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STUDY OF KAI-1 EXPRESSION IN BREAST CARCINOMA

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Abstract

Globally, breast cancer is the most common type of cancer in females and is one of the leading causes of cancer death in women. The advancement in the targeted therapies and the slight understanding of the molecular cascades of the disease have led to small improvement in the rate of survival of breast cancer patients. However, metastasis and resistance to the current drugs still remain as challenges in the management of breast cancer patients. Metastasis, potentially, leads to failure of the available treatment, and thereby, makes the research on metastatic suppressors a high priority. The metastasis suppressors KAI1 (also known as CD82) has been found to inhibit tumor metastasis in various types of solid cancers, including breast cancer. KAI1 was identified as a metastasis suppressor that inhibits the process of metastasis by regulating several mechanisms, including cell motility and invasion, induction of cell senescence, cell–cell adhesion and apoptosis. KAI1 is a member of tetraspanin membrane protein family. It interacts with other tetraspanins, chemokines and integrins to control diverse signaling pathways, which are crucial for protein trafficking and intracellular communication. It follows that better understanding of the molecular events of such genes is needed to develop prognostic biomarkers, and to identify specific therapies for breast cancer patients.

Introduction

Breast cancer is the most common cancer in women, accounting for more than one out of every ten new cancer diagnoses each year. It is the world's second leading cause of death from cancer among women. Milk-producing glands are located in front of the chest wall in the breast. They are located on the pectoralis major muscle, and ligaments support and connect the breast to the chest

wall. The breast is made up of 15 to 20 lobes that are arranged in a circle. The fat that covers the lobes determines the size and shape of the breast. Each lobe is made up of lobules that contain the glands that produce milk in response to hormone stimulation. Breast cancer is always silent. The majority of patients learn about their disease during routine screenings. Others may present with a breast lump that was discovered by accident, a change in breast shape or size, or nipple discharge. Mastalgia, on the other hand, is not uncommon. Breast cancer must be diagnosed through physical examination, imaging, particularly mammography, and tissue biopsy. Early detection improves survival rates. The cancer spreads lymphatically and hematologically, resulting in distant metastasis and a poor prognosis. This describes and emphasises the significance of breast cancer screening programmes.[1][2][3]

Breast cancer has ranked number one cancer among Indian females with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women. Data reports from various latest national cancer registries were compared for incidence, mortality rates.[4] There are numerous risk factors such as sex, aging, estrogen, family history, gene mutations and unhealthy lifestyle, which can increase the possibility of developing breast cancer.[5]

Etiology

Identifying factors associated with an increased incidence of breast cancer development is important in general health screening for women.[6][7] Risk factors for breast cancer can be divided into 7 broad categories:

1. Age: The age-adjusted incidence of breast cancer continues to rise as the female population ages.
2. Gender: Women are more likely than men to develop breast cancer.
3. Personal breast cancer history: A history of cancer in one breast increases the risk of a second primary cancer in the contralateral breast.
4. Histologic risk factors: Histologic abnormalities discovered during a breast biopsy are a significant category of breast cancer risk factors. LCIS and proliferative changes with atypia are examples of these abnormalities.

5. Breast cancer in the family and genetic risk factors: First-degree relatives of breast cancer patients have a 2- to 3-fold increased risk of developing the disease. Genetic factors are responsible for 5% to 10% of all breast cancer cases, but they may account for 25% of cases in women under the age of 30. The two most important genes responsible for increased breast cancer susceptibility are BRCA1 and BRCA2.

6. Risk factors for reproduction: Breast cancer risk is thought to increase with reproductive milestones that increase a woman's lifetime oestrogen exposure. These include menarche before the age of 12, first live childbirth after the age of 30, nulliparity, and menopause after the age of 55. Exogenous hormone use: Therapeutic or supplemental estrogen and progesterone are taken for various conditions, with the two most common scenarios being contraception in premenopausal women and hormone replacement therapy in postmenopausal women.

