Insulin-like growth factors and cancer

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Interest in insulin-like growth factors (IGFs) and their effect on carcinogenesis has increased recently because high serum concentrations of IGF1 are associated with an increased risk of breast, prostate, colorectal, and lung cancers. Physiologically, IGF1 is the major mediator of the effects of the growth hormone; it thus has a strong influence on cell proliferation and differentiation and is a potent inhibitor of apoptosis. The action of IGF1 is predominantly mediated through the IGF1 receptor (IGF1R). IGF1R is involved in several oncogenic transformation processes. The availability of unbound IGF1 for interaction with IGF1R is modulated by IGF-binding proteins (IGFBP1–6). IGFBPs, especially IGFBP3, have independent effects on cell growth, for example, IGFBP3 has proapoptotic activities both dependent on and independent of p53.

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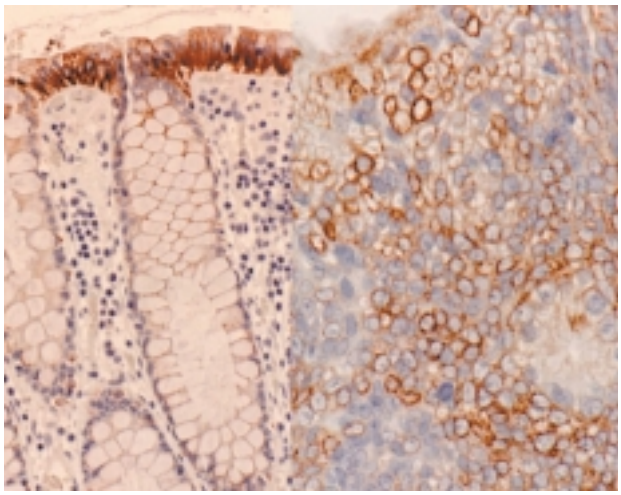

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Figure 1. IGF1R immunostaining in normal colonic crypt (left panel) and colonic adenocarcinoma (right panel).

Several studies have shown a link between serum concentrations of insulin-like growth factor 1 (IGF1) and IGF-binding protein 3 (IGFBP3) with increased risks of breast, prostate, colorectal (figure 1), and lung cancers. A case-control study of breast cancer, conducted within the Nurses' Health Study,[1] measured plasma concentrations of IGF1 and IGFBP3 from tissue samples collected in 1989–90 from women diagnosed with breast cancer before 1994. The investigation included 304 postmenopausal and 76 premenopausal women with breast cancer, and cases were matched with 620 controls by age, time of blood collection, month of sampling, fasting status, menopausal status, and the use of hormone-replacement therapies. Overall, no association was found between IGF and breast cancer. However, if the data were analysed according to menopausal status, the relative age-adjusted risk of breast cancer for the top compared with the bottom tertile in premenopausal women was 2·33 (95% CI 1·06–5·16; p=0·08) and 2·88 (95% CI 1·21–6·85; p=0·02) when analysed on the basis of IGF1 and IGFBP3. Furthermore, if the analyses were limited to 60 cases younger than 50 years (table 1), the respective relative risks were 4·58 (95% CI 1·75–12·0) and 7·28 (95% CI 2·4–2·2). The results did not change when the first year of follow-up was excluded to minimise the possibility of including undiagnosed, latent breast cancer. The results of two other small case-control studies have also shown similar results.[2,3]

At the start of a prospective study of prostate cancer in 1982,[4] in which IGF1 and IGFBP3 were measured, 14 916 male physicians in the USA (age range 40–82 years) provided blood samples, which were frozen and stored. Cases, and controls, were selected from the blood samples over the subsequent years. By 1992, 520 men had been diagnosed with prostate cancer. Of these, 152 had adequate quantities of stored plasma for quantitative analysis. These patients were age-matched with 152 cancer-free men from the same study group. Paired *t* tests were used to compare the mean concentrations of IGF1, IGF2, and IGFBP3 between the cases and the controls. In a univariate analysis, prostate-cancer risk was significantly higher in the highest quartile of circulating IGF1 concentration than in the lowest (relative risk 2·41, [95% CI 1·23–4·74]). When IGF1 and IGFBP3 were adjusted for each other in a logistic regression model (table 1), a stronger association emerged: for the top compared with the bottom quartiles of IGF1 concentrations, the relative risk of prostate cancer was 4·32 (1·76–10·6). Other studies have confirmed these findings.[5–7]

A similar investigation, based on the same bank of plasma samples described above, was carried out on 193 samples from men subsequently diagnosed with colorectal cancer.[8] The follow-up period after plasma sampling was 12 years. Serum concentrations of IGF1, IGF2, and IGFBP3 were measured and compared with values from 318 controls matched for age and smoking status. After adjustment for IGFBP3, the relative risk of colon cancer was 2·51 (95% CI 1·15–5·46; p=0·02). Although these data were consistent with

