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Review Article

The life and works of S100P - from conception to cancer

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Abstract: Since its discovery in 1992, the small, 10.4 kDa calcium-binding protein S100P has gained the attention of researchers from different scientific fields due to its potential roles in both healthy and neoplastic tissues. Although not ubiquitously expressed, in tissues where it is present, S100P is associated with distinct changes in cellular behaviour. In this review we have summarized the evolutionary history of S100P, its expression and involvement in implantation and human embryonic development, as well as important functions in normal tissue and cancer. Finally, we have demonstrated its pivotal role as a potential diagnostic and therapeutic target, which opens promising avenues for further fruitful research on S100P.

Keywords: S100P, embryonic development, cancer

Introduction

S100P is a member of the large family of S100 calcium-binding proteins that mediate Ca^{2+} dependent signal transduction pathways [1, 2]. It was originally isolated from the placenta, (which is reflected in its name "P") by Becker et al. in 1992 [3, 4]. S100P is also relatively novel in evolutionary terms, as it is present only in the genomes of vertebrate species. The expression of this protein has been observed during the rhythmic hormonal fluctuations within the uterine wall, where it may have close association with embryonic implantation, as well as the developing embryo, and plays a functional role in a number of adult human tissues. However, a majority of the published reports describe roles of S100P in diverse human cancers, where it is increasingly recognized as a potential diagnostic and therapeutic target.

Here we present a comprehensive review of the multitude of S100P functions, which are implicated in almost all aspects of cellular behavior.

Ancestral origin

The S100 family (called so due to their solubility in 100% ammonium sulphate at neutral pH) of calcium-binding proteins comprises a large number of proteins with a high degree of structural similarity. Most have shown cell and tissue specific expression, however, some functional redundancy is also possible. Since their discovery in 1965 these proteins have been implicated in a whole host of cellular functions, both intracellularly and as secreted molecules [5, 6].

S100s are considered relatively 'young' in evolutionary terms, as they are present only in vertebrate species [7]. Over 20 S100 proteins have been identified, but the number might still increase with the rapid accumulation of novel genomic sequences of additional vertebrate species. In the human genome, 16 S100 genes (S100A1-A16) cluster in the human epidermal differentiation complex on chromosome 1q21 [8], while S100B, S100G, S100Z and S100P are present on separate chromosomes [9]. In humans, S100P gene maps on the 4th chromosome (4p16), with its homologs being found in the respective chromosomal locations in chimpanzee, dog, Norwegian rat, and opossum. Interestingly, despite being present in a wide number of mammals, including all primates with available genomic sequences, S100P is not expressed ubiquitously and the gene is missing in a number of species, including majority of rodents [9]. This can be due to either