Epidemiology

One in every eight women in the United States (12.4 percent) will develop invasive breast cancer during their lifetime. [8][9][10] In 2018, approximately 266,120 women in the United States will be diagnosed with invasive breast cancer, while 63,960 will be diagnosed with in situ breast cancer. In 2018, about 2550 men will be diagnosed with invasive breast cancer. One in every 1000 men will develop breast cancer during their lifetime. Breast cancer incidence in the United States began to decline in the year 2000. This decrease could be attributed to women's decreased use of hormone replacement therapy (HRT). HRT has been linked to an increased risk of breast cancer. Breast cancer is expected to kill approximately 40,920 women in the United States in 2018. Women under the age of 50 experience larger decreases. In 2008, an estimated 1.38 million new cases of invasive breast cancer were diagnosed worldwide. Female breast cancer incidence ranged from 19.3 cases per 100,000 in Eastern Africa to 89.9 cases per 100,000 in Western Europe in 2008. Early detection and significant advances in treatment have resulted in a decrease in breast cancer mortality rates in North America and parts of Europe over the last 25 years. Breast cancer death rates are rising in many African and Asian countries, including Uganda, South Korea, and India.

Pathophysiology

Breast cancer develops as a result of DNA damage and genetic mutations that can be influenced by oestrogen exposure. Sometimes DNA defects or pro-cancerous genes, such as BRCA1 and BRCA2, are inherited. Thus, a family history of ovarian or breast cancer raises the risk of developing breast cancer. In a healthy person, the immune system attacks cells that have abnormal DNA or abnormal growth. This fails in breast cancer patients, resulting in tumour growth and spread.

The discovery of KAI1

KAI1 (also called R2, C33, IA4, or 4F9) was initially identified from T-cell activation study [11]. The KAI1 gene encodes a 267 amino acid protein that contains four putative transmembrane domains [11]. Later research revealed that immuno-crosslinking of KAI1 induced intracellular calcium mobilisation in lymphocytes and T-cell adhesion, that the cell surface level of KAI1 was up-regulated in response to cell activation and cytokine stimulation, and that KAI1 played an accessory role in T-cell activation [12–14]. KAI1 was also discovered to be a target of a monoclonal antibody that inhibited syncytium formation induced by human T-cell leukaemia virus [13]. A genetic screen to identify metastasis suppressing genes led to the discovery of KAI1's role in cancer progression [115]. Human gene(s) responsible for suppressing metastasis of highly metastatic rat AT6.1 prostate cancer cells were mapped to the short arm of human chromosome 11 using microcell-mediated chromosome transfer [6]. Dong, Isaacs, and Barrett made significant progress in 1995 when they cloned the metastasis suppressor gene on human chromosome 11 p11.2–13 and named it KAI1 [17]. KAI1 is the same as CD82 [17]. KAI1 expression significantly reduces AT6.1 prostate cancer cell lung metastases while not affecting primary tumour growth [17].

KAI1 as a tumor metastasis suppressor

Although KAI1 was initially identified as a prostate cancer metastasis suppressor, a growing body of evidence supports KAI1 as a broad-spectrum invasion and metastasis suppressor during the progression of a variety of solid tumours [17–19]. KAI1 expression in tumours has been extensively studied over the last decade. KAI1 is widely expressed in normal tissues. Its mRNA levels are high in the spleen, placenta, lung, liver, kidney, and prostate, moderate in the pancreas,

skeletal muscle, and thymus, and low in the brain, heart, ovary, stomach, and uterus [17,20]. KAI1 has been shown to be evolutionarily conserved [17,20]. KAI1protein, for example, has 76 percent identity and 82 percent similarity between humans and mice [20]. Although KAI1 is important for cancer progression, its widespread tissue expression pattern and evolutionary conservation suggest that it also plays a role in development. The presence of KAI1 expression in malignant solid tumours predicts a better prognosis for cancer patients [21–24], whereas downregulation or loss of KAI1 expression is consistently found in clinically advanced cancers [22,25–28]. In line with these findings, an inverse relationship between KAI1 expression and cancer invasive and metastatic potential has been observed in a variety of cancers, including prostate [29–31], gastric[32], colon [33,34], cervix [35,36], breast [28,37], skin [38], bladder [23,27,38,39], lung [40], pancreas [41], liver [42,43], and thyroid cancers [44]. Overexpression of KAI1 inhibits cell migration and invasion in vitro and suppresses cancer metastasis in animal models [17,45]. In addition to inhibiting cancer progression, it has been reported that KAI1 induces apoptosis [46,47].

