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REVIEW ARTICLE

Transcriptional regulation and functional implication of S100P in cancer

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Abstract S100P is an EF-hand calcium-binding protein that was originally identified in placenta and subsequently associated with cancer. It is a member of S100 family of proteins that function as extracellular and/or intracellular regulators of diverse cellular processes and participate in various human pathologies. S100P expression was detected in a spectrum of human tumor cell lines and tissues derived from breast, prostate, pancreas, lung and colon, where it was connected with malignant phenotype, hormone independence and resistance to chemotherapy. Overexpression of S100P was shown to promote tumorigenesis and metastasis in diverse cancer models. Functional studies of S100P indicate that its biological activities are exerted through extracellular signaling via RAGE receptor, resulting in increased proliferation and survival, or through intracellular interaction with ezrin, leading to increased cell migration and metastasis. Molecular mechanisms regulating expression of S100P in cancer cells are just emerging. Besides earlier described DNA methylation, recent studies implicate bone morphogenic protein and non-steroidal anti-inflammatory drugs in control of S100P expression during tumor progression. Functional analysis of S100P promoter identified SMAD, STAT/CREB and SP/KLF binding sites as key regulatory elements participating in transcriptional activation of S100P gene in cancer cells. Moreover, the most recent data reveal that expression of S100P is up-regulated by activation of glucocorticoid receptor suggesting that S100P could play a role in therapy resistance mediated by glucocorticoids in solid tumors. Elucidation of S100P regulation is an important step towards understanding biological significance of its tissue distribution and proposing strategies for targeted S100P modulation.

Keywords S100P · Calcium-binding protein · Transcriptional regulation · Cancer

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Introduction

S100P protein belongs to a large S100 protein family involving at least 24 members that show high sequence homology and similar subcellular localization, but differ in expression pattern and functional aspects (Marenholz et al. 2004, 2006). The S100 proteins are low molecular weight (9–14 kDa) acidic proteins that exist as intracellular or secreted homo- or hetero-dimers with composition depending on abundance of individual family members and actual cellular context (Santamaria-Kisiel et al. 2006). They operate via binding of calcium ions to two EF-hand domains, the low affinity N-terminal domain and the canonical C-terminal high-affinity domain (Donato 2003; Heizmann and Cox 1998). In response to calcium binding, the C-terminal domain undergoes refolding that exposes its hydrophobic region and thereby facilitates interactions of S100 proteins with target molecules that mediate spectrum of extracellular and intracellular effects (Heizmann et al. 2002; Santamaria-Kisiel et al. 2006). Calcium binding-mediated activation of intracellular S100 proteins is often accompanied by their relocation to nucleus, cytoplasm or sub-membrane compartments

(Mandinova et al. 1998; Mueller et al. 1999). Besides modulation of calcium homeostasis, S100 proteins can affect signal transduction pathways and influence various cellular processes, such as cell shape, motility, proliferation, differentiation and survival (Donato 2003). Their expression has been associated with several human diseases including cardiomyopathy, diabetes, neurodegenerative disorders and cancer (Heizmann et al. 2002; Marenholz et al. 2004, 2006).

S100P protein, originally isolated from placenta, is a 11 kDa molecule consisting of 95 amino acids (Becker et al. 1992). Its biochemical properties and crystal structure show significant similarities to other S100 proteins (Koltzscher and Gerke 2000; Zhang et al. 2002, 2003). S100P can form both homodimers and less stable heterodimers with S100A1 (Tutar 2006; Wang et al. 2004), it is localized in cytoplasm and/or nucleus, exists in intracellular and extracellular forms and acts in both autocrine and paracrine manner (Arumugam et al. 2005). Based on distribution in tissues and microarray analyses, its expression has been linked to tumor development. Increased levels of S100P were observed in tumor cell lines and carcinomas derived from the breast, pancreas, prostate, lung, colon and ovary in relationship with immortalized, malignant, hormone-independent and chemoresistant phenotype (Arumugam et al. 2005; Parkkila et al. 2008; Surowiak et al. 2007; Wang et al. 2006).