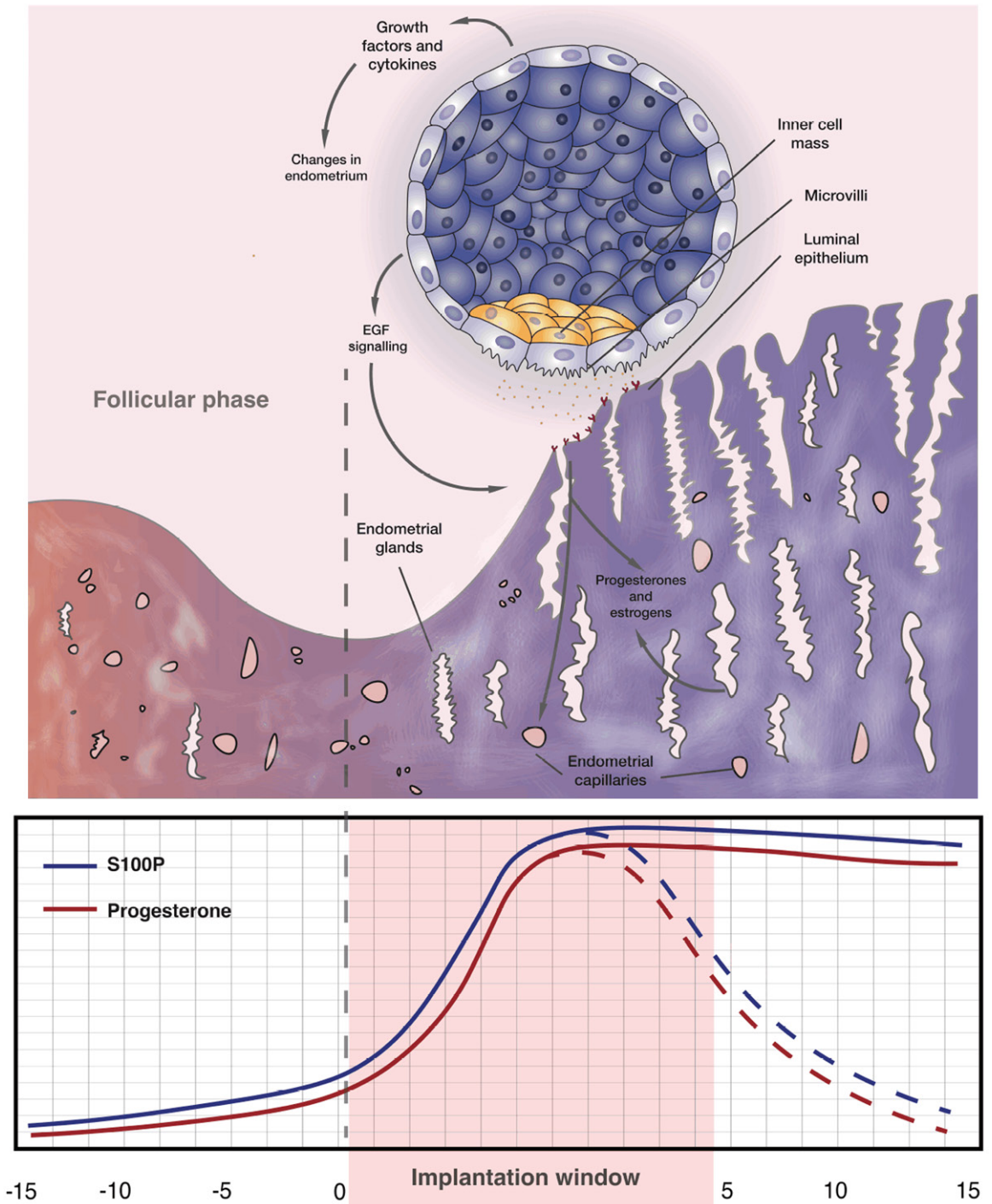

Figure 1. S100P expression during embryonic implantation. During the implantation of the human embryo, S100P expression is closely correlated with the rhythmic hormonal changes in the endometrium, particularly with the levels of progesterone (P4). When a developing blastocyst is implanted, S100P is expressed in both the trophoblastic layer of the embryo, as well as in the endometrium of the uterine wall. When implantation is not achieved, S100P expression in the endometrium returns to a basal level. The graph below the image shows a correlation between progesterone and S100P, and is represented in red and blue, respectively.

methodological issues such as incomplete genome sequencing e.g. in the cow and the fish, or due to the loss of the corresponding genome sequences during speciation.

S100P in implantation and human embryonic development

A receptive endometrium and viable blastocyst are the two necessary conditions for successful implantation, continuation of progressive cell divisions and further development of a living embryo [10, 11]. Interestingly, the rhythmic changes in receptivity of the uterine endometrium correlate with the rise of S100P levels in humans due to hormonal variation, especially with marked increase in progesterone (P4). During the implantation window, which lasts approximately four days, S100P expression surges to levels that are approximately 100 times higher than in other phases of the menstrual cycle [12-14]. This suggests that S100P is potentially a unique biomarker of a receptive endometrium. In addition, it was shown, at least *in vitro*, that expression of S100P also increases significantly in stromal cells after their co-culture with trophoblast cells [15, 16], which implies that S100P may also be involved in interactions at the maternal-fetal interface (**Figure 1**). Clearly, further exciting work to fully elucidate how S100P may encourage or even permit implantation is still awaited for.