How KAI1 suppresses cancer invasion and metastasis

KAI1 controls the activities of its associated proteins. KAI1 most likely prevents cancer metastasis by inhibiting cancer cell migration and invasion. There are two possible mechanisms at work. The first is that KAI1 directly initiates signals that reduce cell motility. This mechanism is less likely due to KAI1's simple structure and the lack of an enzyme motif within its cytoplasmic domain. However, there is some indirect evidence that KAI1 may act as a signal initiator. Tetraspanin ligands, for example, may exist despite the fact that tetraspanins are not known to be typical receptors [48]. Crosslinking of KAI1 with its mAb in T-cells, for example, causes tyrosine phosphorylation of Vav1, SLP76, and Cas-L [49, 50]. However, these effects could also be explained by clustering of the KAI1-associated Tetraspanin Web. In Tetraspanin Web, KAI1 inhibits cell motility by regulating signalling initiated or mediated by KAI1 associated proteins such as integrin and EGFR. This idea is being supported by increasing evidence.

The Tetraspanin Web components that KAI1 associates with include:

(1) tetraspanins such as CD9 and CD81 [51];

(2) integrins such as b1 and b2 integrins [50,52–54],

(3) Immunoreceptors such as MHC-I and -II molecules[54–56] CD4 [54,57], CD8 [57], EWI2/PGRL[58], FPRP/CD9P-1 [59], CD19 [60], and CD46 [61];

(4) growth factors and growth factor receptors such as heparin-binding epidermal growth factor [62] and EGF receptor [63];

(5) intracellular signaling proteins such as PKC [64], and

(6) other proteins such as KITENIN [65] and gamma-glutamyl transpeptidase [66]

KAI1 and Breast Cancer

Breast cancer is the most common type of cancer in females worldwide, and it is also the leading cause of death in cancer patients in many countries. [67] KAI1 was discovered to be the specific gene responsible for the suppression of metastasis in breast cancer patients through studies. [68,69] These studies linked downregulation of the KAI1 gene to breast cancer progression and metastasis. Yang et al. (1997) demonstrated this finding by examining the levels of KAI1 mRNA in various breast cancer cell lines representing different stages of the disease, as well as normal breast cells. They discovered that the more advanced stages had lower KAI1 expression and vice versa. [68] Using immunohistochemistry and Western blot, researchers discovered that the levels of KAI1 protein in breast cancer cell lines matched those of KAI1 mRNA reported in the previous study. [69] Furthermore, similar findings were obtained after examining specimens from 81 breast cancer patients. [69] Yang et al. (2001) found that malignant breast cancer cell lines transfected with the KAI1 gene had less invasiveness and metastasis suppression. [70] This inverse relationship between KAI1 expression and breast cancer stage was also observed in Chinese, Pakistani, and Saudi patients, as well as in other studies conducted in Japan and India. [71-75]

Huang et al. (1998) discovered a link between low KAI1 expression and breast cancer recurrence. [74] A study conducted on 83 Indian breast cancer females found a significant reduction in the expression of KAI1 in metastatic cases compared to non-metastatic cases. [76] They concluded that a decrease in KAI1 expression is associated with aggressiveness and, as a result, a poor prognosis of breast cancer. As a result, the authors proposed that measuring KAI1 expression levels can be used as a prognostic marker for breast cancer and as a guide to plan therapeutic measures for those patients. KAI-1/CD82 metastasis suppressor genes were studied by Latha et al.

(2019). Though the role of KAI1 has been much understood with prostate cancer, it is not explored well in breast cancer. [75]

They looked at CD82 expression at both the transcriptional and translational levels in patients with benign and breast cancer. The relationship between KAI1 expression levels and clinicopathological parameters has been investigated. KAI1 expression [protein levels (P 0.05) and gene] was found to be significantly lower in breast cancer than in benign breast disease. Furthermore, KAI1 expression levels have been found to be strongly related to lymph node status and advanced tumour stages (P 0.05). There is no correlation between age, receptor status (ER, PR, and Her2), age, and tumour grade. The study found that the presence of lymph node metastasis and tumour staging are associated with lower KAI1 expression and can predict the prognosis of breast cancer.

