Review Article

S100 protein in breast tumor

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Abstract

S100 protein is the largest subtribe in calcium binding protein family. According to recent researches, abnormal expression of S100 protein is often related to tumor, including breast tumor. Breast tumor is the most common malignant disease in female with high mortality mainly due to metastasis. Estimating early diagnostic and prognostic markers are helpful to conduct treatment for patients with breast cancer. Accumulating investigations focused on the role of S100 proteins in breast tumor development and metastasis. This paper summarizes the expression situation of S100 proteins in breast tumor as well as its effects on metastasis and prognosis of breast tumor.

Key Words: Breast tumor, marker, S100 protein, tumor metastasis

Introduction

S100 protein family is a kind of calcium (Ca^{2+}) binding protein with cell and tissue specificity,[1] and it is only expressed in human and vertebrates; no S100 protein has been discovered in invertebrates till now.[2,3] It becomes well-known for being soluble in 100% ammonium sulfate solution. Except Ca^{2+}, S100 protein can also be combined with Zn^{2+}, Cu^{2+} and Mn^{2+}.[4-6] 25 members of S100 proteins have been discovered since Moore[7] separated S100A1 and S100B from cow brain in 1965;[1] their encoding genes (16 of them at least) almost distribute on the chromosome lq21.[3] Typical S100 gene contains 3 exons, in which the first exon won't code amino acid. All the S100 proteins will form homodimer and heterodimer[1] to play a role. Each S100 protein has two different EF-hand-shape structure domains; the EF-hand-shape structure domain of each S100 protein is the same at C terminal, while different at N terminal.[8] Each EF-hand-shape structure domain is composed of two spirals (E spiral and F spiral) and a link in the middle; Ca^{2+} is connected with this link,[9] and the two hand-shape structure domains are connected by a hinge region. At present, it has been reported that abnormal expression of S100 protein is related to multiple tumors, such as thyroid cancer,[10,11] renal carcinoma,[12-14] melanoma,[15-17] breast cancer,[18,19] colorectal cancer,[20-22] bladder cancer,[23,24] prostatic cancer,[25,26] lung cancer,[27-29] gastric cancer[30,31] and so on.[32]

Breast cancer is a malignant tumor that seriously affects females' physical and psychological health; it is the leading cause of cancer death among female. According to the global cancer statistics, about 1.2 million women get breast cancer every year in the world on average; and breast cancer accounted for 23% of the total cancer cases and 14% of the cancer deaths in 2008.[33] In Western countries and areas, its morbidity and death rate both take the first place among females' cancers. It is estimated that 235,030 new cases would be diagnosed, and 40,430 estimated deaths would occur in United States in 2014.[34] China is not a country in which breast cancer occurs frequently, but the annual average growth rate is about 1–2% higher than that of countries with high morbidity; it increases at a speed of 3% every year.[35-37] In cities like Shanghai, Beijing and Guangzhou, breast cancer has already become the biggest threat for women among malignant tumors. In Shanghai where the situation is the most severe, the morbidity has developed from 17/100,000 in 1972 to 52.98/100,000 currently, with the increase range exceeding 200%. Moreover, compared with Western countries and areas, breast cancer of Chinese women has characteristics of advance morbidity peak; the average occurrence age is 10 years earlier than that in foreign countries; the average age is 47 years old, and most women patients are from 40 to 49 years old.[38] There are many risk factors that might cause breast cancer, including genetic factors, environmental factors and mental factors.[39] At present, various countries are investing a large number of human resources and material resources in research on genesis and development of breast cancer, so as to take positive prevention measures.

As for breast cancer, glandular epithelial cell of the breast gets gene mutation under the action of multiple carcinogenic factors, which makes cell proliferation out of control.[40] The biological behavior of cancer cells has changed, presenting a disordered and unrestricted malignant growth. As for its histologic manifestations, a large amount of infantilized cancer cells proliferate infinitely and crowd together in disorder; it squeezes and destroys the surrounding normal tissues and damages the normal tissue structure of the breast. At present, it is demonstrated that breast cancer is related to multi-gene mutations.[41,42] This paper summarizes the function of S100 protein in breast tumor.