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Table 1. Correlation between circulating levels of IGF1 and risk of breast[1] and prostate[4] cancer

Plasma IGF	RR	RAR
Breast cancer (premenopausal, <50 years)		
<158 ng/mL	1·0	1·0
158–206 ng/mL	2·64	3·12
>207 ng/mL	4·58	7·28
Prostate cancer		
99–184 ng/mL	1·0	1·0
185–236 ng/mL	1·32	1·94
237–293 ng/mL	1·81	2·83
294–500 ng/mL	2·41	4·32

RR, relative risk; RAR, risk adjusted for IGFBP3.

others indicating an increased risk of colorectal cancer in patients with acromegaly,[9–11] they could not be reproduced in a similarly designed prospective study.[12]

In 1999, a hospital-based case-control study at the University of Texas MD Anderson Cancer Center[13] investigated the relevance of IGF1, IGF2, and IGFBP3 concentrations in 204 patients with newly diagnosed primary lung cancer. These cases were matched to 218 controls by age, sex, race, and smoking habits. The relative risk of lung cancer between the top and bottom quartiles of IGF1 serum concentrations was 2·0 (95% CI 1·1–3·6; p=0·02). After adjustment for IGFBP3, the odds ratio was 2·75 (95% CI 1·37–5·53; p=0.004). However, this study differed from the trials of prostate and colorectal cancers because lung carcinoma was present at the time of blood sampling. Nevertheless, a recently published prospective study, carried out as part of the New York University Women's Health Study Cohort, could not find an association between serum IGF1, IGFBP1, IGFBP2, and IGFBP3 and lung cancer in women.[14]

Most studies have focused on the risk of cancer in relation to serum or plasma concentrations of IGF1, IGF2, and IGFBP3 and have shown that high IGF1 and low IGFBP3 predicts increased cancer risk.

Physiology

The physiological and pathophysiological role of IGFs was reviewed by Zapf and colleagues in 1999,[15] and several extensive reviews addressing the molecular, cellular, and biochemical aspects of IGFs[16–21] and their relation to cancer[22–31] have also been published in the past few years.

The IGF family (table 2) consists of two ligands, IGF1 and IGF2, two cell-membrane receptors, IGF1R (which can form heterodimers with the insulin receptor) and IGF2R (which has two mannose-6-phosphate binding domains and is also called the IGFII/mannose-6-phosphate receptor; figure 2), and six IGF-binding proteins, IGFBP1–6. Recent investigations have added new components to the IGF family. New factors include the insulin-receptor-related receptor (IRR), several IGFBP-related proteins (IGFBP-rP), and a group of IGFBP proteases.

IGF1 consists of 70 aminoacid residues (7·65 kDa) and IGF2 of 67 (7·47 kDa). They share 62% homology in aminoacid sequence and there is 40% homology between the IGFs and proinsulin. More than 90% of circulating IGFs are bound to IGFBP3. IGFs can also bind to other IGFBPs, and less than 1% circulate in an unassociated form. These factors can act in endocrine, paracrine, and autocrine ways, and their effect on growth has been demonstrated in IGF-knockout animals. Disruption of the *IGF2* gene causes a reduction in growth during embryogenesis (a 40% reduction in birthweight is observed). In the postnatal phase, however, the animals develop into normal fertile dwarfs. The biology of IGF1-null mutant animals is more complex: some die shortly after birth, whereas others survive and reach adulthood. The survivors show, among other abnormalities, a delay in ossification and muscle development, and they are infertile. Homozygous IGF1R-knockout mice are only 45% of the weight of wildtype animals at birth and invariably die. Administration of IGF2 in vivo causes various metabolic effects: it increases insulin sensitivity, improves the lipid profile, supports protein metabolism, and improves kidney function and bone turnover.[32] In addition, it can have a positive effect on the cardiovascular system. At the cellular level, IGFs and their binding proteins have effects on cell proliferation, differentiation, and apoptosis. IGF1R signal transduction involves the activation of various intracellular signalling pathways, including the Ras/Raf/MAP kinase and the phosphoinositide-3 kinase pathways (figure 3).[23] Furthermore, communication between IGF receptors and other cell surface receptors such as the oestrogen, integrin, and cytokine receptors, is important.

