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HYPEREXPRESSIVE IGF SIGNALING SYSTEM: A MITOGEN FOR BREAST CANCER

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ABSTRACT

Despite the major discoveries occurred in oncology the recent years, breast malignancies remain one of the most common causes of cancer-related deaths for women in developed countries. Development of human epidermal growth factor receptor 2 (HER2) -targeting drugs has been considered a breakthrough in anti-cancer approaches and eluded to the potential of targeting growth factors in breast cancer (BrCa) therapeutics. The Insulin-like Growth Factor-1 (IGF-1) system was initially recognized as a potential target candidate in BrCa therapy. Despite the promising experimental evidence, the impression from clinical trials is rather disappointing. Several reasons may account for this and the last word regarding the efficacy of this system as a target candidate in BrCa therapeutics is probably not written yet. Herein, we provide the theoretical basis, as well as, a comprehensive overview of the current literature, regarding the different strategies targeting the various components of the IGF-1/IGF-1R axis in several Pathophysiological aspects of BrCa, involving the tumor micro-environment. In addition, we review the hyper activation of the IGF signaling pathway which is implicated in the development, maintenance, progression, survival and chemotherapeutic response of many types of cancer, including ovarian cancer. It is also discussed here that the future challenges, as well as, the development of novel molecules and strategies targeting the system and suggest potential improvements in the field.[1]

KEYWORDS: IGF, Breast Cancer, BrCa, IGF-1R, HER2.

INTRODUCTION

Breast cancer is one of the most common cancers in women in both the developed and less developed world. It is estimated that worldwide over 508 000 women died in 2011 due to breast cancer.[1] Even though breast cancer is thought to be a disease of the developed world, almost 50% of breast cancer cases and 58% of deaths occur in less developed countries also.[2] Breast Cancer is more prevalent in younger age groups**.** In India, we are now witnessing greater numbers of patients being diagnosed with breast cancer to be in the younger age groups (in their thirties and forties). Despite the advances in therapeutics, metastasizing breast cancer remains incurable. The IGF-1 signaling has been well implicated with breast cancer (BrCa) biology. Many components of the IGF-1 system have been suggested as target candidates in Breast Cancer.[1]

Breast Cancer: An insight: Breast cancer starts when cells in the breast begin to grow out of control. These cells form a tumor that can be usually seen on an x-ray or felt as a lump. The tumor becomes malignant if the cells can grow into surrounding tissues or spread to different parts of the body. Breast cancer occurs almost entirely in women, but men can get breast cancer, too. Cells in nearly any part of the body can become cancerous and can spread to other areas. Most breast cancers start from the ducts that carry milk to the nipple which are known to be ductal cancers whereas few start in the glands that make breast milk, lobular cancers. There are also other types of breast cancer that are less common.[2] A small number of cancers start in other tissues in the breast. These cancers are called Sarcomas and Lymphomas and are not really thought of as breast cancers.[1]

How breast cancer spreads: Breast cancer spreads when the cancer cells invade into the blood or lymph system and are taken to distant areas of the body. In breast cancer, cancer cells can enter those lymph vessels and they begin to grow in lymph nodes. Most of the lymph vessels of the breast drain into: (i) Axillary nodes: supraclavicular and infraclavicular lymph nodes (ii) Internal mammary lymph nodes: If cancer cells have spread to the lymph nodes, there is a greater chance that the cells could have taken to the lymph system and spread to other parts of your body. The more lymph nodes with breast cancer cells, the more likely it is that the cancer spread to other organs. Due to this, detecting cancer in one or more lymph nodes usually affects the treatment regimen. In most cases, surgery is needed to remove one or more lymph nodes to check whether the cancer has spread.

Stages of Breast cancer[3]

STAGE 0- Cancer cells remain inside the breast duct, without invading to normal nearby breast tissue.

STAGE 1A- The tumor measures up to 2 cm and the cancer has not spread outside the breast; no lymph nodes are involved.

STAGE 1B- There is no tumor in the breast; instead, small groups of cancer cells, larger than 0.2 millimeter but not larger than 2 millimeters, are found in the lymph nodes or a tumor in the breast which is not larger than 2 centimeters, and there are certain groups of cancer cells – larger than 0.2 millimeter but not larger than 2 millimeters – in the lymph nodes.

STAGE 2A- No tumor can be found in the breast, but cancer cells are found in the axillary lymph nodes (the lymph nodes under the arm) or the tumor measures 2 centimeters or lesser and has spread to the axillary lymph nodes or the tumor is larger than 2 but not larger than 5 centimeters and has not extended to the axillary lymph nodes.

STAGE 2B- The tumor is larger than 2 but not larger than 5 centimeters and has spread to the axillary lymph nodes or may be the tumor is larger than 5 centimeters but has not developed to the axillary lymph nodes.

STAGE 3A- Tumors are not exactly found in the breast. Cancer is found in axillary lymph nodes that are coupled together or to other structures, or cancer may be found in lymph nodes near the breastbone or the tumor is of any size. Cancer then spread to the axillary lymph nodes and are sticking together or to other structures, or cancer may be found in lymph nodes near the breastbone.