In addition to this fundamental role, we have recently discovered that S100P is also expressed in several tissues during embryonic development (**Figure 2**). This expression was first observed in embryos in Carnegie stage 17 (CS17) onwards, initially in the urogenital sinus (**Figures 2A** and **2B**), and persisted within the structure beyond CS23, as expression was observed in post conception week 10 (PCW10). The expression of S100P then extends continuously across the epithelium both in the developing urethra and bladder (with stronger immunoreactivity observed in the bladder) (**Figures 2D** and **2F**), reaching into the lumen of the renal pelvis and to the developing glomerulus (**Figures 2G**, **2H** and **2L**). The embryos in CS19 also showed S100P expression within the allantois (**Figure 2C**), and in CS21 in the hepatic vein (data not shown). In addition to urogenital system, the S100P is also expressed within the developing gastrointestinal tract from CS17 onwards, where it was observed in the stomach and the pylorus (**Figure 2J** and **2**). This is also seen in the later stages, observed in PCW17 and PCW19 (data not shown), again in the epithelium of the stomach, and in the spleen. Further expression in embryonic development was also observed in the epithelium of the gall bladder from CS21 (**Figure 2J** and **2K**), as well as in adrenal glands in CS21 onwards and spleen in PCW14.

S100P expression in adult tissues

Among the healthy tissues, the highest S100P transcript levels have been observed in the esophagus, particularly in the early stages of differentiation of esophageal epithelium. Moderate mRNA expression has been further seen in the stomach, duodenum and large intestine, as well as in the prostate, trachea, bone marrow and in the leukocytes [17]. At the protein level, the highest S100P levels were seen in the placenta and stomach [18]. Additionally, S100P was shown to increase for a brief period within the prostate during the teenage years, after which its levels decline in adults [19].

S100P in cancer

S100P expression has been found frequently, and at high levels, in a variety of different tumor types [18]. Moreover, a wealth of experimental data from both transcriptomic and proteomic analyses, as well as from the functional assays utilizing S100P-overexpressing or silenced tumor cells both *in vitro* and *in vivo* have directly implicated S100P in cancer cell biology. **Table 1** provides a comprehensive summary of major reports documenting S100P expression and role in various cancer types.

The expression of S100P is influenced by several hormones and regulated by a number of transcription factors, and experimental observation has confirmed S100P up-regulation in the presence of androgens [20], SMAD, STAT/CREB and SP/KLF [21, 22], as well as progesterone [23, 24] and retinoic acid [25]. BMP4 has also been identified as a regulator of S100P expression in *in vitro* studies where a positive correlation was observed between the two proteins [26]. Additionally, glucocorticoids have been observed to regulate a number of transcripts, including S100P [27].

Interestingly, in metastatic and androgen refractory prostate cancer cells, a correlation between IL-6 and S100P expression has also been observed, and it has been postulated that IL-6 stimulates S100P expression [28]. Several of these S100P regulators are schematically illustrated in the left hand side of **Figure 3**, shaded in green.

