



Review

A promising novel biomarker for embryogenesis and carcinogenesis: S100P protein

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Abstract

Objectives: Over the past decade, many great improvements have been achieved in cancer detection. Although there are many cancer biomarkers in use, unfortunately most of these biomarkers cannot yet be used efficiently for clinical purposes. Novel and reliable biomarkers are still required for the early detection and prognosis prediction of cancer. In many aspects, S100 calcium-binding protein P (S100P), a protein that is encoded by the S100P gene, is an interesting and promising marker that can enable the detection of many aggressive cancers in the early stages. S100P overexpression seems to be related to cancer aggression because of its capability to promote cell proliferation, invasion, and migration. Once we understand the molecular mechanisms better, S100P may be used as a specific biomarker and even a potential drug target for various cancers. The S100P protein is discussed in this review in relation to its functions and possible usage in the clinical area, mainly focusing on potential use in cancer research.

Keywords: Biomarker, cancer, S100P, tumor

S100 calcium-binding protein P (S100P), is a member of an interesting family, the S100 family of proteins. It is useful to start with some general information about the family, because it appears that there are thought-provoking and often inter-related functions.

1. S100 protein family

The S100 family is a family of proteins with a high degree of structural similarities; they are a small, dimeric, EF-hand (calcium-binding helix-loop-helix domains) superfamily of calcium-binding proteins that has also been shown to bind to other divalent metal ions, like Mg^{2+} , Cu^{+2} , Mn^{+2} , and Zn^{+2} [1-3]. The name was a result of their solubility in 100% saturated ammonium sulphate [4]. There are currently 25 known members of the S100 family, which are tissue-specific [2, 5, 6].

This protein family has important intracellular and extracellular roles. Some of these proteins have been determined to play a critical role in the immune system and tissue repair,

while others have been found to have a role in neuroprotection after brain injuries [7, 8].

Extracellular S100 proteins function through interacting with various cell-surface receptors, but predominantly with receptors for advanced glycosylation end products (RAGE) and/or the toll-like receptor-4 (TLR4) [9, 10]. Both receptors are known to be associated with immune inflammatory responses and tissue repair [11, 12]. Many S100 proteins, such as the S100B and S100A sub-groups, have been suspected to have both pro- and anti-tumorigenic functions in various cancers [13-18].

2. S100P protein

2.1. General information about S100P protein

S100P is a 10.4 kDa, 95-aminoacid residue, calcium-binding protein; it has 2 EF-hands, 1 with low affinity for calcium and 1 with high affinity. S100P has to be homodimeric for proper functioning [19]. Calcium-binding enables and activates its

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interactions with other proteins [1, 20]. Interestingly, S100P is only found in vertebrate species; it seems to be an evolutionarily young protein. The gene is also missing in rodents, with the exception of a few, such as the Norwegian rat and the opossum. S100P gene maps are found on the fourth chromosome (4p16) in humans. The S100P gene is known to have transcription factor binding sites for abscisic acid-responsive element binding protein 6, nuclear factor-KB (NF-KB), NF-KB1, and globin transcription factor binding protein 3 [21].

The S100P protein, since its discovery in 1992, has been studied for its roles in human embryonic development and implantation, as well as its important functions in ordinary tissue and cancer. It is thought to be a potential diagnostic and therapeutic target. The “p” in the name reflects the location of its first isolation, the placenta. Expression of the S100P protein is 90- to 200-fold higher in the placenta than in any other organ [22, 23, 20]. As might be expected, it is predominantly expressed in the early stages of gestation during placental formation, and this high level of expression continues through the first trimester of pregnancy/ It is reduced by 50% during the second and third trimesters of gestation [22, 24]. S100P has been clearly demonstrated to be an important regulator of trophoblast invasion during placentation [22, 24-26]. Interestingly, it was suspected that S100P was more dramatically related to cell invasion than cell migration. But obviously, both are affected by reducing S100P expression, and significant changes in motility and migration distances were detected, as well as a very dramatic reduction in invasion [22].

Proper migration and invasion of trophoblast cells into the maternal endometrial decidua and myometrium is tremendously important; therefore, this protein has mainly been studied for its relationships with implantation success, miscarriages, and fetal growth restriction. An increased level correlates with progesterone stimulation [27].

In healthy adult tissues, the highest S100P transcript levels have been observed in the early stages of differentiation in the esophageal epithelium, and a moderate level of expression has been detected in the stomach, duodenum and large intestine, prostate, trachea, bone marrow, and leukocytes [28]. At the protein level, the highest S100P levels have been detected in the stomach and placenta [29].

The S100P protein is mainly cytoplasmic and but seems to also be found in blood circulation. It has some membrane receptors, such as RAGE, which can be used in an autocrine manner, and this interaction is thought to be promising for future therapeutic strategies [30, 31].

2.2. Significance of S100P

S100P expression has been observed within the uterine wall during rhythmic hormonal fluctuations, and so it was intensively investigated in embryo implantation studies. During the implantation period, S100P expression may increase approximately 100 times beyond the other phases of the menstrual cycle [32-34]. It has been considered that S100P could be a po-

tentially unique biomarker of a receptive endometrium, but how S100P might encourage implantation is still unknown.

