Insulin-Like Growth Factor-I Axis as a Pathway for Cancer Chemoprevention

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Even as chemoprevention is emerging as a realistic and a sensible modality for cancer control, knowledge on the molecular biomarkers and genetic signatures involved in the process of carcinogenesis will further allow customized targeted development of chemopreventive regimens for individualized needs. Insulin-like growth factor (IGF)-I is essential for normal growth; however, studies indicate that the risk of common cancers, such as colon (1), breast (2), and prostate (3), is increased in individuals who have higher circulating levels of IGF-I. Increased IGF-I signaling stimulates proliferation and promotes metastasis of cancer cells and therefore represents a promising target for treatment as well as prevention of cancer (4–8).

IGF Pathway: Background

The IGF pathway comprises a complex system of molecules involved in regulation of a diverse array of biological functions both normal and pathologic (9). IGFs are peptide hormones secreted from many different cells and their "insulin-like" designation originated from experiments in which treatment of serum with antibodies to insulin failed to eliminate all insulin activity. There are two principle IGFs, IGF-I and IGF-II, that have characteristics of both growth factors and hormones. While growth of many cancers is influenced by IGF secreted in distant tissues, there is evidence that in some cancers, IGFs are locally produced. It is quite likely that a cancer may, in the beginning, depend on circulating IGF levels and soon acquire the capability of producing its own supply of IGFs. The latter scenario of an autocrine or a paracrine dependence on IGF may turn a cancer to be more aggressive. IGFs bind to three receptors with differing affinities. The type 1 IGF receptor binds both IGF-I and IGF-II with high affinity. This receptor has been identified in essentially all tissues except liver, and virtually all of the biological activities of the IGFs result from binding to the type 1 receptor. IGF-I receptor (IGF-IR) overexpression has been linked to neoplastic development and it has been suggested that it has a role in regulating proliferation and differentiation even when its expression is low (10). This is attributed to downstream events such as loss of tumor-suppressor gene *PTEN* that may augment signals from IGF-IR (9). The type 2 IGF receptor binds IGF-II with high affinity and IGF-I with low affinity. This receptor seems primarily to be involved in clearance and degradation of IGF-II and does not transduce a signal because it lacks a tyrosine kinase domain. The IGF2R has also been associated with development of cancer because loss of IGF2R results in increased IGF2-initiated IGF-IR activation (ref. 9 and references therein). The insulin receptor binds IGF-I with roughly 100-fold lower affinity than insulin. High concentrations of IGF may stimulate insulin signaling through this receptor. A final important determinant of IGF activity is through a family of at least six distinct IGF-binding proteins (IGFBP) that modulate bioavailability of IGFs in the circulation. Low circulating levels of IGFBPs favor an increased IGF mitogenic activity. Tumor environments usually abound in protesases that can digest IGFBPs to release free IGF resulting in increased IGF signaling. IGFBPs seem to inhibit IGF action by competing with IGF receptors for IGF peptides; however, under certain conditions, several of the IGFBPs apparently are capable of enhancing IGF action by facilitating IGF delivery to target receptors. The fact that IGFBPs have a variety of IGF-independent functions is currently a subject of intense investigation (11–13). Binding of IGF to the receptor initiates a cascade of downstream events, including the activation of tyrosine kinase, phosphorylation of the insulin-receptor substrate (IRS)-1, and subsequent activation of either phosphatidylinositol 3-kinase–Akt-mammalian target of rapamycin or RAF-mitogen-activated protein kinase systems (reviewed in refs. 8, 9, 14–16).

Clinical Translational Advances: IGF Axis as a Target for Cancer Chemoprevention

In recent years, chemoprevention is increasingly being appreciated as an ideal and practical strategy for the management of cancer (17, 18). Chemoprevention is the use of nontoxic natural or synthetic products that can inhibit one or more steps in the process of carcinogenesis with a purpose to modulate the promotion and progression from normal to locally invasive cancer and to arrest the metastatic spread of the disease (19, 20). It is becoming clear that many chemopreventive substances, when given to animals in experimental carcinogenesis protocols or to humans, can delay the process of carcinogenesis (21). Thus, we advocate a practical definition of chemoprevention as "delaying the process of carcinogenesis." Although dietary ingredients can predispose individuals to develop cancer, there is compelling evidence from epidemiologic and laboratory studies that indicates reduced risk of cancer by regular consumption of fruits and vegetables (18). Knowledge on the precise mode of action of dietary ingredients and their toxicity is necessary before they can be recommended for clinical studies and regular human consumption. The fact that increasing levels of IGF-I are associated with an increased risk of cancers suggests that IGF could in fact be an appropriate

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target for cancer chemoprevention. The IGF pathway (Fig. 1) allows several targets for both intervention as well as prevention of cancer.