Expression of S100P in cancer

Abnormal expression of S100P was consistently detected in pancreatic cancer (Crnogorac-Jurcevic et al. 2003; Deng et al. 2008; Dowen et al. 2005; Logsdon et al. 2003; Missiaglia et al. 2004; Ohuchida et al. 2006). Its up-regulation was found to represent an early event in pancreatic carcinogenesis and was correlated with increasing grade of pancreatic intraepithelial lesions (Ohuchida et al. 2006). Several studies of pancreatic cancer-related molecular profiles identified S100P as a gene significantly up-regulated in pancreatic adenocarcinoma (Crnogorac-Jurcevic et al. 2003; Logsdon et al. 2003), in mucinous cystic neoplasms (Fukushima et al. 2004) and in intraductal papillary mucinous tumors of the pancreas (Terris et al. 2002).

S100P gene was also significantly associated with hormone-refractory and metastatic phenotype in prostate tumors (Hammacher et al. 2005; Mousses et al. 2002). Furthermore, expression of S100P was increased in lung adenocarcinomas and could predict distant metastasis and survival in non-small cell lung cancer (Bartling et al. 2007; Diederichs et al. 2004). In breast cancer, S100P protein was connected with immortalization and tumor progression (Guerreiro Da Silva et al. 2000; Schor et al. 2006). Survival of breast cancer patients with S100P-positive carcinomas was significantly (by about seven-fold) worse and positive staining for S100P correlated with two other metastasis-inducing proteins, S100A4 and osteopontin (Wang et al. 2006). All these studies propose possible development of S100P into a cancer biomarker and prognostic indicator for certain tumor types. However, S100P expression is not restricted to neoplastic cells, but is also detectable in various normal cell types. This fact has to be carefully considered when planning diagnostic and therapeutic applications based on S100P targeting (Parkkila et al. 2008).

Contribution of S100P to tumor phenotype

Based on increasing number of functional studies in cell lines and animal models, S100P appears to be directly involved in development of tumor phenotype. Experimental data suggest that S100P may promote cancer progression via its specific roles in cell proliferation, survival, angiogenesis and metastasis.

Overexpression of S100P in PC3 prostate carcinoma cells promotes proliferation and reduces apoptosis in vitro. Moreover, tumor formation from S100P overexpressing cells is dramatically increased when compared to controls. In contrast, silencing of S100P results in prominent cytostatic effects (Basu et al. 2008). Similar results were obtained by S100P overexpression and silencing, respectively, in two model pancreatic carcinoma cells, where S100P levels correlated with the rates of in vitro cell proliferation, survival, migration, invasion and in vivo growth of both subcutaneous and orthotopic tumors (Arumugam et al. 2005). In another pancreatic carcinoma cell line Panc1, forced S100P expression led to changes in levels and organization of cytokeratins and increased cathepsin D expression associated with increased invasive potential (Whiteman et al. 2007).

Furthermore, S100P overexpression increased angiogenesis and metastasis formation from subcutaneous xenotransplants of non-small cell lung cancer cells, whereas small hairpin RNA interference against S100P prevented metastasis formation in mice (Bulk et al. 2008). S100P was identified as a gene differentially expressed between strongly and weakly tumorigenic variants of HeLa cervical carcinoma cells and its overexpression improved spheroid formation and increased in vivo tumorigenic potential of the latter variant (Gibadulinova et al. 2005). In addition, overexpression of S100P induced invasion and metastasis formation in rat mammary model (Wang et al. 2006).

S100P and resistance to chemotherapy

Resistance to chemotherapy is often associated with expression of proteins that protect the cells from apoptosis. In accord with this concept, S100P overexpression protected pancreatic cancer cells from apoptosis induced by 5-fluorouracil (Arumugam et al. 2005) and conferred resistance to camptothecin-induced apoptosis in prostate cancer cells (Basu et al. 2008). Moreover, links between S100P and resistance of neoplastic cells to cytostatic drugs were detected also by other authors (Bertram et al. 1998; Jiang et al. 2005; Song et al. 2009; Surowiak et al. 2007).

On the other hand, chemosensitization effects of S100P level manipulation were observed in ovarian carcinoma cells treated with carboplatin and paclitaxel (Wang et al. 2008) as well as with oxaliplatin, 5-fluorouracil, etoposide and epirubicin (He et al. 2008). Understanding of these conflicting effects of S100P needs further investigation. However, it is well possible that they depend on functional cross-talk S100P with diverse drug-induced pathways in different cellular models.