It was also discovered that S100P was expressed in various tissues during embryonic development. The expression of S100P was intense in the developing urethra, bladder, renal pelvis, developing glomerulus, spleen, and gastrointestinal tract in various stages of embryogenesis [35].

There are many currently known molecular links between the regulation of normal embryogenesis and the induction of cancer; S100P seems to be one of the proteins with roles in both embryogenesis and cancer mechanisms. There are several studies of S100P in different cancer types and it seems to be related to a poor prognosis; S100P is one of the important proteins thought to be related to metastasis. The majority of published reports describe the role of S100P in diverse human cancers, where it is increasingly recognized as a potential diagnostic and therapeutic target; however, the molecular mechanisms have not yet been defined in detail.

It seems that after binding with calcium ions, each S100P protein gains the capacity to form dimers, which are the active form of the protein, and this triggers a confirmation to bind with other proteins [36-39]. The secreted form of this dimer has autocrine and paracrine functions as it interacts with various kinds of receptors, such as RAGE, which can lead to aberrant cell proliferation and malignant transformation [30, 40, 41].

The expression of S100P is known to be influenced by several hormones; it is up-regulated in the presence of androgens, as well as progesterone, retinoic acid, bone morphogenic protein-4, and glucocorticoids [42-46].

2.3. S100P, cancer, and metastasis

It is not a surprise to observe similarities between embryogenesis and carcinogenesis; there are many known molecular links between the regulation of normal embryo development and the induction of cancer. Both have high rates of cell division and cell migration. There are many molecules that are critical for embryonic development and also play a role in the development or alteration of tumors. Important genes that have been identified as important in embryonic development are also active during cancer development. Therefore, it seems that once we understand the behaviors of embryonic cells in terms of division, differentiation, and migration mechanisms, it may be possible to control the “uncontrollable” cancer cells.

S100P protein overexpression has been detected in several malignancies, including breast, colon, prostate, lung, and pancreatic cancers. S100P appears to be a molecule that is important in both embryogenesis and carcinogenesis, particularly by stimulating the invasiveness and motility of aggressive cells [47-49]. S100P expression has been linked to the progression of malignant cells originating from various tissue sources, including the pancreas, lung, colon, and breast [50-62]. Due to its expression in neoplastic lesions and absence in most healthy tissues, S100P has been evaluated both as a potential

biomarker for the detection of several cancers and also as a cause of aggressivity and metastasis.

There are several studies investigating the role of the S100P protein in cancer and metastasis because high levels of S100P expression have been found in a variety of tumor types, such as breast cancer, esophageal cancer, cholangiocarcinoma, cervical cancer, endometrial cancer, colon cancer, ovarian cancer, and pancreatic adenocarcinoma, which are all aggressive cancers [17, 46, 57, 59, 63-65].

As a family, the S100 proteins have been shown to bind to the tetratricopeptide repeat proteins. Recently, S100P was demonstrated to contribute to the degradation of important heat shock proteins, like as Hsp70, Hsp90, and even mutated p53, and so it is thought to be important both in the stress response and in oncogenesis [66].

S100P is also known to be related to cell adhesion and involved in transducing cellular signaling pathways by interacting with important proteins, such as IQGAP1, ezrin, and integrins, and affecting microtubule dynamics, cell-to-cell contacts, and cell proliferation and transformation, motility, and invasion [67-69]. Several signal pathways were evaluated in order to further illuminate the molecular mechanisms of S100P, and it was shown to promote the phosphorylation of extracellular signal-regulated kinase (ERK) and Janus N-terminal kinase, and it was assessed as an important element of the mitogen-activated protein kinase pathway, rather than affecting their protein expression levels [69]. Its receptor, RAGE, increased, but beta-catenin expression was downregulated after S100P transfection [69-71]. It was also observed that S100P stimulated proliferation through p-ERK, p38, and NF- κ B activation, but decreased apoptosis through B-cell lymphoma-extra large upregulation [69]. This may indicate that S100P mainly has roles in bypassing cell apoptosis and increasing the percentage of G1-phase cells. It may cause high proliferation without control.

In addition to its suspected activity in tumor proliferation and invasion, S100P overexpression seems to also be associated with drug resistance in various cancers [58-60], and it may be especially important alongside some commonly used drugs, such as 5-fluorouracil, methotrexate, cyclophosphamide, and etoposide.

Conclusion

S100P protein is an interesting protein to be further investigated. Additional examination of the molecular mechanisms related to this protein may enable us to solve many problems in embryonic implantation, tissue regeneration, and oncology. Especially in the area of cancer research, further experiments and clinical follow-up studies should be conducted to identify specific targets of S100P that have oncogenic functions. S100P is a promising biomarker for use in the detection of aggressive cancers in early invasive stages and/or relapse. Since an abnormally high S100P level might be a major driving factor responsible for a poor prognosis, it may be used as

a prognostic marker, or even a marker to detect possible drug resistance. There are still many aspects of this protein to be explored and interpreted.

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