In 1983, it was determined that both the isoforms have the same amino acid sequences. Subsequently in 1984 it was established that somatotropin stimulated IGF-1 synthesis in many tissues including extra-hepatic tissues\(^5\).

Yakar et al\(^6\) (1999) showed that liver is the major source of IGF-1 and hepatic IGF-1 is unimportant for sustaining normal growth. This study also provided the evidence for locally produced IGF-1. In 2002, it was proved that double gene (liver IGF-1 gene, ALS gene) disruption leads to significant decrease in linear growth in mice and IGF-1 levels were reduced to about 10-15% of normal levels; thus, circulating IGF-1 seems to play a key role in growth\(^1\).

GH stimulation has been shown to regulate gene expression of IGF-1 and many of the IGFBPs. The promoter ALS of IGFBP-3 complex has an identifiable GH-responsive element. Moreover, mRNA encoding of IGF-1, IGFBP-3 and ALS were not co-localized within the same cells in liver. Hepatocytes express IGF-1 and ALS mRNA while IGFBP-3 mRNA is expressed in endothelial cells of liver that do not express detectable levels of GHR mRNA. Thus, the IGFBP-3 is indirectly regulated by GH and mostly the regulation is mediated through IGFs\(^2\).

**Brief introduction**

The IGF system is made up of ligands (IGF-1 and -2), six well characterized binding proteins (IGFBP-1 to -6) and two cell surface receptors (IGFR1 and IGFR2) that mediate the action of ligands\(^2\). Moreover, the IGFBP proteases and the IGFBP related proteins are also considered as the part of the IGF family\(^7\).

Circulating IGF-1 is involved in the growth and development. GH independent role of this growth factor has been observed during embryonic development and reproductive system function. The injection of GH enhances the growth in bone suggesting its IGF dependant role. Moreover, IGF-1 is effective on kidney and spleen\(^2\). IGF-1 increases whole body protein metabolism by increasing protein synthesis and inhibiting proteolysis. IGF-1 has a long term impact on cell proliferation, differentiation and apoptosis\(^8\). Several *in vitro* studies have suggested a role of IGF-1 as a mitogen and have shown that IGF-1 is involved in the cell cycle progression from G1 to S phase whereas IGF-2 weakens the G1 checkpoint after DNA damage\(^9,10\).

IGF-1 plays an important paracrine / autocrine role during normal development and growth of an organism. IGF-1 appears to be a required factor for normal mammary gland development. It is indicated that IGF-1 has the capacity to modulate mammary gland morphology at several points in life including puberty\(^11\).
IGF-2 plays a role during prenatal development. Its over-expression does not cause malignant tumor growth in organs like skin and uterus. In the mammary gland, expression of IGF-2 contributes to tumor formation and this provides the evidence for the role of IGF-2 signaling in malignant transformation. IGF-2 mRNA and protein are over expressed in some benign and malignant tumors.

The IGF-2 concentration is higher than IGF-1 in human of all ages. During postnatal growth, the role of IGF-2 is less important. IGF-2 action on body development occurs at a much earlier stage of life (i.e. during fetal growth). The actions of both IGF-1 and -2 are mediated through IGF receptors; IGF-1 has 2-15 fold higher binding affinity to IGFR1 than IGF-2. IGF-1 and -2 are strong mitogen for a wide variety of cancer cell lines including sarcoma, leukemia and cancers of the prostate, breast, lung, colon, esophagus, liver, pancreas, kidney, thyroid, brain, ovary and uterus.

The growth hormone has no regulatory effect on IGF-2 expression. The expression of IGFs is also regulated by various hormones like estrogens, ACTH (adrenocortico tropic hormone), thyrotrophin, luteinizing hormone, follicle stimulating hormone and human chorionic gonadotropin as well as other growth factors such as platelet derived growth factor (PDGF), epidermal growth factor (EGF) and Fibroblast growth factor (FGF). Diet and nutrition also affect circulating IGF-1 levels.

Within the malignant breast, IGF-1 mRNA is localized to stromal fibroblast surrounding normal breast epithelial cells while high levels of IGF-2 mRNA are found in fibroblasts adjacent to malignant epithelium. This suggests that IGF-2 plays a role in the maintenance of the malignant phenotype. It has been shown that circulating IGF-1 levels were highest in breast cancer patients as compared to controls.