Natural targets/partners of S100P

The S100P-related effects contributing to malignant phenotype are apparently mediated by regulatory molecules interacting with or induced by extracellular and/or intracellular S100P protein (Fig. 1). Among them, prominent position is held by the receptor for advanced glycation end-products (RAGE) that binds secreted

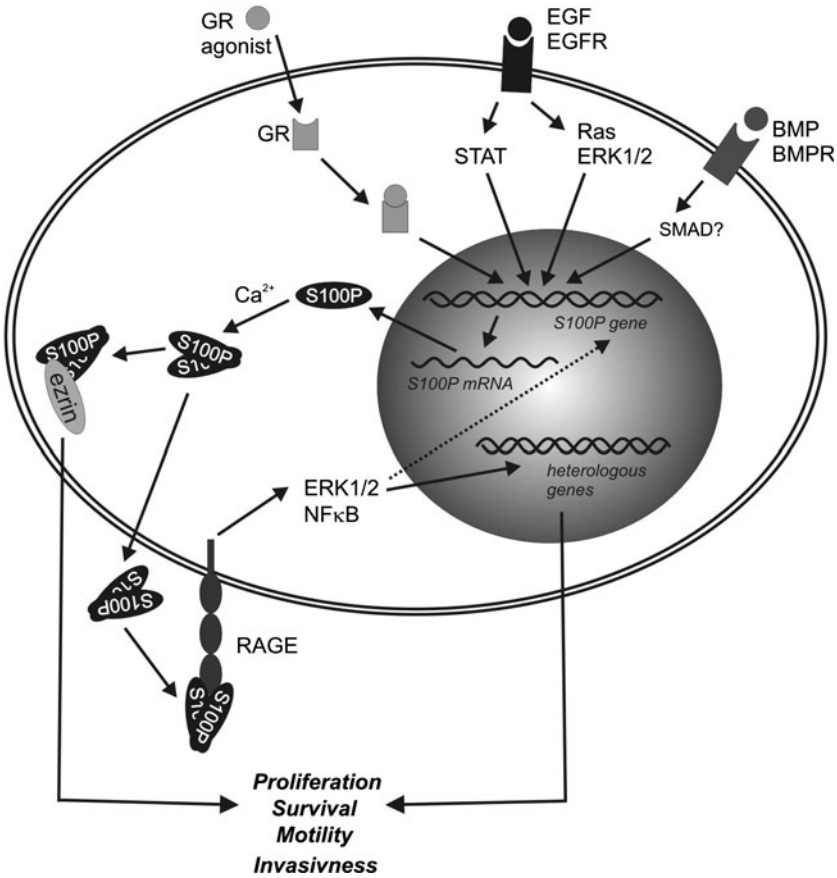

Fig. 1 Simplified illustration of S100P expression and modes of action. S100P is subjected to complex transcriptional regulation that involves different pathways activated by hormones via intracellular GR (glucocorticoid receptor), by growth factors via corresponding transmembrane receptors (EGFR epidermal growth factor receptor, and BMPR bone morphogenic factor receptor) and by other pathways that remain to be elucidated. Signals coming from these pathways appear to be transmitted through ERK1/2 (extracellular-signal regulated kinase) and mediated presumably by STAT, SMAD, NFκB transcription factors. S100P protein is expressed in an inactive "apo" state and triggered by calcium ions to form active dimers. These can operate either in intracellular manner or as extracellular signaling molecules. Inside the cell, binding of S100P to ezrin leads to activation of ezrin, which is a molecule implicated in metastasis. Secreted form of S100P can bind to extracellular ligand-binding site of RAGE (receptor for advanced glycation end-products), and via activation of ERK/MAPK pathway influences gene expression. Both intracellular and extracellular actions of S100P contribute to malignant phenotype via increased cell proliferation, survival, motility and invasion

S100P. RAGE can bind multiple ligands implicated in various diseases, including several members of the S100 protein family, such as S100A12, S100A1, S100B, and S100P (Hofmann et al. 1999; Arumugam et al. 2005; Donato 2007). S100P–RAGE interaction leads to activation of extracellular-regulated kinases (Erks) and NF-kappaB signaling consistently with increased cell proliferation, migration, survival and tumor growth (Arumugam et al. 2004, 2005; Fuentes et al. 2007). These effects can be blocked by agents that interfere with RAGE suggesting that S100P can act in an autocrine manner via RAGE.