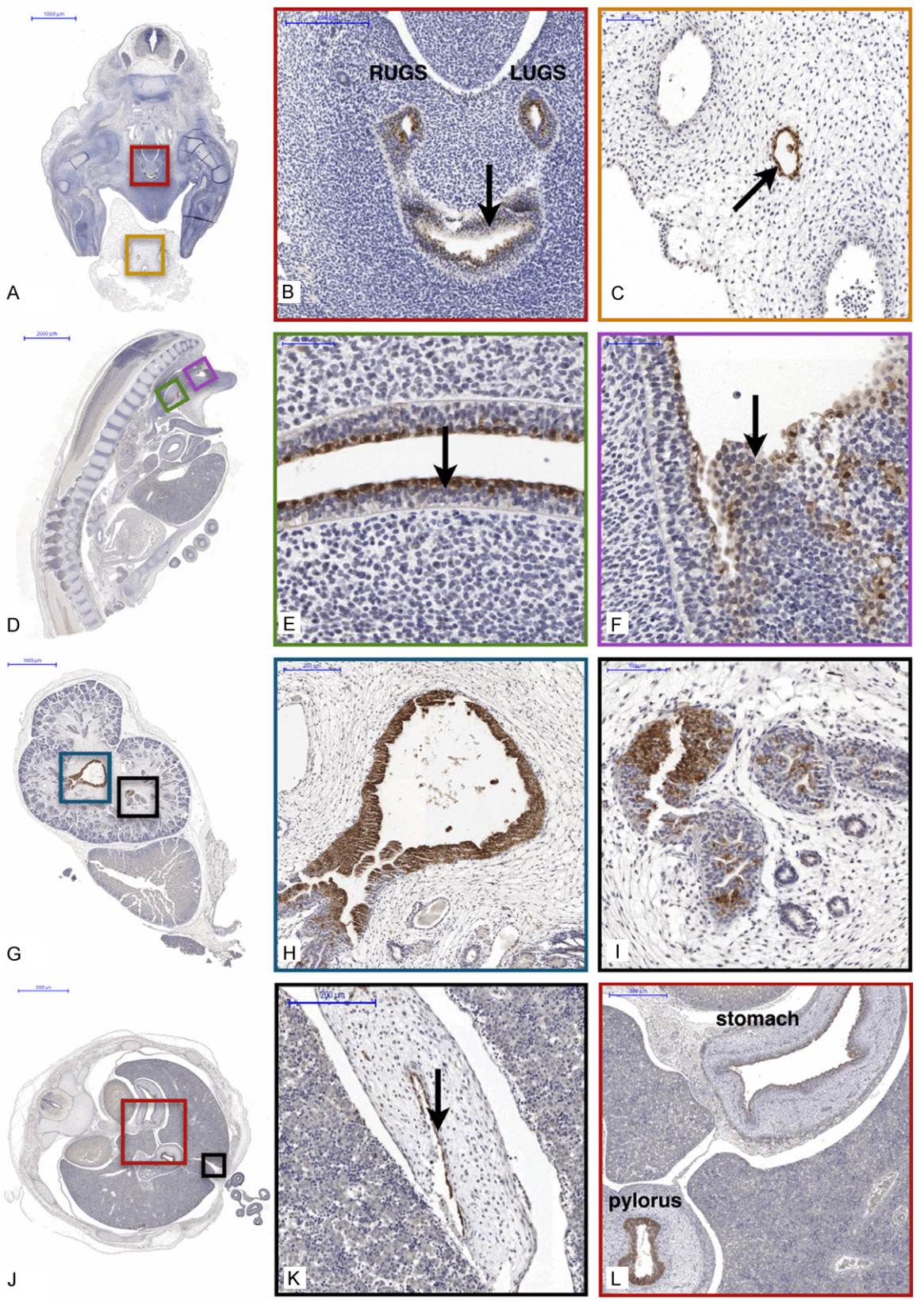

Figure 2. S100P expression in the human embryo. S100P is expressed in the right and left horns of the urogenital sinus (RUGS and LUGS), as well as in the bladder portion of the urogenital sinus (indicated by arrow) in CS17 (A, B), as well as in the allantois (C). In CS21 (D), S100P in the urethral portion of the urogenital sinus (E) shows stronger

immunoreactivity than in the bladder portion (F). In the kidney, expression of S100P is seen in the renal pelvis (G, H) as well as in the glomerulus (I) in PCW10. Further expression is seen in the gastrointestinal tract (J-L), including the gallbladder (indicated with arrow) (K) as well as the stomach and pylorus (I) in CS23.

