IGF-I in Mammary Tumorigenesis and Diabetes

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Abstract. Insulin growth factors (IGFs) are important mediators of growth, development, differentiation and survival of normal and transformed cells. Many complex and diverse types of molecules modulate these actions. In vitro and in vivo experiments have demonstrated that this system (IGF) is strongly related to the establishment of the transformed phenotype. Recent studies confirmed the association between serum levels of IGF-I and diverse malignant diseases while some relationships with other pathologies since Diabetes Mellitus have been described. Currently, IGFs are considered important targets for the study of new therapeutic drugs and strategies for cancer treatment. In this review, we have summarized the latest data specially linking IGF-I and its receptor with breast cancer.

Mortality estimation alone is not enough to understand the real magnitude and trends of the cancer problem and to evaluate the interventions against cancer (1). At present, cancer represents a fatal disease in many developing countries (2). During 1989 and 1990, in Argentina, the most frequent female cancer was breast cancer (36.2%), followed by colon and rectum (14.0%), cervix (9.5%), corpus (5.7%) and stomach cancer (3.0%) (3). Understanding of the biological processes involved in neoplastic progression would provide a basis for the development of new therapies.

Steroids, polypeptide hormones and growth factors act as regulators of cell proliferation in tumorigenic mammary tissue. The insulin-like growth factors I and II (IGFs) act as endocrine, paracrine or autocrine regulators of various biological processes in normal and neoplastic cells. It has been well established that in many cell types, activation of the type I insulin growth factor receptor (IGF-IR) is essential for cell survival, transformation and hormone-independence, the processes that promote tumorigenesis.

Breast cancer cells, like other cells, are governed by cell-cell and cell-substrate interactions. Stability of homeostasis involves the interchange of biochemical information among different factors. In the normal mammary gland and in the breast cancer, IGF-I may play an important role in those interactions. However, these mechanisms are very complex and have not been completely elucidated.

The aim of this work was to review the role of IGF-I and its receptor in the development of mammary cancer and the effect that their interrelations produces on tumor growth.

The IGF system

The IGF system comprises a complex network of ligands (IGF-I and IGF-II), their respective receptors (IGF-IR and IGF-1R), IGF-binding proteins (IGFBPs) and IGFBP proteases. Both IGF-I and IGF-II are polypeptide growth factors with a high degree of homology to insulin (Ins) and many authors (4) include it and its receptor (InsR) in the IGF system. There are also hybrid receptors between IGF-IR and InsR and it is thought that these hybrids behave more like IGF-IR than InsR (Figure 1).

IGF-I (70 residues, MW 7649) and IGF-II (67 residues, MW 7472) are single chain peptides with around 70% sequence homology with pro-insulin (5) and many authors (4) include it and its receptor (InsR) in the IGF system. There are also hybrid receptors between IGF-IR and InsR and it is thought that these hybrids behave more like IGF-IR than InsR (Figure 1).

IGF-I (70 residues, MW 7649) and IGF-II (67 residues, MW 7472) are single chain peptides with around 70% sequence homology with pro-insulin (5). The IGF-I gene is located on chromosome 12q and the IGF-II gene is on chromosome 11p, contiguous with the insulin gene (6). IGF-II is commonly expressed by tumor cells and may act as an autocrine growth factor; occasionally even reaching target tissues and causing tumor-induced hypoglycemia (7). In the fetus, both IGF-I and IGF-II are found at low levels in the serum as well as in most tissue (8). Synthesized
principally by the liver, the level of circulating IGFs are abundant in human at birth. Human and rat total (tIGF-I) serum levels have been widely related to age and sex (9-12). In Sprague-Dawley rats it has been detected that circulating levels of tIGF-I are lower in adult animals compared to animals in the process of growth (11).

The IGF-IR belongs to the tyrosine kinase receptor superfamily and it can be activated by IGF-I, IGF-II or by insulin at supraphysiological concentrations. IGF-IR is transcribed from a single gene as a precursor that is further processed into an α-subunit (706 residues) and another β-subunit (626 residues) (13). The functional receptor is heterotetrameric consisting of two α-subunits and two β-subunits which are linked by disulfide bonds (14). The α-subunits are extracellular and form the ligand-binding domain. The β-subunits, which contain short extracellular and transmembrane segments and a larger intracellular segment, transmit the ligand-induced signal. Binding of IGFs to the IGF-IR causes autophosphorylation and transphosphorylation of the β-subunit of IGF-IR (15, 16). Transphosphorylation of one β-subunit by the other is necessary for receptor activation (4, 17, 18). IGF-IR has 70% homology to the insulin receptor (InsR), with which it shares some of the signaling pathways. Both IGF-I and IGF-II can stimulate the InsR and activate functions mediated by this receptor (19-22). The C-terminus of the IGF-IR (roughly the last 100 amino acids), which has the least homology to the InsR, is dispensable for mitogenesis and protection from apoptosis but it is required for the differentiation and transformation of cells in vitro and in vivo (13, 23).