On the other hand, intracellular S100P was demonstrated to interact with ezrin (Fig. 1), a membrane/F-actin cross-linking protein implicated in metastasis formation. The calcium-dependent S100P binding to N-terminal domain of dormant ezrin unmasks the F-actin binding site (Koltzscher et al. 2003). Resulting activation of ezrin can promote the transendothelial migration of tumor cells. It was therefore proposed that via this interaction ezrin and S100P exert their prometastatic functions (Austermann et al. 2008).

Additional binding partners of S100P were identified using co-immunoprecipitation and affinity chromatography, respectively. These include S100P binding protein S100PBPR (Dowen et al. 2005), and CacyBP/SIP, a calcyclin and Siah-1-interacting protein that can bind several S100 family members (Filipek et al. 2002). Noteworthy, CacyBP/SIP has been identified as a regulatory component of a novel ubiquitinylation complex involved in β-catenin degradation (Matsuzawa and Reed 2001) and it is very well possible that its interaction with S100P can be involved in modulation of this process.

S100P is also capable of interacting with another member of the family S100Z, expression of which appears to be deregulated in some tumor tissues (Gribenko et al. 2001) and with S100A1 (Wang et al. 2004). Unlike S100P and S100Z, which are both expressed in tumors, the S100P/S100A1 heterodimer is composed of two subunits of potentially different functions.

Subcellular localization of S100P

Data regarding subcellular localization of S100P differ and describe either nuclear/supranuclear or cytoplasmic or membrane position depending on the cell/tissue type and experimental settings (Guerreiro Da Silva et al. 2000; Parkkila et al. 2008; Sato and Hitomi 2002). It is conceivable that subcellular distribution of S100P reflects functional status of the protein and its actual interactions. Interestingly, intracellular translocation of some S100 proteins was observed in response to changes in intracellular calcium levels as well as a consequence of binding of homologous extracellular S100 protein to RAGE (Hsieh et al. 2003, 2004; Mandinova et al. 1998). In accord with this paradigm, S100P is translocated to cell periphery upon binding to ezrin (Koltzscher et al. 2003), whereas binding to S100PBPR stimulates translocation of S100P to nucleus (Dowen et al. 2005). These and similar mechanisms could explain inconsistencies in various S100P studies and suggest that S100P localization is a dynamic process. This process apparently requires dimerization because F15A mutated version of S100P that is unable to dimerize, is also incapable of translocation (Koltzscher et al. 2003).

Regulation of S100P expression

A number of microarray and immunohistochemical studies show that S100P transcription and protein expression correlate with characteristic features of malignant phenotype in various types of tissues. However, only few reports describe phenomena and/or factors that regulate S100P expression.

In the prostate carcinoma cell lines and tissues, expression of S100P depends on hypomethylation of S100P gene (Wang et al. 2007). S100P gene was identified as a hypomethylation target also in pancreatic cancer (Sato et al. 2004) and in cervical carcinoma cells (Jakubickova et al. 2005). These findings are consistent with a view that hypomethylation of cancer-promoting genes is an important molecular mechanism involved in tumor development (McCabe et al. 2009).

Furthermore, it was shown that S100P expression in prostate cancer is controlled by androgen and IL-6 via androgen receptor (Amler et al. 2000; Averboukh et al. 1996; Hammacher et al. 2005). Similarly, progestins regulate S100P via progesterone receptor in breast cancer cells (Bray et al. 2005).

Interesting connection was found between bone morphogenetic protein BMP-4 and S100P in a pancreatic cell line, where BMP-4 was shown to induce transcription of S100P, although identity and position of a regulatory element mediating this transactivation was not determined (Hamada et al. 2009). However, BMP-4 is an active component of epithelial–mesenchymal transition, an important phenomenon preceding acquisition of metastatic phenotype, and therefore regulation of S100P via BMP-4 might explain association of S100P with increased migration, invasion and metastasis.

Various NSAIDs, including celecoxib, upregulate S100P expression in human gastric carcinoma cells via activating transcription factor 4 (ATF4) involved in the endoplasmic reticulum stress response. This seemingly paradoxic effect

of anti-cancer drugs stimulating expression of cancer-related molecule might represent protective cellular mechanism responsible for reduction of therapeutic efficacy of NSAIDs (Namba et al. 2009). This view is supported by the fact that transfection of cells with S100P expression plasmid or siRNA either suppressed or stimulated anti-tumor activity of celecoxib.