Table 1. S100P in cancer

Basal cell carcinoma of the salivary gland	S100P is used for differentiating basal cell neoplasms from adenoid cystic carcinomas [93].
Breast Cancer	S100P is one of the markers of cancer initiation, is expressed in ductal hyperplasia, in lesions with high-risk of progression, in situ and invasive ductal carcinomas, and is associated with poor prognosis. Its expression correlates with ERBB2/Her2/neu, ER (estradiol) and P4 expression [94-102].
Cholagiocarcinoma	S100P expression is a strong indicator of the early stages of cholangiocarcinoma with increased expression correlating with progression from low to high grade biliary intraepithelial neoplasia (BilIN) [103], and is a sensitive biomarker for detecting cholangicarcinoma [70].
Cervical cancer	S100P is upregulated in all stages of cervical adenocarcinoma [104-107].
Colon cancer	S100P is highly expressed in non-dysplastic tissue from ulcerative colitis patients with high-grade dysplasia [108], and may be used to distinguish flat adenoma from normal mucosa [109, 110]. The overexpression of S100P in colorectal cancer cells promotes metastasis [111], and acts as a potential prognostic biomarker [112].
Esophageal cancer	S100P is downregulated in esophageal squamous cell carcinoma [113, 114].
Endometrial Cancer	S100P expression is higher in endometrial cancer than in normal endometrium and increases with tumor grade [38].
Gastric cancer	Immunohistochemical analysis of tissue microarray shows S100P expression in >75% of gastric cancers; its downregulation in gastric cancer cell lines leads to apoptosis and inhibition of colony-formation. In contrast, low expression of S100P is linked to poor patients' outcome [115, 116].
Hepatocellular carcinoma	S100P is a novel prognostic factor in HCC that can predict survival in patients with advanced tumor stage or early recurrences [117, 118].
Lung cancer	S100P is one of five genes found consistently deregulated in meta-analysis of 12 cDNA array studies. Its expression is observed in early stages of non-small cell lung cancer (NSCLC) and lung adenocarcinoma, and with S100A2 and trypsinogens is predictive of metastatic progression and poor survival in NSCLC [119-122].
Melanoma	S100P, RAGE and ezrin are significantly higher in melanomas than in benign nevus pigmentosus, and metastatic melanoma in comparison to the primary tumor [123].
Oral cancer	S100P is one of the salivary biomarkers in oral squamous carcinoma that can detect cancer recurrence in patients in remission [74, 124].
Ovarian cancer	High expression of S100P is correlated with shorter overall survival after chemotherapy [125, 126]; conversely, this is also noted in clear cell adenocarcinoma of the ovary which express low levels of S100P [127].
Prostate cancer	S100P is expressed in only 18.5% of prostate cancers, and its expression is significantly lower in cancer than in normal prostate and benign prostate hyperplasia [11]. However, it is one of the highest expressed genes in the androgen – independent CWR22 prostate cancer xenografts [128, 129]. Additionally, it correlates with metastatic progression of hormone refractory prostate cancer cells [130].
Pancreatic adenocarcinoma	S100P is expressed in the precursor lesions of pancreatic ductal adenocarcinoma (PDAC), as well as throughout all stages of PDAC development and progression, and is involved in growth and invasion of cancer cells [50, 131-134].
Mucinous cystic neoplasms	S100P is expressed in pancreatic mucinous cystic neoplasms (MCN) [59, 135].
Intraductal papillary mucinous tumors	Intraductal papillary mucinous tumors (IPMTs) in the pancreas are also expressing S100P [136, 137].
Urothelial cancer	S100P is a diagnostic biomarker of urothelial cancer [138, 139], and acts as a potential marker for distinguishing urothelial from squamous differentiation [140].

Structure and function of S100P

Structurally, S100P belongs to a family of small dimeric members of the large EF-hand superfamily of calcium-binding proteins, although it has been shown to bind other divalent metal ions, like Mg^{2+}, Cu^{2+} and Zn^{2+} [1, 2]. It is a 95 amino acid residue protein, comprising two EF-hands, first one with the low affinity for calcium binding and the second, canonical one, which binds calcium with high affinity. S100P monomers readily interact with one another with high affinity, and homodimer formation is deemed obligatory for S100P functions [29].