Curcumin, a polyphenol isolated from the rhizome of the plant *Curcuma longa*, exerts strong anticancer effects against several cancers (22). Beevers et al. (23) showed that curcumin (20 μmol/L) treatment of rhabdomyosarcoma cells decreased both basal as well as IGF-I–stimulated cell motility. Curcumin dose-dependently inhibited IGF-I–stimulated phosphorylation of mammalian target of rapamycin at Ser^{2448} and Ser^{2481} and also inhibited S6K1 and 4EBP1, two best-characterized downstream effector molecules of mammalian target of rapamycin. These findings were not cell type specific because similar effects were observed in DU145 (prostate), MCF-7 (breast), and HeLa (cervical) cancer cells.

Genistein, an isoflavonoid derived from soyabean *Glycine max*, is reported to have antitumor activity (24). It inhibits tyrosine kinase activity associated with growth factor receptors and also inhibits growth of several tumor cell lines. In HT-29 colon cancer cells treated with genistein (25-100 mmol/L), inhibition of cell proliferation and induction of apoptosis were observed to be mediated through inhibition of IGF-IR signaling (25). Genistein decreased IGF-I–stimulated phosphorylation of IGF-IR, IRS-1, and Akt, and recruitment of phosphatidylinositol 3-kinase/p85 to IGF-IR (25). In the transgenic adenocarcinoma of mouse prostate model, 250 mg genistein/kg in diet, starting at 5 weeks of age, significantly down-regulated IGF-IR, extracellular signal-regulated kinase (ERK)-1, and ERK-2 but not IGF-I (26). However, at low doses, genistein (1 μmol/L) has been shown to result in enhanced tyrosine phosphorylation of IGF-IR and IRS-I on IGF-I stimulation of MCF-7 cells (27).

Tea polyphenols derived from the leaves of the plant *Camelia sinensis* have been shown to possess remarkable cancer chemopreventive properties (28). These effects have been shown to be

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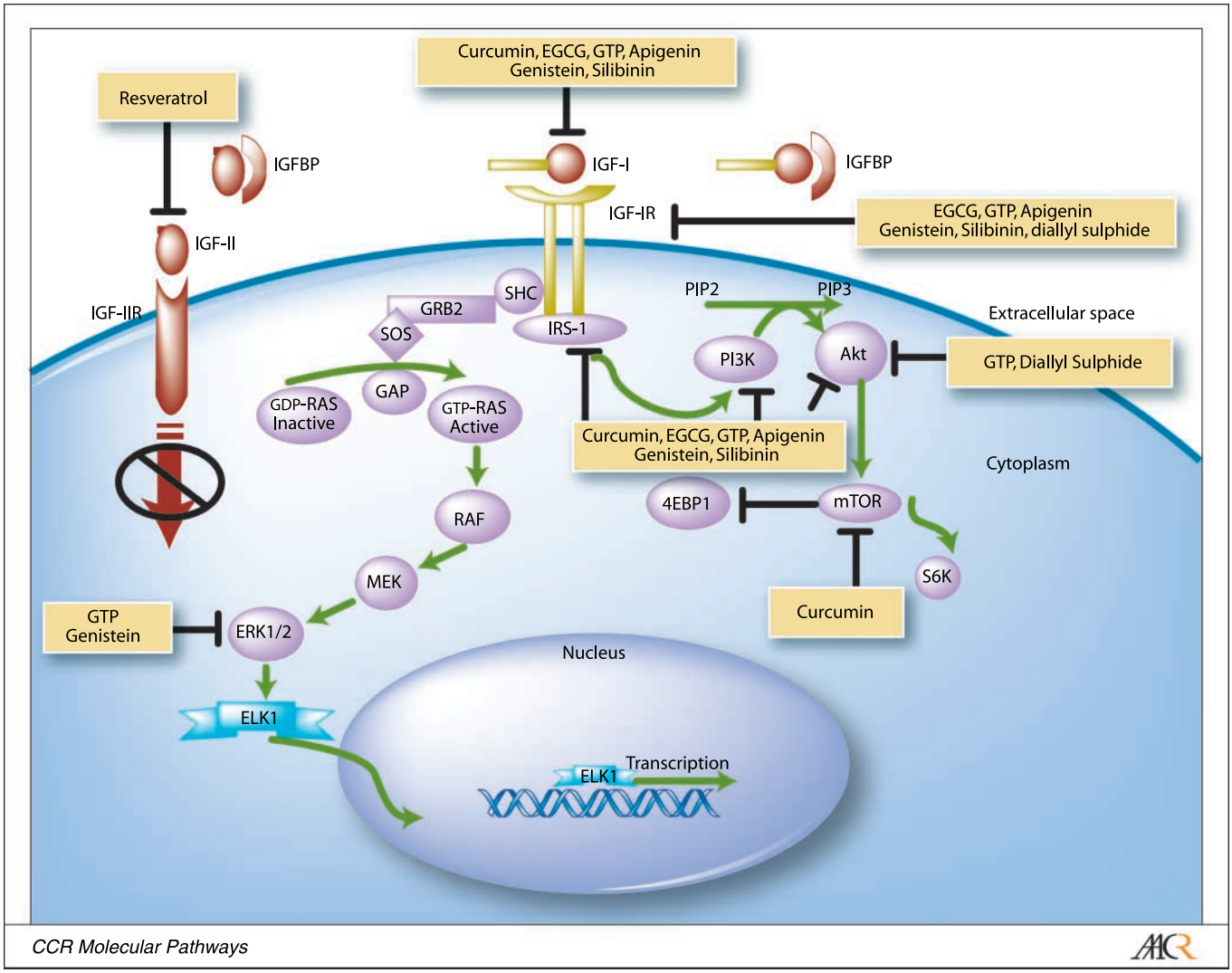