The IGF-IIR/mannose-6-phosphate (M6P) receptor is a bifunctional glycoprotein with no homology to the InsR. This receptor binds IGF-II and lysosomal enzymes bearing the M6P recognition marker at distinct binding sites. It binds IGF-II with high affinity but it also recognizes IGF-I. This receptor serves to target lysosomal enzymes to lysosomes and thus plays a key role in the degradative system of the cell (24-27). The IGF-II and the IGF-IIR

Figure 1. Schematic representation of IGF system.
Figure 2. IGF-IR signaling transduction (adapted from reference 4).

Figure 3. Schematic representation of the autocrine, paracrine and endocrine regulation (adapted from reference 92).
genes are parentally imprinted in the mouse and in humans. Relaxation or loss of imprinting has been recognized as a putative epigenetic mutational mechanism in carcinogenesis. It is now clear that both IGF-II and IGF-IR are important regulators of growth and development in fetal life, during oncogenesis and possibly during differentiation and tissue remodeling (26).

In biological fluids, IGFs are normally bound to IGFBPs. There are, at present, six classic and well characterized binding proteins: IGFBP-1, -2, -3, -4, -5 and -6. IGFBPs act not only as carriers of IGFs, increasing the half-life of the IGFs, but also function as modulators of IGF availability and activity. In recent years, knowledge of the biological roles of IGFBPs has expanded. In addition to modulating IGF bioactivity, IGFBPs are capable of important biological actions independent of their abilities to bind IGFs. Evidence implicates the direct association of IGFBPs with a variety of extracellular and cell surface molecules with consequent effects upon important biological processes, such as modulation of bone cell proliferation and growth arrest of breast and prostate cancer cells (28-31). Recently, several groups of cysteine-rich proteins with structural and functional similarities to the IGFBPs have been described and these were sub-grouped as IGFBPBrPs (proteins related with the IGFBPs). An unexpected action of some of these proteins is their ability to bind insulin with an affinity at least equal to their ability to bind IGFs (29, 31-33). In this way, a new superfamily of proteins is formed and it is quite probable that the list of these molecules will keep growing.

IGF-IR signaling

The activity of IGF-I is known to be mediated by high affinity to the IGF-IR. Upon ligand binding, the IGF-IR tyrosine kinase is activated leading to autophosphorylation and transphosphorylation of the β subunit. Phosphorylation of specific Tyr and Ser residues creates binding sites for IGF-IR signaling substrates. The more characterized IGF-IR signaling molecules are insulin receptor substrate 1 (IRSs) and src-homology 2/collagen alpha proteins (SHC). Both of these substrates became rapidly tyrosine phosphorylated by the activated IGF-IR. These phosphorylated proteins are able to associate with different SH2-containing proteins and to stimulate multiple pathways (Figure 2). For instance, IRS-1 activates phosphatidylinositol-3-kinase (PI-3K) through association with the p85 regulatory subunit of PI-3K. IRS-1 also activates the Ras/MAP cascade through GRB2/SOS, SYP phosphatase, as well as other pathways involving adapters Nick and Crk (34, 35). Tyrosine phosphorylated SHC, like IRS-1, recruits GRB/SOS complexes and activates the RAS/MAP pathway (36, 37). SHC is a common substrate of most tyrosine kinase receptors, cytoplasmic tyrosine kinases and certain phosphatases. In addition, both IRS-1 and SHC are known to be associated with molecules involved in cell-cell and cell-substrate adhesion (38). Hence, cellular response to IGF-I most definitely depends not only on the number of available IGF-I receptors but also on the cellular context and is subject to modification by different extracellular stimuli.

