



Technical Bulletin No. 9 *Last Updated: September 2004*
The Role of the IGF System in Cancer
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Insulin-like Growth Factors (IGFs) are important mediators of growth and development. They are synthesized by almost every tissue in the body, although the liver is the predominant source. IGFs are potentially available to cells via autocrine, endocrine and paracrine pathways, making them some of the most available growth factors in the microenvironment of cells. While the IGF system is crucial for normal growth and development, it can also play key roles in cellular transformation, and the survival and growth of malignant cells.

IGFs are mitogenic, promoting cell cycle progression, and in some instances inhibiting apoptosis. Both IGF-I and IGF-II are equally effective as mitogenic agents, with only slight differences in their potencies (4). *In vivo*, IGF-I is important for normal growth postnatally and in the development and differentiation of many organ systems. IGF-II plays a critical role during fetal growth and brain development and is found in the central nervous system throughout life. Free [IGF-I] and [IGF-II] are low in normal adult serum, as most is bound to the IGF binding proteins (**IGFBPs**), but high serum [IGF] and altered [IGFBP] often correlate with the risk of malignancy. Many cancer cells obtain growth advantages by the autocrine expression of IGF-II.

The IGFs signal mainly through the IGF Type I receptor (**IGF1R**), but their bio-availability is modulated by the non-signalling IGF Type II receptor (**IGF2R**) and a complex network of six IGFBPs that bind IGFs with a higher affinity than the IGF receptors, with IGF release dependent on the actions of a range of IGFBP proteases.

IGF Receptors - IGF1R and IGF2R

IGF1R, is a tyrosine kinase, trans-membrane receptor expressed in most body tissues and required for normal growth of cells (see *GroPep Technical Bulletin No. 7*). Binding of IGF to IGF1R triggers a variety of intracellular signalling events involving the Ras/Raf/MAP kinase, PI3'kinase/AKT/PKB and other pathways. These control cellular proliferation, resistance to apoptosis and cellular differentiation. If these pathways are disturbed they can influence cancer development. As a result of significant cross-talk between growth factor signalling pathways, there is no clear delineation of one pathway to a particular outcome.

In cell culture, overexpression of the IGF1R has been shown to promote transformation and enhance cell survival in response to selected cytotoxic agents, while cells that are disrupted for IGF1R genes are refractory to transformation by almost all viral and cellular oncogenes (5). Furthermore, studies from knock-out mice have shown that low levels of IGF-I and IGF1R are associated with animal longevity (8).

The **IGF / IGF1R** axis also mediates the mitogenic effects of other oncogenes, hormones, retinoids and growth factors (1,4).

The insulin-like growth factor receptor, IGF2R, also known as the cation independent, mannose-6-phosphate receptor, is a tumor suppressor protein. It binds IGF-II with 100 fold higher affinity than IGF-I, but not insulin.

IGF2R downregulates growth signals in many cell types by one or more of the following mechanisms:

- a) by binding, internalizing and then degrading IGF-II
- b) by endocytosis of lysosomal proteases e.g. cathepsins to lessen tumor invasion
- c) facilitating the activation of TGF- β and thus increasing growth inhibitory signals on target epithelial cells.

IGFBPs

There are 6 classical IGF binding proteins which modify and site-direct the actions of the IGFs. Details of their properties are given in *GroPep Technical Bulletin No. 8*.

Modulation of IGFBP Activity by Proteases:

Proteolytic cleavage of IGFBPs increases the availability of autocrine and paracrine IGFs for proliferative and invasive purposes.

IGFBPs are cleaved at specific sites by a range of proteases including Prostate-specific antigen (PSA), matrix metalloproteases (MMPs), cathepsin D, thrombin and serine proteases. The majority of protease-sensitive sites are localized in the central non-conserved domain of the IGFBPs. Following limited proteolysis, IGFBPs exhibit a dramatically reduced affinity for IGFs and some IGFBP fragments have IGF independent activities (1).

The IGF System and Cancer

There is epidemiological evidence that high circulating levels of GH / IGF-I are a risk factor in hormonally responsive epithelial cancers - breast, prostate, colon (2,4). High levels of IGFs, some IGFBPs and IGF1R are associated with many cancers and increased serum levels of IGFs and alterations in serum IGFBP levels may become indicators of malignancy (1). This suggests that intervention to control the availability of IGFs and IGFBPs (e.g. protease resistant IGFBPs), selective inhibition of IGF1R or increased levels of soluble IGF2R may be of therapeutic value in the treatment of a number of cancers.

Epidemiological Studies and Cancer

To date there is inadequate evidence to determine the potential role of serum [IGFs] and [IGFBPs] as prospective markers for cancer detection. Three large prospective studies have identified high levels of serum IGF-I and low levels of IGFBP-3 as risk factors in the development of prostate (6), colorectal (10) and breast (7) cancer. However other studies in breast (1) and prostate cancer (15) have given ambiguous / conflicting results e.g. serum IGFBP-3 levels in breast cancer have been shown to be decreased, increased and unchanged (1):

Cancer	Ref.	Serum [IGF]	Serum [IGFBP]
Breast	(7)	IGF-I ↑	IGFBP-3 ↓
Prostate	(6)	IGF-I ↑	IGFBP-3 ↓
	(12)	IGF-I ↑	IGFBP-3 ↓
	(15)	IGF-I ↑	IGFBP-3 no association
	(14)		IGFBP-2 inversely related to progression
Colon	(10)	IGF-I ↑	IGFBP-3 ↓
Bladder	(16)	IGF-I ↑	IGFBP-3 ↓ (predictive)
Adenomas	(13)	IGF-II ↑	
Acute childhood leukemia	(11)		IGFBP-3 ↓ predicts survival
Lung	(9)	no association	IGFBP-1, 2, 3 no association

Large prospective studies need to be carried out, so that changes in serum IGFBP levels can be correlated with the advent and / or development of particular cancers (2). It is known that low serum IGFBP-3 levels are often associated with breast cancer and high IGFBP-2 levels with prostate cancer, but whether IGF and IGFBP levels in serum can be used as a diagnostic aid in cancer detection has not been validated, even for IGFBP-3, the only IGFBP for which diagnostic kits are available.

Obviously more long-term prospective studies are required to determine whether the changes that occur in IGF and IGFBP levels during development of particular cancers can be detected sufficiently early to be of diagnostic value.

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