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RESEARCH ARTICLE

New Insights into the Role of the Insulin-Like Growth Factors in Breast Cancer

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ABSTRACT
The insulin-like growth factor-1 hormonal axis has emerged in recent years as a promising therapeutic target in oncology. Empirical support to this view was provided by pre-clinical studies showing that insulin-like growth factor-1 receptor expression and activation constitute fundamental prerequisites for breast cancer development. Unfortunately, the vast majority of phase III clinical trials using monoclonal antibodies against the receptor have been disappointing. As a result of these negative outcomes there is an urgent need to identify predictive biomarkers that may identify potential responders. The present review article is aimed at providing an overview of the role of the insulin-like growth factor-1 axis in breast cancer. Circulating insulin-like growth factor-1 constitutes a risk factor for a number of malignancies, including breast cancer, and various members of the insulin-like growth factor-1 system are produced by the tumoral cells or by stromal cells. In addition, we provide evidence that the mechanism of action of insulin-like growth factor-1 involves interactions with the estrogen receptor as well as with the breast cancer gene-1. Finally, lifestyle factors that are related to insulin-like growth factor-1, such as obesity, have been suggested to have an effect on breast cancer.

Keywords: insulin-like growth factor-1 (IGF1); IGF1 receptor; breast cancer; BRCA1; estrogen receptor.

Introduction

Breast cancer is the most frequent malignancy in women. The disease is responsible for the greatest number of cancer-related deaths among women as one in eight to ten women will develop the disease during their lifetime[1]. According to the World Health Organization, breast cancer accounts for 25% of all female cancers and 12% of all cancers[2,3]. Cellular and molecular mechanisms that can explain the etiology and progression of the disease were sought in order to allow improved diagnosis and treatment. The insulin-like growth factor (IGF) system constitutes a growth factor network of major importance in the development of breast cancer. The IGF system has a direct effect on cellular proliferation and survival. Furthermore, components of the IGF axis interact with a number of genetic and environmental factors that have been implicated in breast cancer etiology, including various high-penetrance genes (e.g., BRCA1, BRCA2, p53, PTEN). The IGF axis emerged in recent years as a promising therapeutic target and major efforts are being invested in order to translate experimental and preclinical data into solid medical protocols[4-6]. The aim of this review article is to provide an updated overview of the role of the IGF axis in the specific context of breast cancer.

The insulin-like growth factor system

The insulin-like growth factors (IGFs) are involved in normal growth and differentiation of most organs as well as in a wide array of pathological states. The IGFs developed early in evolution, possibly as regulators of cellular proliferation in relation to nutrient availability[7]. The role of the IGFs as mediators of the growth hormone (GH)-stimulated incorporation of sulfate into cartilage was demonstrated more than 60 years ago[8]. The specific, GH-activated serum factor that was originally termed *'sulfation factor'* and then *'somatomedin'* is now accepted as IGF1[9]. The IGF system comprises three ligands, insulin, IGF1 and IGF2 (Figure 1). Circulating IGF1 levels are dependent on liver production, which is tightly controlled by pituitary-derived GH. In addition to its classical endocrine role, many extrahepatic tissues produce IGF1, which exhibits also paracrine and autocrine modes of action. Both IGF1 and IGF2 activate a common cell-surface receptor, the IGF1 receptor (IGF1R), which signals mitogenic, antiapoptotic and transforming activities[10]. The IGF1R is coupled to several intracellular second messenger pathways, including the *ras-raf*-MAPK and PI3K-AKT signaling cascades[11,12]. The IGF1R is vital for cell survival, as illustrated by the lethal phenotype of mice in which the *IGF1R* gene was disrupted by homologous recombination[13]. Of importance, IGF2 has also an important role in breast cancer and a significant portion of its effects are mediated by the A-isoform of the insulin receptor[14]. The IGF2 receptor is responsible for removing the highly mitogenic IGF2 from the circulation and is apparently not involved in intracellular signaling.