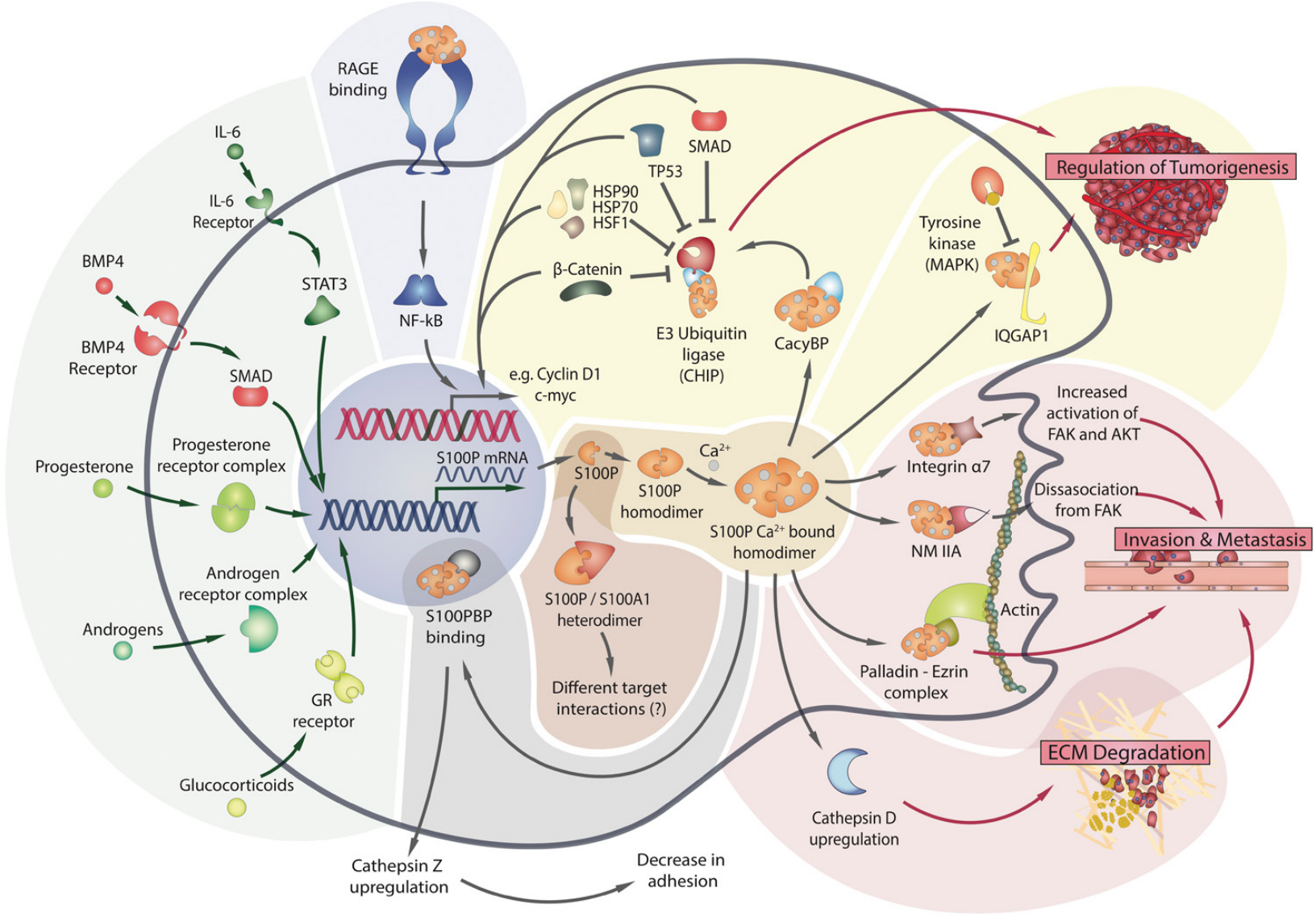

Figure 3. S100P interactions. A summary of known S100P pathways within and outside of the cell is illustrated, starting with transcriptional regulators of S100P expression (green shading). The protein is capable of forming heterodimers (in brown) as well as homodimers (in orange), with most known interactions occurring with the latter. The intercellular interactions are divided into those associated with tumorigenesis (in yellow), regulation of migration, invasion and metastasis (red shading) and translocation into the nucleus (in grey). The extracellular interaction with RAGE is shown in blue.

Binding of calcium to the EF-binding sites opens the C-terminus of the S100P protein and enables the interactions with other proteins [1, 3]. However, heterodimers of S100P with other S100s, e.g. S100A1 have also been observed [30]. The differing interfaces between S100P homodimers and S100P/S100A1 heterodimers could, through changing the conformation of the adjacent C-terminal region, potentially modulate the interaction of S100P with its target proteins, with important functional repercussions. However, this needs to be further established [30].

S100P interacts, directly or indirectly, with a number of different proteins. Through these interactions, S100P integrates and regulates various signaling pathways with a number of important functional outputs that are schematically summarized in **Figure 3**.

S100P (and several other S100s) has previously been demonstrated to bind to tetratricopeptide repeat region (TPR) domains of proteins in a Ca^{2+}-dependent manner. Recently, S100A2 and S100P were shown to interact with a TPR containing U-box E3 ubiquitin ligase CHIP ('C terminus of Hsc70- interacting protein'), resulting in inhibition of CHIP-mediated ubiquitination and proteasome degradation of Hsp70, Hsp90, HSF1, Smad1 and mutated p53 [31]. The importance of heat shock proteins not only in stress response but also in oncogenesis [32-34], Smad1 in TGF-β signaling, and multifaceted roles of p53, all testify to S100P as a powerful modifier of carcinogenesis involved in tumor cell proliferation, differentiation, apoptosis, invasion and metastasis.