The effect of IGF-I on cell proliferation

The cell cycle may be divided in to four major phases: the presynthetic phase (G1), the phase of synthesis of ADN (S), the premitotic phase (G2) and mitosis (M). Quiescent cells are in the G0-phase. In the presence of certain competence factors such as platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF), cells enter G1; progression factors such as IGF-I and epidermal growth factor (EGF) are then required for progression through G1- into S-phase (18, 20, 39, 40). As eukaryotic cells undergo division, they must pass two critical checkpoints in the cell cycle. One is the transition from G1 to S where DNA synthesis begins, and the other is the passage from G2 to M, where mitosis begins. Cyclins play an important role in cell cycle control (41). In breast cancer cells, IGF-I induces the expression of the gene of cyclin D1 in the early G1-phase, which could be the principal mechanism by which this factor induces progression of the cell cycle (18, 42).

It has been demonstrated that IGF-I stimulates a mitogenic response in fibroblasts, chondrocytes, osteoblasts, keratinocytes, thyroid follicle cells, smooth and skeletal muscle cells, neuronal cells, mammary epithelium cells, oocytes, Sertoli cells, erythroid progenitor cells and several cancer cell lines (5, 43-45).

Most normal cells require more than one growth factor for cell cycle progression. Fibroblasts require a combination of IGF-I and PDGF or EGF for growth (46-48).

Targeted disruption of the IGF-I receptor gene resulted in growth-retarded mouse embryos. Growth was reduced to about 70% compared to normal mouse embryos, strongly suggesting that the IGF-IR plays a major role in embryogenic growth. However, growth is also, to a certain extent, IGF-IR-independent. Fibroblast cell lines established from mouse embryos that were homozygous for the targeted disruption of the IGF-I receptor gene showed mitogenic capabilities, suggesting that the IGF-IR is not an essential requirement for the cell cycle to occur. However, the IGF-IR is probably required for the cell cycle to be maintained at a normal rate (39, 40, 49, 50). Further studies are necessary to resolve these important issues.

The effect of IGF-I on cell death

A cellular action of the IGFs that is complementary to their stimulation of cell proliferation is their capacity in certain cells to inhibit cell death (51-53).
Down-regulation of the IGF-IR by different molecular strategies causes massive apoptosis of tumor cells in vivo and in vitro (54-59). As a consequence of the extensive apoptosis of tumor cells, down-regulation of the IGF-IR function results in inhibition of tumorigenesis and metastases (23, 60-63). This experimental evidence has given the basis to numerous investigations which have IGF-IR as the target for new therapies for the treatment of cancer (23, 64).

The effects of IGF-I on cell differentiation

The action of the IGF-IR may often be thought of as contradictory because this receptor may regulate proliferation and also differentiation processes (23, 65). In most cell types in culture (mouse embryo fibroblasts like 3T3, human diploid fibroblasts, some epithelial cells), IGF-IR sends an unambiguous mitogenic signal. Indeed, IGF-I was originally classified as a stimulatory growth factor necessary for the transition of cells from G1- to S-phase (66). In other cell types it may stimulate either proliferation or differentiation or both. So, under certain conditions, myoblasts, osteoclasts, adipocytes, oligodendrocytes, neurons and hematopoietic cells may be induced to differentiate by IGF-I (67). The participation of IGF-I in differentiation has been mainly studied in cultured myoblasts. Myoblasts in culture are undifferentiated cells which can grow indefinitely in serum, but they are capable of differentiating into myocytes if the serum is removed or decreased. If, after serum removal, the cells are incubated with either IGF-I or IGF-II, they are stimulated to proliferate, but the stimulation is short-lived and is followed by differentiation (68). In hematopoietic cells, differentiation occurs only after one or two cycles of replication (69-71). It has been described that the cells stimulated with Granulocytic-Colony Stimulating Factor (G-CSF), proliferate and differentiate (69). The cells grow in number but also differentiate. Similar observations were performed when the hematopoietic cells were stimulated with IGF-I. Usually differentiation is followed by cell death (72).

In many cases, the signaling transducted by IGF-I is contradictory. This hypothesis is based on the fact that, on the one hand, the activation of IGF-IR induces mitogenesis and cell death inhibition and, on the other, it induces differentiation in some cell types. This last action, although important, has been less investigated (23). It remains, then,
necessary to further investigate these signals which probably depend not only on the cell type, but also on the participation of different domains of the IGF-I receptor, on the number of activated receptors on the cell surface, on the different molecules involved in the signal transduction and on the extracellular context.