Fig. 1. IGF-I and its downstream effector molecules provide a proliferative signaling system in many different cell types and several targets for dietary agents. *In vivo* IGF-I may stimulate the growth of some types of cancer. On one end of IGF-I signaling is the association of the receptor tyrosine kinase with Shc, Grb2, and Sos-1 to activate ras and the mitogen-activated protein kinase cascade (raf, Mek, ERK) resulting in activation of ELK transcription factors. On the other end is phosphorylation of IRS-1 and phosphatidylinositol 3-kinase (*PI3K*) activation followed by Akt phosphorylation and activation of mammalian target of rapamycin (*mTOR*). Several dietary agents, such as green tea polyphenol (*GTP*), lycopene, curcumin, silibinin, and apigenin, directly interfere with circulating levels of IGF-I and its receptor. Resveratrol targets the levels of IGF-II and inhibits IGF signaling by inhibiting IGF-IR. Curcumin down-regulates the mammalian target of rapamycin and also inhibits phosphatidylinositol 3-kinase/Akt signaling. Genistein and GTP also inhibit ERK1/2 that is activated through IGF signaling.

partly due to the ability of tea polyphenols to inhibit IGF-I–induced signaling. Treatment of human prostate cancer cells DU145 with low doses of black tea polyphenols (20 μg/mL) substantially reduced IGF-I–mediated Akt phosphorylation (29). This effect was found to be partly due to the reduced autophosphorylation of IGF-IR. Human and rat glioblastoma cell lines treated with epigallocatechin-3-gallate, the main constituent of green tea polyphenols, reduced cell viability and induced apoptosis, and IGF-I was observed to be involved in these effects (30). Oral infusion of green tea polyphenol inhibits development and progression of prostate cancer in the transgenic adenocarcinoma of mouse prostate model (31). This inhibition was observed to be associated with lowering of IGF-I with concomitant increase of IGFBP-3 (31, 32). The modulation IGF/IGFBP-3 ratio was found to be associated with an inhibition of protein expression of phosphatidylinositol 3-kinase, phosphorylated forms of Akt (Thr^{308}) and ERK1/2 (32). Colon cancer cell lines Caco2, HT29, SW837, and SW480 express high levels of the IGF-IR, and that both SW837 and SW480 cells display constitutive activation of this receptor (33). Treatment of SW837 cells with epigallocatechin-3-gallate (20 μg/mL) caused within 6 hours a decrease in the phosphorylated form of the IGF-IR protein. At 12 hours, there was a decrease in the levels of both IGF-I protein and mRNA and within 3 to 6 hours there was an increase in the levels of both IGFBP-3 protein and mRNA. When SW837 cells were treated with epigallocatechin-3-gallate for a longer time, i.e., 96 hours, a very low concentration of epigallocatechin-3-gallate (1.0 μg/mL) also caused inhibition of activation of IGF-IR, a decrease in the IGF-I protein, and an increase in the IGFBP-3 protein (33).

Resveratrol, a bioflavonoid found in many plants, including grapes, has cardioprotective and cancer chemopreventive properties (34). The expression of IGF-IR mRNA was inhibited in a dose-dependent fashion in human breast cancer MCF-7 cells treated with resveratrol (10^{-5} mol/L), suggesting inhibition of IGF-IR may be involved in growth inhibition by resveratrol (35). Vyas et al. (36, 37) showed that resveratrol regulates IGF-II gene expression in a dose-dependent manner in MCF-7 and T47D breast cancer cell lines. Treatment of MCF-7 and T47D cells with resveratrol (10^{-6} mol/L) caused stimulation of precursor IGF-II mRNA and protein and this effect was blocked by coincubation with 17β-estradiol (36). Cell growth stimulated by resveratrol (10^{-6} mol/L) was blocked by addition of a blocking IGF-IR antibody, or the antiestrogen tamoxifen. In contrast, resveratrol (10^{-4} mol/L) at higher concentration inhibited IGF-II secretion and cell growth in MCF-7 and T47D cells. No change in IGF-I was observed with resveratrol treatment at any dose (36). In a subsequent study from the same laboratory, resveratrol was found to inhibit cathepsin D, an enzyme whose expression is promoted by IGF-II in estrogen receptor–positive breast cancer cells (37).