In addition, regulation of S100P expression appears to involve a feedback loop in which ectopic expression of S100P at high level leads to suppression of endogenous S100P mRNA (Rehbein et al. 2008). This may serve to keep expression of S100P within certain limits compatible with optimal cell growth and survival.

Nevertheless, all these observations represent only fragments of the complex regulation of S100P. In order to shed more light on the multifaceted mechanisms of transcriptional control of S100P gene, thorough promoter investigation was initiated in our lab. In the first study, we defined transcription initiation site, cloned the 5′ upstream region of the S100P and identified the core promoter including the most important *cis*-regulatory elements with consensus sequences for STAT/CREB, SMAD and SP1/KLF transcription factors and for glucocorticoid receptor (Gibadulinova et al. 2008). These regulatory elements are compatible with the cancer-related expression pattern of S100P gene, because they respond to signal transduction pathways that are frequently activated in tumors and cross-talk (Black et al. 2001; Kassel and Herrlich 2007; Schoneveld et al. 2004). Accordingly, activity of S100P promoter is increased by EGF and hydrocortisone and decreased by inhibitors of SP-1, MAPK and PI3K pathways.

In the next step, activating effect of hydrocortisone was confirmed with another glucocorticoid dexamethasone. The induction was abolished with glucocorticoid receptor antagonist mifepristone supporting the view that the signaling was accomplished via glucocorticoid receptor (GR). Interestingly, in HeLa cells we observed co-expression of S100P and GR suggesting that S100P expression depends on presence of GR (Tothova et al, submitted). Supporting data were recently obtained by microarray analysis of HeLa cells (Kino et al. 2009) that revealed independent and cooperative regulation of S100P transcription by GR alpha and GR beta. These effects were corroborated in HCT116 colorectal carcinoma cells. It remains to be verified whether this relationship exists in a broader spectrum of cells and tissues.

Altogether, S100P gene expression is subjected to complex regulation that includes several transcription factors. With this point of view, it is difficult to propose how these pathways cross-talk and drive expression of S100P in different tumor types and situations.

Future prospects

Existing data collectively indicate that S100P protein is a functional component of cancer phenotype and that it could potentially serve as a diagnostic marker, prognostic/predictive indicator and possibly also as a therapy target (Guerreiro Da Silva et al. 2000); (Crnogorac-Jurcevic et al. 2003; Dowen et al. 2005; Mousses et al. 2001). However, the information on S100P distribution in various tissue types is still insufficient to propose meaningful strategies for these applications. Despite several microarray data, which clearly show S100P as a molecule associated with different aspects of malignancy, we are still lacking correlation studies that would reveal patterns of S100P protein co-expression with other cancer-related and signaling proteins. It would be also interesting to analyze co-expression or complementary expression of S100P and other S100 family members, particularly those associated with metastasis, such as S100A4. These correlation studies would add additional dimension to our knowledge of S100P significance in cancer.

Many aspects of S100P presence and specific roles in different cancer types await clarification though better understanding of its elaborate regulation at the transcriptional level. This would allow for directed modulation of S100P levels via interference with upstream regulatory pathways. Nonetheless, transcriptional regulation of S100P is very complicated, involves many signaling traits depending on stimulus, cell type, physiological context, levels of transcription factors, etc. and would therefore require big efforts.

In spite of this complicated background, some promising directions can be seen already at this stage. For example, relationship between the hormone activation of glucocorticoid receptor and expression of S100P could have important implications for cancer biology, because glucocorticoids are frequently used as components of many chemotherapy regimens due to anti-inflammatory effects, reduction of nausea and acute toxicity in normal tissues. However, recent data suggest that glucocorticoids may be associated with therapy resistance in solid tumors. It is believed that this is caused by decreased proliferation rates in response to glucocorticoids underlying protection of tumor cells from cytotoxic effects of chemotherapeutic drugs (Mattern et al. 2007). Indeed, also S100P was associated with therapy resistance in several tumor types. Therefore, it is possible that at least part of the effects of glucocorticoids is accomplished via increased S100P expression. From this point of view, it would be interesting to look particularly at the correlation between glucocorticoid receptor and S100P, since it might provide useful information for cancer management.

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