**IGF-I in normal mammary gland**

There is important evidence that stromal cells can influence epithelial behavior by secreting growth factors and/or by altering the composition of the extracellular matrix in which the epithelial cells reside. Early experimental evidence showed that normal mammary development is not possible in the absence of the pituitary gland (73, 74). Early on, a group of researches (75) proposed that the growth hormone (GH) was responsible for early mammary development and that prolactin was involved in the preparation of breast tissue for post partum lactation. This hypothesis was forgotten for the next 25 years, despite the support of solid experimental evidence. Later, pure hormones could be obtained through recombinant technology and the important role of GH in mammary development was confirmed (76). More recently, it was demonstrated that IGF-I is essential for early mammary gland development and that it fully mediates the action of GH in this process (77-80).

**The involvement of IGF-I in mammary transformation**

It has been well-established that the reproductory history of a woman is associated with breast cancer risk, which may be reduced by inhibited or decreased exposure to steroid hormones. It has been documented that early pregnancy, late menarche and early menopause provide a protective effect against breast cancer (81-84). Despite this evidence, we have much to learn about how estrogen and progesterone integrate with other signals and how they may be involved in the processes that lead to breast cancer. In addition to estrogen, breast cancer cells respond to various stimuli including growth factors and cytokines. There is abundant evidence that IGF-I affects breast cancer growth. Studies from different laboratories indicated that IGF-I acts synergistically with estrogen to stimulate cell growth and blockade of its action results in tumor growth inhibition. Investigations performed to clarify the role that IGF-I plays in mammary carcinogenesis have been fundamentally focused on the study of its function as an endocrine, autocrine and paracrine modulator. IGF-I transcripts were rarely identified in malignant breast epithelial cells either in vitro or in vivo. Rather, IGF-I transcripts were found prevalently within fibroblasts surrounding the breast epithelium. These data have suggested that, in human breast cancer, IGF-I may act as a paracrine growth promoter, being produced in normal stromal tissues and exerting a mitogenic action on the adjacent epithelium of normal or malignant breast (Figure 3) (85-87).

In our laboratory, we have induced an experimental model of mammary tumor in diabetic rats (88, 89). We have found that these animals develop lower number of tumors per rat, with a higher latency period and a lower tumor growth rate than non-diabetic animals. We have also found that tumors developed in diabetic rats clearly showed a benign histological pattern in more than 80% of the biopsies analyzed. Our results have been associated with lower IGF-I plasmatic levels during tumor induction in diabetic rats compared to control animals of the same age (90). IGF-II was found in at least one breast cancer cell line as well as in breast tumor specimens from patients biopsies (91). These results suggest that, in some cases, IGF-II may act as an autocrine growth promoter. In conclusion, IGF-I may serve as a paracrine growth factor in normal breast while IGF-II may act as a growth promoter in breast, cancers via both paracrine and autocrine mechanisms (92). Besides, IGF-I may act as an endocrine growth modulator in breast cancer and it is studied extensively in patients with breast cancer; the results of these investigations showed that levels were higher than in normal patients of the same age (93). Later, it was observed that elevated IGF-I plasma levels could be associated with higher mammary cancer risk in pre-menopausal women (94, 95). These findings may be related to IGF-I actions in mammary tumor promotion.

IGF-IR may be overexpressed in epithelial mammary cells, which may suggest that an increase in receptor content could have relevance in the malign transformation (96). This receptor is expressed on the surface of malignant breast epithelial cells and tumor cells are continuously exposed to IGFs. Hence there are many opportunities for interaction (97). It has been suggested too that chronic stimulation of a high number of IGF-IR may be critical for the onset of tumorigenesis (98).

Several researches have reported the involvement of IGF-IR in the development of breast cancer (47, 99, 100). It was demonstrated that it is expressed in a high percentage of biopsies of human mammary tumors (50-93%). In many cases, this expression was higher in benign tumors or in the normal mammary epithelium (101-104). Experiments performed in our laboratory have revealed that all analyzed NMU-ip-induced tumors were IGF-IR-positive. In normal mammary tissue the expression was significantly lower than in tumoral tissue. When we studied the expression of this receptor in tumor induction, we found that the expression increases early in the mammary tissue of NMU-injected rats (105). The mechanisms leading to these changes in the IGF-IR expression are not clear yet but they do not seem to be associated with an amplification of the gene, since this situation was only detected in 2% of the analyzed cases. It is known that the IGF-IR is an absolute
requirement for the establishment and maintenance of the transformed phenotype, both in vivo and in vitro (50, 106, 107). Important relationships have been established between IGF-IR and tumor suppressor genes: it has been suggested that BRCA1 represses the activity of co-transfected IGF-IR promoter reporter constructs in a number of breast cancer-derived cell lines and that the IGF-IR gene may be a novel downstream target for BRCA1 action (108, 109). Recent data indicate that over-expression could be related to a diminution of IGF-IR transcription due to an aberrant expression of the tumoral suppressor protein p53. Wild-type p53 has the potential to suppress the IGF-IR promoter in the postmitotic, fully-differentiated cell, thus resulting in low levels of receptor gene expression in adult tissues (110-112).