Figure 1

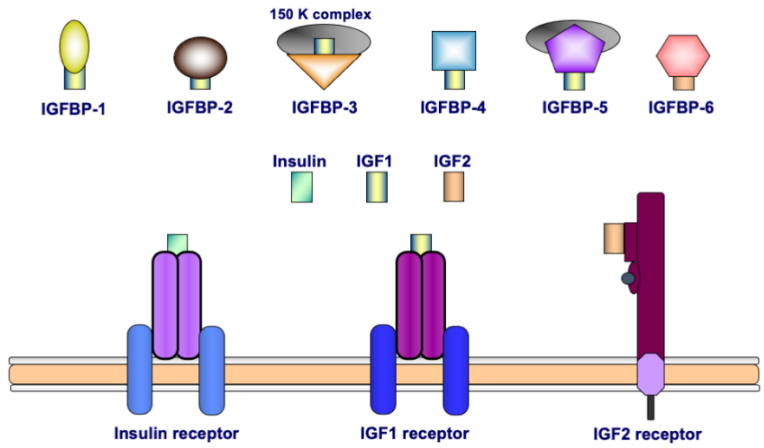

Figure 1. The IGF axis. IGF1 and IGF2 bind to the extracellular domain of the IGF1R and induce autophosphorylation of the tyrosine residues in the intracellular domain of the receptor. The bioavailability of the ligands is controlled by a family of IGF-binding proteins (IGFBP1-6). The most abundant IGFBP in serum is IGFBP3, which circulates as a ternary complex including the BP itself, the ligand, and an acid-labile subunit. The affinity of the IGFBPs for the ligand is usually higher than that of the IGF1R. The ratio between free and IGFBP-bound IGF is important in determining the potency of the growth factor.

Malignant cells, including breast, ovarian, prostate, colon, hematopoietic, renal and others, show an abundant expression of IGF1R[15-17]. Accumulated data suggest that up-regulation of the *IGF1R* gene constitutes a common paradigm in different types of cancer[18]. The IGF system includes, in addition, at least six high-affinity IGF binding proteins (IGFBP1-6)[19,20]. All IGFBPs are secreted by breast tumors and their expression is usually correlated with estrogen receptor status[21]. In serum, the vast majority of circulating IGF1 and IGF2 is found in a ternary complex with IGFBP3 and an acid labile subunit. This complex modulates IGF action by protecting the growth factors from proteolysis and prolonging their half lives in the circulation. In general, the IGFBPs inhibit the metabolic and proliferative actions of the ligands, although some IGFBPs display IGF-potentiating effects as well.

Circulating insulin-like growth factor-1 as a risk factor

Systematic reviews and meta analyses have suggested that high circulating IGF1 concentrations are associated with an increased risk of premenopausal breast cancer[22] and other malignancies[23]. Specifically, in a prospective nested control study (Nurse's Health Study) the relative risk (RR) of breast cancer in premenopausal women was 4.6 in the upper tertile of IGF1 values in comparison to women in the lower tertile[24]. The RR increased to 7.3 when the concentrations of IGFBP3 were included in the analysis. Breast tumors express all of the component of the IGF system, including ligands, receptors and binding proteins[16,25]. Circulating IGF1 stimulates the proliferation of breast cancer cells in an endocrine fashion[26]. In addition, stromal cells adjacent to the tumor cells produce IGF1 as well that seems to act in a paracrine fashion[27].

It is important to emphasize that IGF1, *per se*, is not genotoxic. In other words, even supra-pharmacological doses of the hormone can not induce neither mutations nor malignant transformation. However, once a malignant transformation has occurred, cell survival of *already* transformed cells depends on IGF1 action[28]. In terms of the '*two-hit*' hypothesis, IGF1 action is regarded as a second, *i.e.* a permissive, event that follows a first, or oncogenic, event. The disruption of internal checks and control mechanisms associated with the neoplastic phenotype is further emphasized by the finding that IGF1 action can override the cellular signals of apoptosis[29].

Insulin-like growth factor-1, lifestyle factors and breast cancer

Lifestyle factors that are related to IGF1 have been suggested to have an effect on breast cancer incidence[30]. For example, IGF1 concentrations are usually higher in obese than in lean subjects[31]. Consistent with this finding, most epidemiological studies provide evidence that obesity increases the risk of postmenopausal breast cancer. Given the obesity and diabetes epidemics in the Western world, the impact of nutrition on the IGF system in the context of breast cancer is the focus of major research efforts[32] (Figure 2).