Expression of S100 Protein in Breast Tumor

Different types of breast cancers will express a large number of different genes at different development phases,[43,44] in which S100 protein has attracted high attention due to its high expression level. At present, it is known that abnormal expression of multiple S100 proteins is associated with breast cancer, including S100A2, S100A4, S100A6, S100A7, S100A8, S100A9, and S100A11.[18]

Different S100 proteins are also differently expressed in breast cancer, with both up-regulated expression and down-regulated expression. Currently, S100 proteins, which is up-regulated in breast tumor include S100A6, S100A7, S100A8, S100A9, S100A11, S100A15, S100P, and S100Z, while S100A2[45] and S100A4[46] are down-regulated. S100A7, S100A8, and S100A9 are expressed at a high

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level only in ductal carcinoma *in situ*.[47] Nikitenko *et al*. discovered that S100A4 mRNA had a higher expression in primary malignant breast tumor than in benign tumor specimen;[48] further research revealed that the expression of S100A4 in breast tumor microenvironment was higher than the expression in the internal part of tumor tissue.[46] However, Moog-Lutz *et al*. discovered that S100A7 was expressed in breast cancer tissue, but not in para-carcinoma tissue.[49] S100A7 is highly similar to S100A15, but only S100A15 protein is expressed in breast cancer specimen, while S100A7 is sporadically expressed.[50] In addition, S100A11 undergoes nucleocytoplasmic translocation in the development process of breast cancer, which is supposed to take effect in tumor cell proliferation.[51]

Moreover, the recent researches indicated that, hormones and inflammatory factors can regulate the expression levels of S100 in breast cancer cell: Interferon-gamma can promote expression of S100A7 in MDA-MB-468 cell by activating STAT1 pathway,[52] as well as other proinflammatory cytokines such as oncostatin-M and interleukin-6 can also induce S100A7 expression in breast cancer cell lines;[53] relaxin will restrain the expression of S100A4 in breast cancer cell line MDA-MB-231;[54] estradiol can induce expression of S100A7 in ER-positive cells.[49]

Function of S100 Protein in Tumor

Normally, after binding with Ca^{2+}, S100 protein will expose the hydrophobic amino acid residues that will combine with the target protein. Therefore, combination with Ca^{2+} is the key point for S100 protein to play a role in the process of tumor metastasis.

S100 proteins present functions both inside and outside the cell. Intracellular effects include: (1) Regulating phosphorylation level of protein, for instance, S100A4 and S100B can inhibit p53 phosphorylation and thus suppress its activity;[55] (2) adjusting enzyme activity, for example, S100A4 can regulate the matrix metalloproteinase (MMP) activity,[56,57] S100A2 will reduce the activity of cyclooxygenase-2 (Cox-2),[58] and S100A8 and S100A9 can increase the tumor cell invasion by activating p38-MAPK;[59,60] (3) controlling calcium homeostasis: The dimer of S100A2 and S100B can be used as carrier of Ca^{2+} to regulate Ca^{2+} balance in the cell;[61,62] (4) managing components of cytoskeleton, e.g. S100A4 can interact with cytoskeletal protein F-actin[63] and myosin,[64] and influence cells shape and motility through myosin;[65,66] (5) modulating activity of transcription factor; we now discover that S100A7[67] and S100B[68] can enhance activity of nuclear factor kappa B (NF-κB), while vascular endothelial growth factor (VEGF)-A, transforming growth factor-P and tumor necrosis factor-alpha will induce expression of S100A8/A9.[69] In addition, S100A2 is able to promote transcriptional activity of p53,[70] while S100A4 and S100B will inhibit the activity of p53.[55] Extracellular S100 protein mainly expresses intracellular effects as leukocyte chemotactic agent and macrophage activator[59,71] through the cell surface receptor for advanced glycation end.[72]

Sl00 Protein and Breast Tumor Metastasis

Metastasis is often the last and fatal process in the development process of tumor; different rumors will express different proteins in metastasis process and possess tissue tendency. It was reported that breast tumor tended to metastasize toward bone and lung one century ago.[73] At present, there exists a viewpoint: The specific gene expression pattern acquired at early stage of the tumor is necessary for tumor metastasis during the later stage, and there is no metastatic specific gene.[74-76] Metastasis of breast tumor will often cause death of cancer patients, and the current chemoradiotherapy can only finitely extend the survival time and relieve the symptoms of patients with tumor metastasis. Recent researches indicated that abnormal expression of S100 protein is related to metastasis of breast tumor, mainly including S100A2, S100A4, and S100A7.[77]

Plasma and tissue S100A4 protein and mRNA levels can be a potential marker for metastasis and prognosis of renal cell carcinoma,[14] due to that S100A4 is associated with tumor invasion and metastasis. Overexpression of connective tissue growth factor (CTGF) in MCF-7 cell promoted the migration ability of tumor.[78] The migration ability induced by CTGF was inhibited after knocking down S100A4 in MCF-7/CTGF cells, while would recover by transfected S100A4 into MDA231/AS cells, indicating that CTGF promoted tumor cell migration through S100A4. In addition, the results of gene expression profile of MDA-MB-435s suggested that S100A4 was related to the expression of integrin a6 β4, while integrin α6 β4 is associated with motility, invasion and metastasis ability of cells.[79] Furthermore, S100A4 and osteopontin are considered as metastasis inducing proteins; S100P is also related to osteopontin and contribute to metastasis.[80]