The cross-talk between IGF-IR and ER

Even after normal breast epithelial cells acquire the characteristic phenotype of malignancy, it is quite evident that breast cancer cells continue to respond to extracellular signals. Estrogens are required for normal mammary gland development and in some cases they are also required for breast cancer cells. Estrogen regulation of breast cancer cell growth can be modulated by complex interactions with a variety of growth factors, particularly IGF. IGF-IR and ER are coexpressed in some breast cancer cells and there is a complex cross-talk between the two pathways (112).

Nearly all the IGF system is under ER control. In this way, ER positively regulates the transcription of IGF-I (113), IGF-II (114, 115), IGF-IR (116), IGFBPs (117) and IRS-1 (118-121). We have studied the relationship between IGF-IR expression and the tumor response after bilateral ovariectomy in rats injected with NMU. Thus, the IGF-IR expression was significantly lower after ovariectomy, while this expression showed an important variability in growing tumors after ovariectomy. These results may indicate that the IGF-IR expression loses its normal regulation when estrogenic control is lost (105). Estradiol enhances the IGF-IR signaling by inducing the expression of insulin receptor substrate 1 (IRS-1) and it results in an enhancement of tyrosine phosphorylation of IRS-1 after IGF-I stimulation, followed by increased mitogen-activated protein kinase, phosphoinositide 3'kinase and Akt activation (Figure 4). Estradiol can also potentiate the effect of IGF-I on the expression of cyclin D1 and cyclin E and it may indicate that estrogens potentiate the effect of IGF-I on IGF-IR signaling, and they are also implicated in IGF-I actions on the regulation of the cell cycle (122).

Anti-estrogenic therapy of breast cancer

Endocrine therapy plays a key role in the treatment of breast cancer. The anti-estrogen tamoxifen is the usual first-line treatment in patients with hormone-responsive tumors. While tamoxifen is thought to exert its anti-tumor effects by acting as an estrogen antagonist, other mechanisms also contribute to those effects (123-125). Response to tamoxifen in advanced breast cancer and prolongation of disease-free survival is largely restricted to patients with ER-positive tumors. However, a minority of approximately 13% of patients with ER-negative tumors also respond to this therapy (95, 126).

Tamoxifen and its derivatives such as droloxifene and pure anti-estrogens ICI 164,384 and ICI 182,780, inhibit IGF-IR-dependent proliferation. It has been demonstrated that the anti-IGF-IR action of tamoxifen and ICI 182,780 is accomplished by down-regulation of IRS-1/PI-3K signaling (98, 112). Anti-estrogens also inhibit IGF-IR expression and tyrosine phosphorylation, but only in the presence of IGF-I. In its absence tamoxifen and ICI 182,780 enhance IGF-IR phosphorylation, which suggests that these drugs may modulate mechanisms that involve IGF-I-dependent phosphatases (98, 114). Several studies have shown that treatment with tamoxifen causes a moderate decrease in the plasma IGF-I levels (93, 127-129). It has been seen that ER-positive tumors that respond to anti-estrogen action are also more IGF-I-dependent in such a way that, when the IGF-I levels shrink with tamoxifen, the efficacy of this drug against the tumors is favored (130). Many investigations have been oriented to understand the mechanisms by which tamoxifen reduces IGF-I levels. There is experimental evidence for both a direct and an indirect inhibitory effect on IGF-I gene expression. The indirect mechanism involves the suppression of pulsatile growth hormone secretion by anti-estrogens (131). Evidence for the direct effect comes from studies using hypophysectomized animals. Those that had received the anti-estrogen showed reduced IGF-I gene expression (132). However, more investigations are necessary to elucidate the mechanism involved in the IGF system when an anti-estrogenic therapy is employed.

