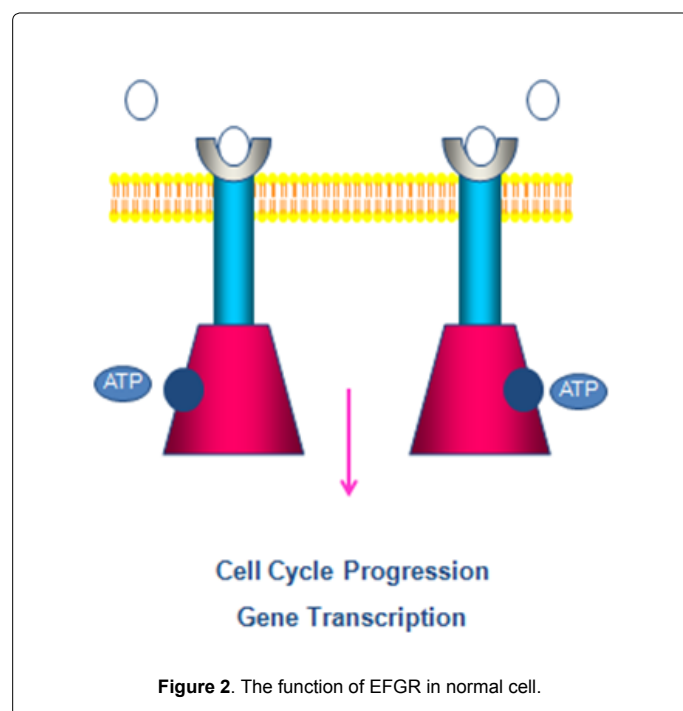
Figure 1. The different domains of the epidermal growth factor receptor.

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