Expression of S100A4 in breast cancer model of rodent is related to tumor metastasis rather than tumorigenesis,[63] the expression of MMTV-neu gene and introduction of S100A4 gene in transgenic mice will obviously promote metastasis of tumor.[81] Moreover, C-terminal of S100A4 is necessary for inducing metastasis.[82] Overexpression of S100A4 in breast tumor cell will promote cell motility and invasion, and such change does not rely on the reduction of intercellular matrix.[83] According to the immunohistochemical analysis result of 312 patients with primary breast tumor after minimally invasive surgery, S100A4 presents close correlation with osteopontin ($P < 0.001$), while the latter one plays an important role in the genesis and development process of tumor.[84] Relaxin treatment on MDA-MB-231 cells for 24 h enhanced the motility of cells mediated by S100A4; however, long-time treatment of relaxin reduced the expression of S100A4, decreasing cell motility and invasion.[85] Furthermore, S100A1 can regulate the activity of S100A4,[86] as well as reduce cell motility and invasion induced by S100A4.[87]

S100A2 acts as tumor suppressor gene in some tumors, while it is tumor-promoting gene in some other tumors.[88,89] Expression of the S100A2 protein is a prognostic marker for stage I nonsmall cell lung cancer.[28] Currently, investigations

indicated that the lack of S100A2 is related to the development of malignant cells rather than the genesis of early tumors.[45] Expression of S100A2 in invasive cancer cell line can reduce their metastasis ability.[90]

S100A7 is associated with multiple invasive tumors and a marker of poor survival.[91] An mRNA Microarray and serial analysis of gene expression analysis revealed that S100A7 is closely related to MHC II and CD74 in MDA-MB-231 cell, indicating a role of S100A7 in early metastasis of breast tumor by regulating immune reaction.[92] Consistently, S100A7 can enhance MDA-MB-468 cells invasion and metastasis by activation of NF-κB signaling pathway and inducing the downstream target genes MMP-9, MMP-13 and angiogenesis associated VEGF expression.[93,94] S100A7 contains c-Jun activation domain-binding protein 1 (Jab-1) binding site, depending on which can increase the activity of NF-κB and P-Akt, as well as an increase tumorigenicity of tumor cells.[67,95] S100A7 can suppress the expression of p-HER2, P-SHP2 and p-Src in MCF-7 and MDA-MB-468 cells.[96] Al-Haddad *et al*. analyzed 57 patients with invasive breast cancer, the results indicated that S100A7 was a marker of invasive cancer with functions of chemotactic factor.[97] In addition, Kennedy *et al*. discovered that BRCA1 could regulate the expression of S100A7, and the lack of BRCA1 would result in an increase of S100A7 expression.[98]

Breast cancer is a kind of heterogeneous disorder, and different patients have obviously different prognosis and survival time. There are many factors that affect breast cancer prognosis, such as tumor size, lymphatic metastasis situation, progesterone receptor situation, and DNA-ploid situation. Through molecular classification, several molecular markers related to poor prognosis of breast cancer have been discovered. Recent researches showed that S100 protein is not only related to tumorigenesis, development, invasion and metastasis of breast tumor, but also closely associated with prognosis of tumor patients. Emberley *et al*.,[99] examined 122 patients with estrogen receptor-negative invasive ductal carcinoma, the observation supported that S100A4 was an important prognosis factor, related to survival period of tumor patients.[100,101] Moreover, Wang *et al*.,[80] carried out follow-up visit for 303 breast cancer patients for 20 years, and they found that the survival period of S100P-positive patients was 7-fold shorter than that of negative patients.

Prospective

S100 protein is a conserved protein family with highly similarity; however, the expressions are different in the development process of breast tumor. Among them, S100A2, S100A4, and S100A7 play important roles in the tumor development. With continuous deepening investigation, novel S100 protein interaction and modification will certainly be discovered, and S100 protein will also become an important diagnosis and prognosis marker gradually. However, the specific function of S100 protein in the development progression of breast tumor is unclear. It is known at present that S100 protein plays different roles in intracellular and extracellular, loss of any function will result in cancer. Intracellular S100 protein plays different roles depending on calcium level in the cell. By constructing different transgenic animal models, the functions of S100 under normal and pathological conditions can be studied. However, the molecular mechanisms of S100 protein including S100A2, S100A4, and S100A7 is still unclear at present, it is speculated that S100 protein probably plays an important role in tumorigenesis, tumor development, and metastasis through the interaction with other proteins like MMP, cytoskeletal protein, p53, Jab-1, Cox-2, and BRCA1. In addition, further study is still required in transcriptional and posttranscriptional regulation of S100 protein and the potential functions of these proteins in tumor.

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