Lycopene, present in tomato, is associated with reduced prostate cancer risk (38). Lycopene suppressed IGF-I–stimulated growth of endometrial, mammary, and lung human cancer cell lines (39). Growth stimulation of MCF7 mammary cancer cells by IGF-I was markedly reduced by physiologic concentrations of lycopene. Lycopene treatment markedly reduced the IGF-I stimulation of tyrosine phosphorylation of IRS-1 and binding capacity of the AP-1 transcription complex. These effects were associated with an increase in membrane-associated IGFBP (40). Lung cancer risk is associated with higher plasma levels of IGF-I and/or lower levels of IGFBP-3. Effect of lycopene supplementation at a low dose (1.1 mg/kg/d, which is equivalent to an intake of 15 mg/d in humans) and a high dose (4.3 mg/kg/d, which is equivalent to 60 mg/d in humans) was investigated on plasma IGF-I/IGFBP-3 levels, in lungs of ferrets with or without cigarette smoke exposure for 9 weeks (41). Ferrets supplemented with lycopene and exposed to smoke had significantly higher plasma IGFBP-3 levels and a lower IGF-I/IGFBP-3 ratio than ferrets exposed to smoke alone (41). The effect of lycopene supplementation in a rat model of prostate cancer resulted in reduction of IGF-I expression, suggesting lycopene might interfere with the autocrine or paracrine action of IGF-I in prostate tumor progression (42).

Silibinin, a naturally occurring flavonoid antioxidant found in the milk thistle, has been shown to have potent antiproliferative effects against various cancer cell lines. In an androgen-independent prostate cancer, PC-3 cell line silibinin treatment (0.02-20 μmol/L) resulted in an increased IGFBP-3 accumulation in the conditioned medium and a dose-dependent increase of IGFBP-3 mRNA in the cells. These effects were reversed by an IGFBP-3 antisense oligodeoxynucleotide. Silibinin treatment also reduced IRS-1 tyrosine phosphorylation, indicating an inhibitory effect on the IGF-IR–mediated signaling pathway (43). Similar effects were observed in a prostate cancer xenograft mouse model implanted with DU145 cells. The *in vivo* anticancer effects of silibinin were associated with an increased accumulation IGFBP-3 in mouse plasma (44).

Various other natural agents have been identified as potential cancer chemopreventive agents that interfere with the IGF-I pathway. Tumor inhibitory effects of apigenin, a dietary flavonoid abundantly present in fruits and vegetables, were observed to be associated with increased accumulation of IGFBP-3 in the serum and tumors of a xenograft mouse model of prostate cancer with a simultaneous decrease in serum IGF-I levels (45). In cell culture studies, apigenin treatment resulted in cell growth inhibition and induction of apoptosis, which correlated with increased accumulation of IGFBP-3 in culture medium and cell lysate. These effects were associated with significant reduction in IGF-I secretion and with inhibition of IRS-1 tyrosine phosphorylation (45). A constituent of processed garlic diallyl trisulfide induced apoptosis in PC-3 and DU145 human prostate cancer cells. Treatment of PC-3 and DU145 cells with apoptosis-inducing concentration of 40 μmol/L resulted in a rapid decrease in Ser^{473} and Thr^{308} phosphorylation of Akt leading to inhibition of its kinase activity. The inactivation of Akt was associated with down-regulation of IGF-IR protein level and inhibition of its autophosphorylation (46).

Concluding Remarks

Higher IGF-I levels are associated with an increased risk for cancer development and therefore allows a rationale target for tailoring customized cancer chemopreventive regimens. Dietary agents that interfere with IGF signaling offer a foundation for developing nontoxic agents that override any toxicity associated with synthetic IGF inhibitors. Long-term use of several natural agents in preclinical settings in general has not produced any undesirable side effects. However, it is realized that before making final recommendations, detailed toxicology

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of such agents must be evaluated. A reasonable concern associated with the use of these chemopreventive agents to intervene IGF axis could be an interference with insulin action. It is prudent to examine this issue by assessing glucose metabolism in both preclinical as well as phase I and II clinical trials. Although several dietary agents have been shown to modulate IGF-I axis, our knowledge of the precise mechanisms is still obscure. These agents are proving to be unique based on their targeted action on cancer cells and their ability to spare normal cells. Finally, there is a need for preclinical and clinical trials that examine the effect of natural agents on the IGF pathway. These clinical trials could benefit from examining circulating blood levels of either IGFs or their binding proteins.

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