IGFR1 and IGFR2 are glycoproteins located on cell membrane. Both receptors differ completely in structure and function. IGFR1 is a tetramer of two identical α and two identical β subunits which structurally resembles the insulin receptor. The IGFR1 activates receptor tyrosine kinase (RTKs) activity. Binding of IGFs to IGFR1 activates RTKs and triggers a cascade of reactions of two downstream pathways - MAPK and PI3K - leading to cell survival, cell proliferation, inhibition of apoptosis as well as cell transformation. IGFR2 has no tyrosine kinase activity. It binds only to IGF-2 and acts as an antagonist by reducing its biologic activity. It can be considered as the potential tumor suppressor molecule as it scavenges circulating IGF-2.

The six IGFBPs (IGFBP1-6) have some structural homology as well as 40-60 % amino acid sequence identity. They affect the cells in IGF dependant and independent manner. By
binding to the ligands, they serve as circulating reservoirs transporting IGFs, prolonging their half lives and regulating access of IGF ligands to the receptors. Due to their post-translational modification, they have different binding affinities for IGFs. The IGFBPs are able to bind to specific cell membrane receptors as well as attach to the cell surface or to extra cellular matrix. Depending on the concentration, phosphorylation status and proteolytic fragmentation, the same binding protein can have both inhibitory and stimulatory effects. The IGFBPs can translocate from the extracellular compartment to the nucleus in rapidly dividing cells. Several hormones and the growth factors are involved in the regulation of IGFBPs. Certain proteases are important in release of ligand from binding protein to receptors. Thus, IGFBP3 has an important role in regulating IGF bioavailability and action.

IGFBP-1, -2, -3 and -5 have been found to have dual regulatory effects on IGFs (i.e. suppressing or enhancing effect). Three independent studies have shown that IGFBP-1, -2 and -5 possess the IGF independent effects on cellular activity whereas others showed that IGFBP-3 regulated the mitogenic actions of IGFs along with the IGF dependant function. It was also shown to have IGF independent inhibitory effect on cell growth. IGFBP-4 and -6 can inhibit the mitogenic actions of IGFs. Proteolysis of IGFBPs is achieved by IGFBP proteases and has a regulatory impact of IGFBPs on IGF action.

Estrogen enhances the mitogenic effect of IGF-1 and stimulates production of IGFR1. It also expresses the synthesis of some IGFBPs in the breast tissue. In breast cancer cells, it lowers the IGFR2 expression and increases IGFBP proteases. In reciprocation, IGF-1 enhances the expression of ER in breast cancer cells. IGF-1 can enhance ER induced gene transcription in absence of estrogen and IGFBPs in contrast suppress the transcriptional activation initiated by ER.

To date, majority of studies have focused on the association with serum/plasma levels of IGF-1, -2, IGFBP-3 and their combinations. These studies have provided reasonably consistent support for higher risk of solid tumor in association with increased IGF-1 levels.

IGF-1 levels have been shown to be higher in the plasma and serum of breast cancer patients. However, some studies have shown no differences between cases and controls. A higher IGFR1 has been observed in breast cancer tissues as compared to normal tissues. High IGFBP-3 is generally associated with the decreased risk of cancer. Increased risk of breast cancer is associated with the higher ratio of IGF-1 to IGFBP-3. Conversely, a case-control study of breast cancer suggested a higher risk associated with high levels of IGFBP-3.
A study on endometrial cancer showed lower IGF-1 in cases than controls\(^{30}\). A study with post-menopausal endometrial cancer showed increased IGF-1, lower IGFBP-1 and no difference in IGFBP-3 compared to controls. A study measured IGF-1 gene transcription in endometrial tumor tissues and has found that there is no difference in production of IGF-1 and IGFR1 even in presence of a low IGF-1 gene transcription\(^{31}\).

In prostate cancer, the patients showed higher levels of serum IGFBP-2 than benign prostatic hyperplasia and controls\(^{32}\). The IGFBP-3 levels have been shown to be low in serum\(^{32}\) and tumor tissues\(^{33}\) of prostate cancer where as a higher expression was noted for IGF-2, IGFBP-4, and IGFBP-5\(^{34,35}\). IGF-1 levels may be increased in serum and tumor tissues of patients with ovarian cancer\(^{36}\). Overall, there are inconsistencies in the pattern described above which does not allow a firm conclusion but these data suggest that the entire IGF axis has a role in the tumor development.

Inconsistent results have been obtained with respect to clinico-pathologic prognosticators and survival. Overall, it would appear that IGF levels have little value in predicting cancer prognosis but it is actively involved in regulating cell growth and death. This led to a speculation of their possible role in tumor growth and development\(^{37}\).

Several strategies are being developed to target the IGF system. The dietary intervention may be useful to decline IGF-1 and reduce risk of developing cancer. The blocking antibodies, antisense oligonucleotides\(^{38}\) and IGFR1 tyrosine kinase inhibitors are the different strategies being applied to down regulate IGF signaling\(^{39,40}\).