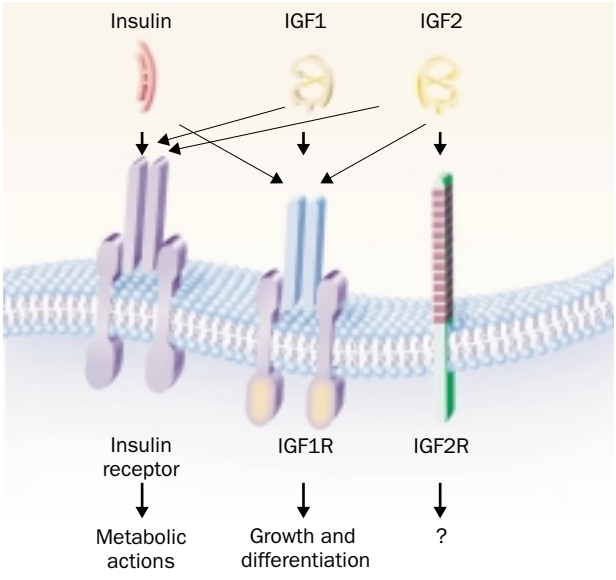
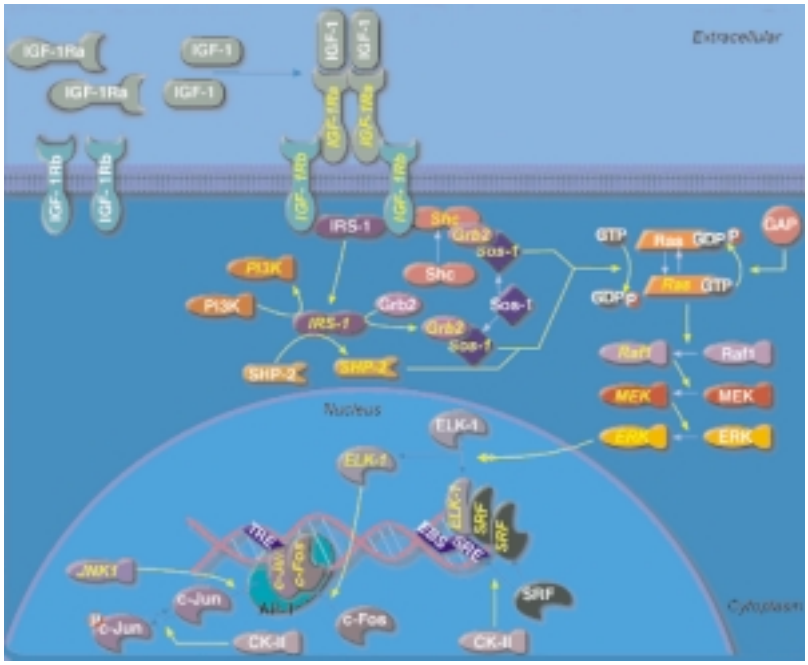


*Figure 2. Binding of circulating insulin and IGFs to target cells. Insulin and IGF1 receptors are structurally homologous and are both tyrosine kinases. IGF2R differs structurally from the insulin receptor and IGF1R and is thought to function primarily as a scavenger receptor for IGF2. insulin binds to its own receptor and to IGF1R. IGF1 and IGF2 bind to the insulin receptor. The relative affinities of ligands are indicated by the width of the arrows in the upper part of the diagram. (Reproduced from: Le Roith D. Insulin-like growth factors, N Engl J Med 1997; **336:** 633–40).*



Courtesy of BioCarta

Figure 3. IGF1 Signalling Pathway. IGF1 provides a mitogenic signal to act as a growth factor on many target cells. One component of IGF2 signalling involves activation of the ras and MAP kinase cascade. Activation of the MAP kinase pathway leads to modifications of transcription factors including AP1.

IGF1/IGF1R: proliferation, differentiation, and transformation

The role of IGF1R in malignant transformation is well documented and was recently reviewed by Valentinis and Baserga.[33] *IGF1R* is overexpressed by many tumour cell lines.[34,35] Targeted disruption of the *IGF1R* gene, which suppresses the expression of IGF1R and thus inhibits function, can abolish cell transformation.[36] Fibroblast cell lines established from mouse embryos in which the *IGF1R* gene is disrupted, cannot be transformed by oncogenes such as SV40 large T antigen, activated Ras, or the bovine papillomavirus E5 protein.[37–39] The growth-promoting and transformation-maintaining characteristics of IGF1R are the result of its potent antiapoptotic activity. These features have been shown in several systems,[40–42] including the prevention of etoposide-induced apoptosis by IGF1 and IGF1R.[43] The number of IGF1Rs on the cell surface is a major factor determining cell survival.[41]