Figure 2

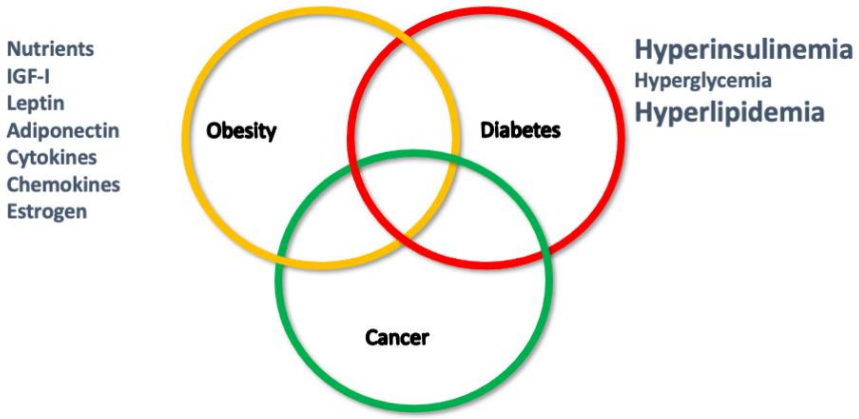

Figure 2. How can the metabolic syndrome, obesity and diabetes affect breast cancer development? Obesity, diabetes and the metabolic syndrome affect breast cancer development and progression via a number of mechanisms and factors. Epidemiological data identified IGF1 as an important risk factor for the disease.

Interaction of insulin-like growth factor-1 with breast cancer genes

The interaction of IGF1 with a number of high-penetrance breast cancer genes has been explored in recent years[33,34]. The breast and ovarian cancer susceptibility gene (*BRCA1*) is a transcription factor involved in DNA damage repair, cell growth and apoptosis[35,36]. Mutations in the *BRCA1* gene are detected in a considerable portion of families with inherited breast and/or ovarian cancer[37]. *BRCA1* mutation carriers have an approximately 87% cumulative risk of developing breast cancer by age 70[38]. In terms of its mechanism of action, BRCA1 was shown to represses the activity of the *IGF1R* gene in breast cancer cell lines[39,40]. Consistent with this finding, BRCA1 deficiency leads to increased expression of various IGF system members in multiple experimental systems, including BRCA1-deficient mice, primary mammary tumors and cultured human cells[41]. IGF1R levels in tumors from patients carrying *BRCA1* mutations were elevated when compared to tumors from sporadic (non-familial) breast cancer patients[42] (Figure 3). In addition, expression of the IGF1 ligand was markedly enhanced in tumors of *BRCA1* mutation carriers in comparison with matched sporadic tumors[43]. Furthermore, evidence in support of a complex, bi-directional interplay between the IGF1 pathway and tumor suppressor BRCA1 was provided by studies showing that IGF1 increases *BRCA1* gene expression and enhances *BRCA1* promoter activity[44]. In conclusion, experimental and clinical evidence emphasize the convergence of IGF1R-mediated cell-survival pathways and BRCA1-mediated tumor protective pathways. While these interactions have been primarily characterized in familial cancers (due to the high incidence of *BRCA1* mutations), it is clear that IGF1R and BRCA1 might also be involved in the etiology of sporadic cancers.