The E3 ubiquitin ligase also regulates β-catenin degradation [35, 36]. β-catenin is a constituent part of a protein complex with E-cadherin and α-catenin that form the adherens junctions [37], which are necessary for the creation and maintenance of epithelial cell barriers and cell-cell adhesion; adherent junctions form a dynamic link to the actin cytoskeleton [37].

Increased S100P affects β-catenin in an additional way, through stimulation of its cytoplasmic to nuclear translocation (at least in endometrial cancer cells) where β-catenin interacts with T-cell factor/lymphoid enhancing factor (TCF/LEF), resulting in increase in the expression of Cyclin D1 and c-myc. Both of these genes are critically involved in cellular proliferation and differentiation [38, 39]. Similarly, S100P downregulation leads to a concomitant downregulation of Cyclin D1 and CDK2, resulting in suppressed cellular growth and increased apoptosis in hepatocellular carcinoma [40].

Finally, a ubiquitinylation complex comprising Siah-1, CacyBP/SIP and Skp1 proteins (CacyBP is a calcyclin i.e. S100A6-binding protein which binds several S100 proteins, including S100P), is involved in β-catenin degradation [41], suggesting that several S100s, including S100P connects calcium homeostasis with protein ubiquitinylation and degradation [42].

S100P is also an important interacting partner of IQGAP1 [43], an ubiquitously expressed multidomain scaffolding protein involved in transducing signaling pathways downstream of various cell surface receptors, such as receptor tyrosine kinases, G protein-coupled receptors and several integrins, with wide repercussions on regulation of actin cytoskeleton, microtubule dynamics, and cell-cell contacts. This is particularly important in cancer, where IQGAP1 is thought to contribute to the transformed cell phenotype by regulating signaling pathways involved in cell proliferation and transformation, weakening of cell : cell adhesion contacts, stimulation of cell motility and invasion [44]. Heil et al. have shown that after EGF stimulation of HeLa cells, which increases intracellular Ca^{2+}, S100P binds to IQGAP1 and interferes with its tyrosine phosphorylation. This impairs the B-Raf binding to IQGAP1, and through reducing the MEK1/2 intermediate, modulates MAPK signaling cascade. The interaction between S100P and IQGAP1 was shown to occur through the IQ domain of IQGAP1 and the first EF hand loop of S100P, rather than C-terminus, thus representing a new structural principle of interaction of S100P with the target protein [43, 45].

Ca^{2+}-bound S100P is known to bind to and activate dormant ezrin, a multidomain regulatory protein that links cytoskeleton to plasma membrane allowing its interaction with F-actin, which facilitated transendothelial migration of lung squamous carcinoma cells [46, 47]. Similarly, through interaction with cytoskeletal protein nonmuscle myosin II (NMIIA), increased levels of S100P reduced the number of FAS (focal adhesion sites), reducing thus adhesion

and increasing cell migration [48]. In addition, in lung cancer cells, S100P affects migration and invasion through interaction with integrin Alpha 7 (α7), which is mediated by FAK/AKT-ZEB signaling [49]. In pancreatic cancer cells, S100P was also recently shown to interact with another binding partner, S100PBP, a protein with no homology to any characterized protein, and which, through regulation of cathepsin Z and integrin αvb5 modulates cell adhesion [50, 51]. Furthermore, S100P overexpression was also shown to correlate with increased expression of another S100 family member, S100A6, as well as the aspartic protease cathepsin D, both of which are involved in migration and invasion of pancreatic adenocarcinoma cells [52].

Finally, S100P can act in an autocrine manner via Receptor for Activated Glycation End Products (RAGE) to stimulate cell proliferation and survival via the NF-kB pathway [53, 54]. S100P (along with several other S100 proteins [55]) acts as initial activator of the pathway via NF-κB/Rel complexes that translocate to the nucleus and induce the expression of a large number of diverse target genes [56]. The S100P-RAGE interaction has recently been employed as a novel therapeutic strategy and will be further discussed in the Therapeutic section of this review.