IGF1R signalling can induce many effects including differentiation, transformation, and prevention of apoptosis. The factors that influence these different effects are not fully understood, but the insulin receptor substrate 1 (IRS1) is known to be involved: in the absence of IRS1, IGF1R transmits a signal that promotes differentiation. In contrast, when IRS1 is expressed, the signal is mitogenic and antiapoptotic.[33]

IGF2

Compared with IGF1, high concentrations of IGF2 circulate in serum. High serum IGF2 and IGFBP2 have been found in patients with colorectal cancer, with a trend towards higher concentrations in advanced disease.[45] IGF2 is predominantly expressed during embryonic development and acts primarily via IGF1R, whereas IGF2R/M6P functions as a "scavenger" receptor for IGF2. Most primary tumours and transformed cell lines overexpress IGF2 mRNA and protein,[34] and IGF2 is assumed to act in an autocrine manner. Overexpression of IGF2 in colon cancer is associated with an aggressive phenotype, and the loss of imprinting (loss of allele-specific expression) of the *IGF2* gene may be important in colorectal carcinogenesis.[46]

IGFBP3: a mediator of apoptosis

Baxter[48] reviewed the IGFBP3 antiproliferative signalling process, involving a β-importin-dependent transport mechanism, which promotes factor transport to the nucleus, and requiring an active transforming-growth-factor beta-signalling pathway.

One of the most important human tumour-suppressor proteins, p53, which mediates cell-cycle arrest and apoptosis, induces the *IGFBP3* gene. p53 activates *IGFBP3* expression in response to DNA-damaging ionising radiation. Consistently, breast carcinoma cells, which lack wildtype p53, are relatively resistant to radiation. However, transfection of such cells with *IGFBP3* cDNA causes an increase in apoptosis.[47]

In contrast to IGFBP3, IGFBP2 is associated with malignant adrenocortical tumours. Overexpression of IGFBP2 causes a striking increase of malignant growth and altered cellular morphology by IGF-independent mechanisms.[49] Similar data are also available for the other IGF-binding proteins, albeit less conclusive.

Table 2. Molecular characteristics of members of the IGF family

	Molecular weight (kDa)	Number of aminoacids	Gene location
IGF1	7·7	70	12q22–12q24
IGF2	7·5	67	11p15
IGF1R	225	α-subunit: 706 β-subunit: 626	15q25–15q26
IGF1R	270	2450	6q25–6q27
IGFBP1	25·3	234	7p12–7p14
IGFBP2	31·4	289	2q31–2q34
IGFBP3	28·7	264	7p12–7p14
IGFBP4	26·0	237	17q12–17q21
IGFBP5	28·6	252	2q31–2q24
IGFBP6	22·8	216	12q13

IGF, insulin-like growth factor; IGFBP, IGF binding protein; IGF1R, IGF1 receptor (tetrameric: 2α, 2β-subunits); IGF2R, IGF2 receptor.

Search strategy and selection criteria

Data for this review were identified by searches of Medline and CancerLit. References identified from within retrieved articles were also used. Only references published in English were selected, and there was no limitation on year of publication. Abstracts from the first symposium on IGF and cancer (Halle, Germany, September 2000) were also included.

Cancer prevention and treatment

IGF1 accelerates the progression of precancerous changes to invasive lesions. Thus, on the basis of epidemiological and experimental studies, a decrease in serum IGF may help reduce the risks of breast, prostate, and colon cancer, especially for members of high-risk families. Tamoxifen has been used successfully in chemoprevention of breast cancer,[50] and several studies show that it reduces IGF1 serum concentrations.[51,52] At this time, however, the part that IGF1 plays in the antioestrogenic mechanism is unknown but its decrease in concentration in response to tamoxifen suggests an important role. Other substances known to lower IGF1 production, or interfere with IGF signalling, which may be possible candidates for chemoprevention, include suramin (an inhibitor of various growth factors),[53,54] vitamin D3 analogues,[55] retinoic acid derivatives, and lycopen carotenoids.[56] Fenretinide, a derivative of retinoic acid, induces a moderate decline in IGF concentrations in women aged 50 years or less.[57] A 5-year treatment regimen with fenretinide may reduce the risk of secondary malignancy in premenopausal women with breast cancer.[58]

Cancer treatment strategies interfering with IGF1R signalling have been developed and the results of a pilot study of antisense oligodeoxynucleotide against IGF1R in malignant astrocytomas are promising.[59] Antibodies against IGF1R are also available and show antitumour activity in vitro.[60–62] These agents may be useful in future diagnostic and therapeutic strategies.

In summary, evidence now suggests that IGFs are important in carcinogenesis and that high concentrations are predictive of increased cancer risk. Both existing drugs and various newly developed agents acting through the IGF pathways have great potential as chemopreventives for certain types of cancer.

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