STAGE 3B- The tumor may be any sized and has spread to the chest wall and/or to the skin of the breast and may have spread to axillary lymph nodes that are clumped together or to other structures or cancer may have spread to lymph nodes near the breastbone.

STAGE 3C- There may either be no sign of cancer in the breast or may be a tumor of any size and may have spread to the chest wall and/or the skin of the breast and the cancer spread to lymph nodes around the collarbone and the cancer may have spread to axillary lymph nodes or to lymph nodes near the breastbone.

STAGE 4- The cancer has spread (or metastasized) to various parts of the body.

The IGF system: The insulin-like growth factor (IGF) system is a complex system comprising transmembrane growth factor receptors,[4] growth factor ligands, high affinity IGF binding proteins (IGFBPs), IGFBP proteases and low affinity IGF binding protein related proteins (IGFBP-rP) that regulate Pathophysiological processes involved in glucose metabolism and cell proliferation. The IGF signaling pathway comprises the transmembrane receptors, insulin-like growth factor receptor type I (IGF-1R), insulin receptor (IR) -A and -B, the orphan receptor insulin related receptor (IRR) and insulin-like growth factor receptor type II (IGF-2R). Growth factor ligands include IGF-I, IGF-II and insulin. Ligand binding to IGF-1R and IR transduces downstream signaling via the canonical phosphatidylinositolkinase (PI3K)-AKT and RAS-extracellular signal-regulated kinase (ERK) pathways. Hyper activation of the IGF signaling pathway is implicated in the development, maintenance, progression, survival and chemotherapeutic response of many types of cancer, including ovarian cancer. This has led to the development of many therapeutic strategies inhibiting or preventing activation of the IGF signaling pathway in cancer cells predominantly via IGF-1R blocking antibodies and tyrosine kinase inhibitors inhibiting both tyrosine kinase domains of IGF-1R and IR.[5]

IGF Receptors

IGF-1R, IR and IRR are structurally and functionally related receptors existing as homo- and/or heterodimers. Each receptor dimer is composed of two monomers containing an extracellular α-subunit and transmembrane β-subunit, which are linked together by disulfide bonds in a β-α-α-β rearrangement. Both subunits are synthesized as a single precursor polypeptide and processed to a functional receptor by proteolytic cleavage of the α- and the β-subunit in the trans Golgi network before transportation to the cell surface. High sequence homology between IGF-1R, IR and IRR allows for the formation of heterodimers comprising one α-subunit and one β-subunit of the respective receptor. Heterodimer formation occurs by random assembly of the receptor monomers and reflects the molar ratios of the individual receptors. Therefore, less abundant receptors are usually expressed in heterodimer formation.[3]

IGF and Normal Mammary Tissue

IGFs plays an important role in proliferation and survival of it in the mammary gland, particularly during puberty and pregnancy. IGF-I is a potent mitogen for mammary epithelial

cells and in combination with mammotrophic hormones, such as estrogen receptor (ER), it induces ductal growth in mammary gland explants cultures. In one of the animal study, IGF-I also plays a role in the maintenance of the adult mammary gland during lactation. In lactating transgenic mice, over expressed Igf1 gene undergo ductal hypertrophy and fail to show normal mammary gland involution following weaning. The same group also demonstrated that IGF-I slows the apoptotic loss of mammary epithelial cells during the declining phase of lactation.[6] It is known that IGFs is one of the developmental/essential survival factors for the mammary gland, although other factors such as epidermal growth factor (EGF) and its homologues also deliver intracellular signals that suppress apoptosis.[7] Direct evidence for IGFs as survival factors comes from culture studies. IGF-I or IGF-II can inhibit the apoptosis process of mammary epithelial cells by serum withdrawal. It has been recently established that this is achieved through PI3K and MAPK signals that ultimately inhibit activity of a proapoptotic protein, BAD and enhance expression of another antiapoptotic protein Bcl-xL. Indirect evidence came from the transgenic mice.[6] over expressing IGFBP-5 in the mammary gland, these mice had reduced numbers of alveolar end buds, with decreased ductal branching and increased expression of the pro-apoptotic molecule caspase-3, and decreased expression of pro-survival molecules of the Bcl-2 family.[8]

IGF and Breast Cancer

The IGFs and IGF-IR function to promote proliferation inhibit death and stimulate transformation in breast cancer cells. High levels of serum IGF-I are associated with an increased risk of breast cancer in premenopausal women. Although IGF-I is rarely expressed in primary breast cancer, IGF-II message is more frequently detectable in breast cancer cells compared to normal cells.

Studies in transgenic mice have revealed an important role of IGF-I in mammary tumorigenesis, ie; Transgenic mice expressing human des(1-3) IGF-I display an increased incidence of mammary tumors. More, studies suggest that mice deficient in liver-expressed IGF-I have a reduced ability to develop mammary tumors. In human studies, circulating IGF-I levels are higher in breast cancer patients than in controls. In addition, group studies have shown that higher levels of circulating IGF-I are associated with an increased risk of breast cancer in premenopausal women.[6] The IGF-IR, the primary mediator of the biological actions of IGF-I, has been detected in a majority of primary breast tumor samples with

overexpression in 30% to 40% of breast cancers. Furthermore, IGF-IR autophosphorylation has been found to be elevated in human breast cancer suggesting that this is an active pathway in primary breast cancer.