S100P and diagnostics

Due to its expression in neoplastic lesions and absence in most healthy tissues, S100P has been evaluated as a potential biomarker for detection of several cancers, most commonly using immunohistochemistry approaches. Several studies have highlighted S100P as a marker of pancreatic adenocarcinoma (PDAC) as its expression increases as precursor lesions PanINs (pancreatic intraepithelial neoplasias) progress [50, 57]; moreover, S100P has been identified as a possible marker of intraductal papillary mucinous neoplasms (IPMNs) [58] as well as mucinous cystic neoplasms [59], additional potential precursor lesions for PDAC. As a member of a panel, e.g. with mesothelin and/or KOC, S100P showed potential in correct differentiation of true PDACs from borderline cases in cytological assessment of EUS obtained biopsies or surgical resections [60-62]. S100P, mesothelin and IMP3 have also been found as useful biomarkers in gallbladder adenocarcinoma [63], as well as in extrahepatic bile duct carcinoma [64, 65].

In cholangiocarcinomas, S100P was proposed to be an effective diagnostic marker in combination with maspin, pVHL and insulin-like growth factor II mRNA-binding protein 3 in bile duct biopsies [66], in distinguishing adenocarcinoma from benign biliary epithelium on endoscopic bile duct biopsy specimens, as well as for distinguishing between cholangiolar-type intrahepatic from bile duct intrahepatic cholangiocarcinomas. Furthermore, bile levels of S100P were significantly higher in cholangiocarcinoma patients compared to those with cholelithiasis [26, 67-70].

Interestingly, S100P has also been identified as potential non-invasive biomarker of oral squamous carcinoma in saliva [71-74]. Finally, S100P has been observed in patients with early stage breast cancer, and its expression has been associated with poor prognosis and survival [75]; particularly important is its potential value as a diagnostic marker of triple negative breast cancer [76].

S100P as a therapeutic target

Because of its established functional roles in cancer, S100P has been considered a valuable therapeutic target. Several attempts have been made to inhibit either S100P, its targets, or its interactions, of which one has gained much attention recently - the interaction between S100P and RAGE [77, 78]. *In vitro* attempts to inhibit this interaction was first achieved with cromolyn, and more successfully with its 5-methyl analogue [79, 80], both of which bind to the C-domain of S100P, interfering thus with its binding to RAGE [81].

However, a recurring issue with cromolyn is lack of specificity for S100P as it binds to other S100 proteins, as well as its low biodistribution and bioavailability.

Alternative methods of inhibiting S100P, now intracellularly, have been conducted using antisense mRNA retroviral transfection in colon [82], gastric [36], breast [83], and glioblastoma [84] cancer cell lines, and have resulted in a decrease of cellular motility and metastatic potential. Finally, anti-S100P antibodies have been tested both *in vitro* and *in vivo* and have shown promising results as both single agents and in combination with chemotherapeutic drugs, such as gemcitabine in pancreatic cancer [85].

S100P expression was found to be associated with cancer resistance to several chemotherapeutic agents, and its silencing sensitized the cancer cells *in vitro* to doxorubicin [86], cisplatin [87] and oxaliplatin [88]. Furthermore, S100P has also been associated with drug resistance in gastric [89] and pancreatic cancers [90]. Therefore, blocking S100P function might also be expected to improve responses to other therapeutic treatments. However, this needs to be carefully assessed, as some conflicting reports exist, for example, in ovarian and gastric cancer cells, where, at least *in vitro*, overexpression of S100P led to sensitization of cancer cells to carboplatin and paclitaxel [91], and oxaliplatin, respectively [92].

Despite this, S100P appears to represent a potentially very effective anti-cancer target, at least for in some cancer types, and further development of anti-S100P specific therapies will likely prove to be a fruitful and productive field of investigation.

Conclusion

In this review, we have summarized the current knowledge on S100P with the addition of our own recent observations of S100P expression in human embryonic development.

Despite its relatively short evolutionary history, functions of S100P in vertebrates are vital, from involvement in the earliest steps of embryonic implantation and subsequent embryonic development to exerting the important roles in both healthy adult and cancer tissues. It is, however, for the latter, that S100P has gained most of its existing attention, as it can be potentially utilized as both a diagnostic/prognostic marker and a promising therapeutic target. Since its roles have far-reaching cross-disciplinary implications, spanning from reproductive physiology and embryonic development to inflammation and oncology, studying S100P will thus continue to be an important and fruitful research topic.

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Disclosure of conflict of interest

None.

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