Zhu and colleagues discovered that KAI1 can be regarded as a promising biomarker to predict the prognosis of many types of cancer, including breast cancer, in a recent meta-analysis of 29 eligible studies, reporting that the overall survival of cancer patients increased significantly with the positive expression of KAI1. [77] However, the authors cautioned that their findings should be interpreted with caution due to some unavoidable limitations in the meta-analysis, such as patient heterogeneity (e.g., age, tumour type, ethnicity) in the studies. In a recent study, researchers advocated for the use of noninvasive methods to diagnose and track the progression of breast cancer, such as "liquid biopsy" obtained from body fluids (e.g. blood, urine). [78]

This recommendation is based on their discovery that KAI1 is expressed on exosomes, which are excreted into body fluids, and that exosomal KAI1 has an inverse relationship with breast cancer stage; the more advanced stages showed lower expression of exosomal KAI1. A group of Saudi researchers studied the expression of KAI1 in 90 formalin-fixed breast cancer tissue obtained from Saudi patients in an attempt to investigate the mechanism underlying the downregulation of KAI1 in breast cancer, a process that precedes metastasis. [73] They used two antibodies against KAI1: one targeted the protein's carboxyl terminal and the other the large extracellular loop. Because truncated/spliced KAI1 was associated with more advanced cases of breast cancer, the study concluded that alternative splicing is the mechanism by which KAI1 is downregulated in advanced cases of breast cancer. Another KAI1 variant has been described as a mechanism for downregulation of this gene in advanced cases of breast cancer, involving the insertion of a 274-

bp intronic region between exons 8 and 9. [72] Miller et al. (2018) used video image processing to assess cell motility in the MDA-MB-231 breast cancer cell line and found that cells with the spliced variant of KAI1 had higher cell motion as well as increased cell growth and proliferation when compared to cells expressing the wild type of KAI1. [79] Another recently reported mechanism is the role of one of the GTPases, RhoC GTPase, in reducing the gene expression of KAI1 in an invasive form of breast cancer. [80] This study reported that after transfecting two breast cancer cell lines with a specific anti-RhoC GTPase, the authors observed an increase in the expression of KAI1. Interestingly, a study found a link between KAI1 downregulation and oestrogen receptor expression in breast cancer tissue. [81] They proposed that oestrogen receptor plays a role in KAI1 gene repression. The gene expression analysis with and without CD82 in microarray technique reveals the critical role of KA11 in regulating prostate cancer and suggests that it could be an effective biomarker for treatment and prevention. [82]

Discussion

Guo and colleagues discovered a significant inverse relationship between TNM stage and KAI1 mRNA expression in gastric cancer patients. Similarly, KAI1 expression was found to be inversely related to clinical stage in cervical cancer patients (P0.05). [83,84]

Malik and his colleagues discovered that early stage breast tumours (TNM1) had significantly higher levels of KAI1 transcripts than late stage tumours in a previous study on breast cancer (TNM2, 3 and 4). [85]

Shi Nae Lee et al. also reported in their study that immunohistochemical KAI-1 protein expression was decreased or negative in 39 of 50 metastasis cases (78 percent), compared to 8 of 53 cases with no metastasis (15.1 percent). There was a statistically significant difference (p0.05). KAI-1 protein immunohistochemistry expression was significantly lower in cases with higher modified Black's nuclear grade (p=0.027) and larger tumour size (p=0.039). Western blot analysis revealed positive bands at 29.5 kDa in 8 of 19 cases without metastasis (42.1 percent), but not in any of the 17 cases with metastasis (p=0.0024). Their findings suggest that, in addition to its role in the growth and progression of human breast ductal carcinoma, KAl-1 may play an important role as a metastasis suppressor gene. Furthermore, decreased expression of KAI-1 protein in breast ductal carcinomas could be used to predict poor prognosis. [86]

Conclusion

The low expression of the KAI1 might indicate a more aggressive form of breast cancer. Loss of KAI1 is taken as an important prognostic marker in forecasting the prognosis of breast cancer. However, only a limited number of studies about the role of KA11 in cancer patients is available. A better understanding of KAI1 function at the molecular level would help in developing prognostic biomarkers and therapeutics for breast cancer.

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