Figure 3

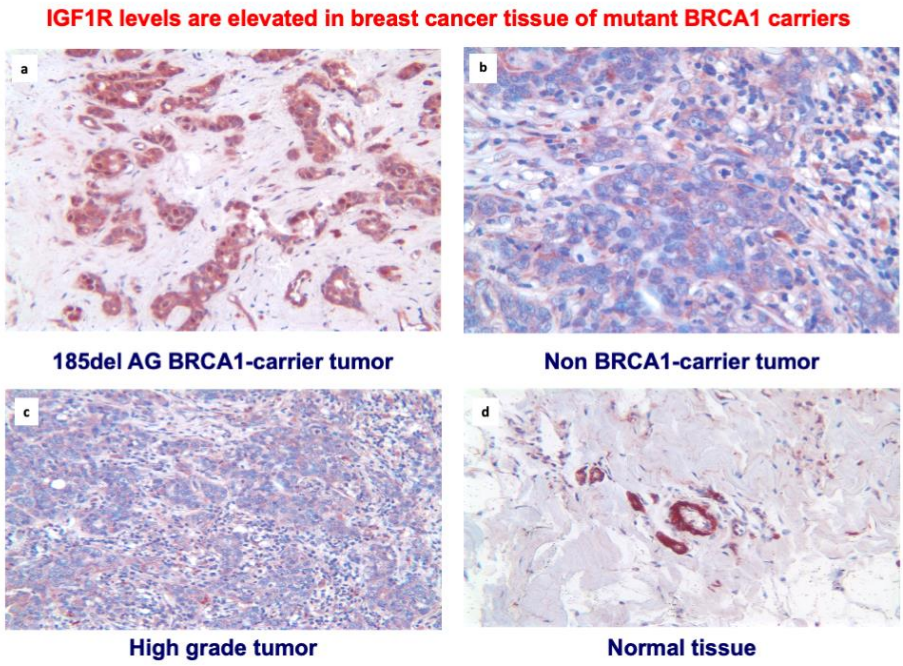

Figure 3. Immunohistochemical analysis of IGF1R levels in 185delAG BRCA1 mutant-carrier and non BRCA1-carrier tumors. (a) 185delAG BRCA1-carrier tumor; (b) Non-BRCA carrier tumor; (c) High grade tumor; (d) Normal tissue. Data adapted from Maor et al[42].

Interaction of insulin-like growth factor-1 with the estrogen receptor

Estrogen receptors (ER) are highly expressed in the mammary glands and are required for normal gland development[45]. Activation of the ER by estrogen causes internalization of the receptor complex and association with DNA. The ER complex recruits transcription factors and regulates the expression of a series of target genes involved in cell proliferation and differentiation[46]. Estrogens and IGF1 are synergistic in their actions as they differentially regulate c-myc and cyclin D1 to cooperatively stimulate breast cancer cell proliferation[47]. In the absence of estrogen, IGF1 can activate the ER and increase the expression of its downstream target genes. Furthermore *IGF1R* gene transcription in breast cancer cells is controlled by ER activation[48]. Prolactin, a polypeptide hormone, is essential for mammary gland development and lactation. Increased prolactin levels in plasma are associated with an increased

risk of breast cancer in postmenopausal women[49]. IGF2 is a required intermediate for prolactin-induced proliferation in mammary epithelial cells. In addition, prolactin directly upregulates *IGF1* and *IGF2* gene expression[50]. Given the important roles of the IGF and ER signaling pathways in the pathophysiology of the mammary gland, understanding the cellular and molecular basis of the interactions between these hormonal systems is of major translational relevance.

Targeted therapy of the insulin-like growth factor-1 system

Targeting of the IGF1 axis emerged in recent years as a promising area in oncology[4,51,52]. Targeting methods are evaluated for their ability to: (1) inhibit cancer cell proliferation, survival, and anchorage independent growth *in vitro*; (2) reverse tumor growth and metastases formation *in vivo*; and (3) sensitize cancer cells to chemotherapy, radiotherapy, hormonal and biological therapies. Various methods were developed to downregulate IGF1R expression and signaling, including selective inhibitors as well as specific monoclonal antibodies. Unfortunately most clinical trials led to disappointing results[53]. Hence, identification of molecular predictors of sensitivity to IGF1R inhibitors (*i.e.*, biomarkers) constitutes a critical field of research[54]. Extensive molecular profiling revealed that a number of components of the IGF pathway, including IRS2 and IGFBP5, may play key roles in determining the sensitivity of cancer cells to humanized IGF1R antibodies[55]. Similarly, IGF1R expression levels and activation status, as well as additional downstream mediators, might also help selecting patients for targeting therapy[56-58].

Conclusions

In summary, we have provided evidence that the IGF hormonal axis is an important player in breast cancer development. The biological actions of IGF1 are tightly linked to a number of high penetrance breast cancer genes, particularly BRCA1. In addition, we have demonstrated that IGF1 interacts with the estrogen receptor signaling pathway. Elucidation of the complex interplay between these important signaling pathways will have a major impact on our understanding of basic molecular oncology processes as well as on our ability to design and optimize breast cancer therapies.

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