Insulin receptor substrate-1 (IRS-1), the primary signaling molecule activated in response to IGF in MCF-7[9] human breast cancer cells, is reported to be overexpressed in some primary breast tumors and a high IRS-1 are associated with a decreased disease-free survival in a subset of patients with all tumors. Activation of specific IRS species are associated with distinct biological effects. Activation of IRS-1 signaling was associated with cell growth, whereas insulin receptor substrate-2 (IRS-2) signaling was associated with cell motility. Nagle et al. showed that mammary tumor cells obtained from IRS-2 knock-out mice were less invasive and more apoptotic in response to growth factor deprivation than their WT counterparts. However, IRS-1(-/-) tumor cells express only IRS-2, were highly invasive and were resistant to apoptotic stimuli. These data suggest that signaling pathways downstream of IGF-IR may ultimately be responsible for the malignant phenotype mediated by this growth factor signaling system.[10]

Effects of other Breast Cancer Therapy on the IGF System

On the other hand, breast cancer chemotherapy also affects IGFs. It has been reported that serum IGFBP-3[11] falls significantly following initiation of chemotherapy in breast cancer patients, those individuals with a decrease in IGFBP-3 greater than the median had significantly poorer survival (median survival 5.5 months vs 18 months). Another clinical trial showed that plasma IGF-I concentration significantly decreased after the first cycle of cyclophosphamide, methotrexate and 5-fluorouracil adjuvant chemotherapy in breast cancer patients. Retinoids[6] such as fenretinide (4-HPR) inhibit breast cell growth while decreasing IGF-I and increase IGFBP-3. Proline analogues of melphalan can be effectively transported into the MDA-MB 231 cells, evoking higher cytotoxicity, with reduction in IGF-I receptor and MAP kinase expression. Tamoxifen[12] also affects the IGF system. Raloxifene, a selective estrogen receptor modulator being tested in cancer prevention trials, significantly decreased IGF-I and IGF-I/IGFBP-3 ratios when compared to placebo.

Thus, it is clear that anti-proliferative agents affect IGF system signaling. These associations do not prove a cause and effect relationship, however, given the role of IGF signaling in cell survival, the down regulation of this signaling pathway is consistent with the effects of many anti-cancer drugs.[13]

Combination of Anti-IGF[6] Strategy with Chemotherapy

In theory, inhibition of survival pathways by blocking IGF-IR signaling while enhancing apoptotic stimuli has appeal. Combination of anti-IGFIR antibody αIR3 with doxorubicin resulted in increased cytotoxicity in IGF-I stimulated cells than with chemotherapy alone. Similar enhancement of chemotherapy effects have been shown in Ewing's sarcoma cells.[9,15] A tyrosine kinase inhibitor of IGF-IR, Tyrphostin AG1024 shown a marked enhancement in radio sensitivity and amplification of radiation-induced apoptosis which was associated with increased expression of Bax, p53 and p21, and a decreased expression of Bcl-2.[11] Another study demonstrated that co-targeting IGF-IR and c-kit synergistic inhibit proliferation and induction of apoptosis in H209 small cell lung cancer cells.[14] There is also evidence that somatostatin analogues may enhance the effect of tamoxifen in animal models by suppressing plasma IGF-I and –II levels.[8,9]

Conclusions and Perspectives

The IGF-IR is a promising target in breast cancer therapy because it signals to multiple pathways required for maintenance of the malignant phenotype. For the role of IGF-IR in cell survival, it is logical to combine anti-IGF therapies with conventional agents. Indeed, the preclinical data suggest that blockade of IGF-IR induces apoptosis and lowering a “survival threshold” with disruption of this signaling system should enhance chemotherapy efficacy.

There are many difficulties that will need to be taken in account before the combination of anti-IGF therapy with antimicrobials. There are many ways that IGF signaling could be targeted. As noted by Professor Baserga, the phenotypes regulated by IGF-IR are not restricted to survival alone, since proliferation is also affected by IGF-IR, it will be important to consider scheduling and choice of chemotherapeutic agent when designing appropriate combinations. It is evident that anti-metabolites would be less effective when combined with anti-IGF because of the requirement for cells in cell cycle during synthesis of DNA for anti-metabolites to function. The prospect of efficiently targeting the IGF-1 system in BrCa is certainly attractive.[16, 17] Further insight on the molecular mechanisms driving the disease via the IGF-1 system will open new avenues for the diagnosis and treatment of BrCa. However, it is clear that anti-IGF therapies will soon find their way into clinical trials. Hopefully, the vast experience with preclinical model systems will guide us in the optimal development of these agents. Furthermore, our findings may have important therapeutic and prognostic

implications because they identify IGF-IR as a potential new target for pharmaceutical strategies seeking to enhance tumor cure.

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