The insulin-like growth factor system as a target in breast cancer

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Summary

Evidence from several experimental systems has shown that the insulin-like growth factors (IGFs) can stimulate breast cancer proliferation. Since IGF action is mediated by interaction with specific cell surface receptors, interruption of these signalling pathways could result in inhibition of cellular growth. In all extracellular fluids, the IGFs are associated with high affinity binding proteins, the IGFBPs. Although the function of each IGFBP is not known, it is clear that under certain circumstances the IGFBPs can bind the IGFs and prevent receptor activation, and thus might have a role in a targeted approach to breast cancer therapy. Here we present our studies using IGFBP-1 to inhibit growth of the breast cancer cell line MCF-7.

Introduction

Breast cancer is a lethal disease because of unregulated tumor growth at primary and metastatic sites. A major contributor to tumor growth is unregulated cellular proliferation. Therefore, an obvious goal for cancer treatment is to target the factors that regulate cellular proliferation.

In vitro growth of breast cancer cells can be influenced by several substances including polypeptide growth factors. Many different growth factors have been shown to stimulate breast cancer cell growth, including the insulin-like growth factors (IGFs). Here we will discuss the IGF system in breast cancer and also examine ways to inhibit breast cancer growth by interfering with the IGF growth stimulatory pathways.

The IGF system components

The IGF system is composed of a family of interacting ligands, receptors, and binding proteins. Detailed reviews of these components have recently been published [1-4].

Two ligands, IGF-I and IGF-II, have been identified [5]. They are highly homologous to each other and to pro-insulin. The major hepatic production of IGF-I is regulated by growth hormone, although IGF-I mRNA can be detected in many other tissues as well. During puberty, IGF-I levels rise and are responsible for the linear growth of the skeleton. Mutation of the growth hormone receptor gene results in nearly undetectable circulating IGF-I levels and dwarfism [6]. In contrast, the normal physiologic role for IGF-II
in human is less well understood. In animals, IGF-II appears to be important in fetal development, as levels fall dramatically shortly before birth; humans, however, maintain high IGF-II levels throughout life. Recent studies show that IGF-II gene disruption in mice resulted in viable dwarf animals [7,8]. Disruption of both the IGF-I and IGF-II genes resulted in more severely growth-retarded animals that die shortly after birth due to respiratory failure. Thus, in animals, it appears that both IGF-I and IGF-II have growth regulatory roles in fetuses and in intact animals. Moreover, the IGFs may play a critical role in regulating the cell cycle (see below).

At least two receptors exist for the IGFs. The type I receptor (IGFR1) is homologous in structure to the insulin receptor. It is a glycosylated heterotetramer complex composed of two extracellular α subunits and two β transmembrane subunits that have tyrosine kinase activity [9,10]. This receptor has roughly equal affinity for both IGF-I and IGF-II, and mediates much of the mitogenic response to the IGFs. In vitro systems have clearly shown that IGFR1 functions to enhance progression through G1 of the cell cycle [11-13], and recent gene disruption experiments have underscored the central importance of this receptor in controlling the cell cycle [7]. Mice with a disrupted IGFR1 gene died of respiratory failure within minutes of birth, much like the animals that cannot synthesize IGF-I or IGF-II. These animals were dwarfs and had hypoplastic tissues (including the respiratory muscles), suggesting that lack of either the IGFs or IGFR1 resulted in a prolonged cell cycle length with underdevelopment of critical organs. Thus, IGFR1 is not essential for cell growth, but its loss of function results in a profound disruption of cellular proliferation.

The second well characterized IGF receptor is completely different in structure from IGFR1 [14,15]. The type II IGF receptor (IGFR2) has a large extracellular domain and a very short intracellular domain that lacks tyrosine kinase activity or any known signal transduction function. In addition to binding IGFR2, this receptor also binds enzymes bearing mannose-6-phosphate signals and other growth factors. Transmembrane signaling in the IGFR-II may result from coupling to a guanine nucleotide binding protein (G protein), although mitogenic stimulation through this receptor has not been shown [16,17].

In addition to these well characterized receptors, at least two other subtypes have been described. A hybrid between αβ IGFR1 dimers and αβ dimers of the insulin receptor has been identified [18-20]. This hybrid receptor appears to function as an IGF, rather than insulin, signaling molecule [19]. And finally, gene disruption studies have suggested that there is yet another unidentified receptor for IGF-II [8]. Animals with disrupted IGF-I and IGF-II genes were non-viable and more severely growth-retarded than animals that did not express IGFR1. Mice with a disrupted IGF-I gene were similar in phenotype to animals with a disrupted IGFR1 gene, suggesting that IGF-I only interacts with IGFR1. In contrast, animals that did not express either IGFR1 or IGFR2 were variably rescued from lethality and survivors had nearly normal birth weights, showing that loss of both cloned IGF receptors did not mimic loss of both ligands. One way to explain these findings is that IGF-II interacts with another still unidentified receptor (IGF2-XR) that compensates for the loss of both known receptors.

In the circulation, both IGF-I and IGF-II are bound to high affinity binding proteins. Six IGF binding protein (IGFBP) species have been cloned [21]. They are found in all extracellular fluids, and a substantial body of evidence suggests that these proteins can regulate IGF action. For example, IGFBPs have been shown to both augment and inhibit IGF action by altering receptor/ligand interactions. IGFBP-1 when phosphorylated avidly binds IGF-I and neutralizes its activity by blocking receptor/ligand interaction. In contrast, unphosphorylated IGFBP-1 weakly binds IGF-I and has been shown to enhance IGF-I action [22]. Thus, IGFBP-1 can regulate IGF-I action in opposite directions depending upon its phosphorylation state. In