The physiological role of the IGF-I

IGF-I is found in plasma and in other body fluids as well as in cell-conditioned medium, bound to IGFBPs with high affinity and specificity. IGF-I is principally synthesized by the liver, but it may also be produced locally in the majority of tissues where it may act in an autocrine and paracrine manner (126, 133). IGF-I stimulates bone formation, protein synthesis, glucose uptake in muscle, and neuronal survival and myelin synthesis (134). IGF-I also stimulates the synthesis of protein of the extra-cellular matrix in chondrocytes, osteoclasts, fibroblasts and endothelial cells. In normal rats, the infusion of IGF-I causes hypoglycemia because glucose withdrawal is stimulated, but it offers a minimal effect on the suppression of hepatic glucose production (120).
Serum levels of IGF-I are affected by age, sex and nutritional status. Fasting or caloric and protein restriction start off resistance to GH and therefore a reduction in IGF-I hepatic synthesis (135). The concentrations are low at birth, increase substantially during childhood and puberty, and begin to decline in the third decade of life. These changes are consequent on the growth hormone secretion (136).

The IGF system and Diabetes Mellitus

Diabetes Mellitus is a clinical syndrome where an IGF-I role in the cell growth and metabolism has been noted (137). Apparently, and to a different degree according to the diabetes sub-type, insulin resistance as well as deficiency in insulin secretion appear as the main entities.

Insulin-deficient diabetic rats have low IGF-I levels and low growth rates. IGF-I treatment restores the growth rate but it does not normalize the blood glucose (138). IGF-I stimulates the peripheral glucose uptake and the glycogen synthesis in insulin-deficient diabetic rats, despite the resistance that these animals showed to the action of insulin on those metabolic processes (139, 140). Although both insulin and IGF-I restore growth rate in diabetic rats, insulin produces a proportionally higher increase in body fat while IGF-I increases organ and lean body weight at the expense of fat. This pattern of growth response may reflect the high abundance of insulin receptors in adipocytes (141). The ability of IGF-I to increase the sensitivity to insulin in patients with DMNDI has been demonstrated. These studies have led to the use of IGF-I in the treatment of insulin resistance (40, 142). However, many more studies must be encouraged aimed at the adverse effects that this treatment may carry.

Finally, thiazolidinediones (TZD), other anti-diabetic compounds, have been recently used. These drugs have an anti-hyperglycemic activity and do not reduce the basal glycemic activity in normal patients. There is some evidence that TZD present an anti-proliferative action in some cell lines (143). Their effects are mediated through Peroxisome Proliferator-Activated Receptors (PPARs). These receptors are members of the superfamily of nuclear receptors and may act as transcription factors. PPARγ, a member of this family, is quite abundant in adipose tissue where it may activate adipocyte differentiation (144, 145). PPARγ is also expressed in other tissue where its role is not well known yet. It is known that some colon cancer cell lines express PPARγ and their ligands are able to inhibit proliferation of these cells. Also, PPARγ is expressed in primary breast adenocarcinomas and its activation reduces malignancy (146, 147). These data suggest that PPARγ may present anti-tumoral effects, although the involved mechanisms are not completely known. Recently it has been demonstrated that PPARγ activation, through its natural ligand, 15-deoxi-Δ12,14-prostaglandin J2, prevents IGF-IR phosphorylation and cell proliferation in MCF-7 cells (148). In this way, PPARγ has become an important target for the development of new drugs that can be employed in the treatment and prevention of cancer.

The IGF system as a target for cancer therapies

Epidemiological studies have shown that circulating IGF-I is positively, whereas circulating IGFBP-3 is negatively, associated with a risk for breast, colon and prostate cancer (149). However, long-term studies in a pediatric population treated with GH or IGF-I have not shown an increased risk of neoplasia. The anti-estrogen tamoxifen has been successfully used in the treatment of breast cancer (150); as is known, this agent acts partially by inhibiting the transcription of IGF-I through attenuating the response of IGF-IR to IGFs (126). Similarly, agents that up-regulate IGFBP-3 may have an anti-tumor effect in vivo and in vitro (151). In our previous paper, we demonstrate that low levels of circulating IGF-I, dramatically decrease the incidence of mammary tumors induced by N-Nitroso-N-Methylurea in rats (105).

Currently, IGF-IR is signaled as one of the most important targets for new anti-cancer strategies due to the fact that the IGF-IR overexpression or activation prevent apoptotic events (152). The major problem of the clinical use of these therapies is the ubiquitous expression of IGF-IR. However, the use of antagonists of IGF-IR may offer a new hope for cancer treatment.

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