

Gene Section

Review

S100A4 (S100 Calcium Binding Protein A4)

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Abstract

Review on S100A4, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: 18A2, 42A, CAPL, FSP1, MTS1, P9KA, PEL98

HGNC (Hugo): S100A4

Location: 1q21.3

Local order

The 1q21 locus harbours the epidermal differentiation complex (EDC) encompassing a 2.05 Mbp of human genomic DNA. The S100 family genes except the S100beta are arranged in the following order: 1 cen-S100A10-S100A11-THH (trychohyalin)-FLG (filaggrin)-IVL (involucrin)-LOR (loricrin)-S100A9-S100A12-S100A8-S100A7A-S100A7P1-S100A7L2-S100A7P2-S100A7-S100A6-S100A5-**S100A4**-S100A3-S100A2-S100A16-S100A14-S100A13-S100A1-1qtel. S100beta is located on 21q22.3 (Schäfer et al., 1995; Marenholz et al., 1996; Mischke et al., 1996; GeneLoc version 2.41: pseudogenes S100A7P1: HGNC 21654, S100A7P2: HGNC 21656). S100A11 pseudogenes have been listed (Pseudogenes.org); they are not shown here.

The 18A2 cDNA/mRNA (S100A4) was cloned and

its structure, translation product and tissue distribution were described by Jackson-Grusby and colleagues. The sequence of 18A2 was similar to that of the 2A9 clone described by Calabretta and colleagues.

DNA/RNA

Note

Starts 153516089 bp from pter; ends 153522612 bp from pter; 6524 bases; orientation minus strand.

Homo sapiens chromosome 1, GRCh37 primary reference assembly.

NCBI reference sequence: NC_000001.10, NT_004487.19.

Description

The human S100A4 gene has four exons. Exon 1 is non-coding and exons 2 and 3 are coding exons. Exon 2 with the start codon and encodes N-terminal EF hand and exon 3 encodes the C-terminal EF-hand. The fourth non-coding exon occurs in the 5'-UTR.

Transcription

Two variant RNA transcripts from Source Search. The NM_019554 is a longer transcript. NM_002961 possesses alternate 5'-UTR; both encode the same protein isoform.

NCBI reference sequence NM_019554 ver 01954.2 564 bp mRNA; NM_002961 ver 002961.2; 512 bp mRNA.

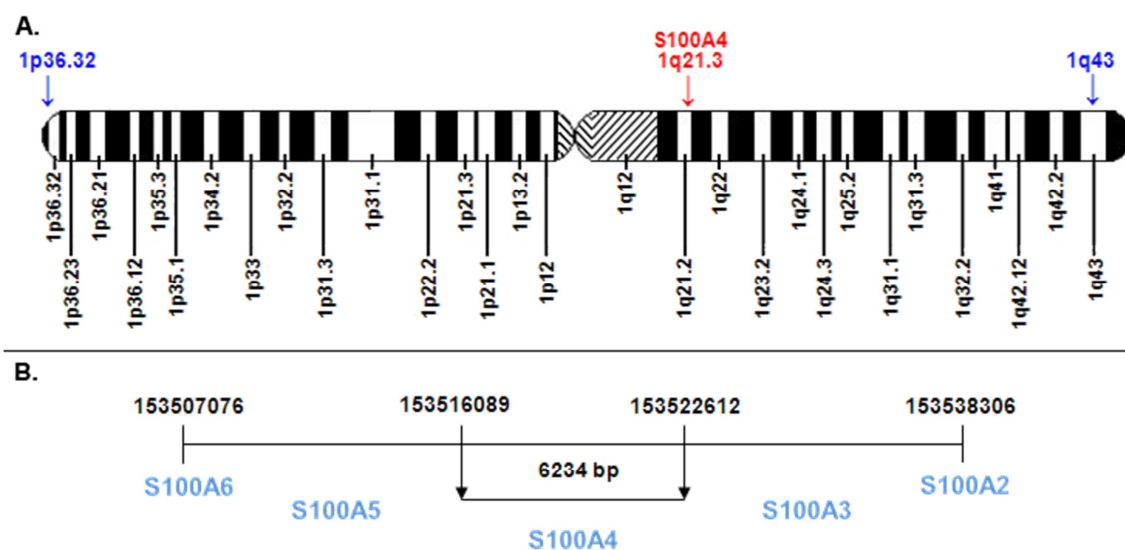


Figure 1. A. Chromosome 1 ideogram showing the location of S100A4 based on National Library of Medicine Handbook. B. The position of S100A4 is based on Entrez Gene ID 6275 (not drawn to scale).

Splice variants have been reported of S100A4. In human osteosarcoma, alternative splicing within the 5'-untranslated region (UTR) generates the two variants. Both variants, hu-mts1 and hu-mts1 (var), contain one open reading frame, differ slightly in translational capacity; possess similar stability. The hu-mts1 and hu-mts1 (var) splice variants with exons 1, 2, 3, and 4 and another with exons 1, 3 and 4, may be differentially expressed. The hu-mts1 (var) is expressed in the colon but not in the liver; it was not found in leukocytes, neutrophils, macrophages and lymphocytes. The hu-mts1 variant predominated in human breast carcinoma (SK-BR-3) and lung carcinoma (A549) is predominant (Ambartsumian et al., 1995). The differential association of the variants has been described in gastric cancers, which seems to relate to disease state possibly relates to progression; however the expression status of the variants in the lymph node metastases is not known. A splice transcript with loss of non-coding exon 1a/1b, but exons 2 and 3 present has been described in infiltrating carcinoma of the breast by Albertazzi et

al.. One would note nonetheless that Alternative Splicing and Transcript Diversity (ASTD) have listed 12 variant transcripts.

Regulation of transcription

Binding sites for several transcription factors have been identified in the promoter of S100A4. SABiosciences ChIP-qPCR Assay database lists 19 p53 binding sites.

Multiple NFAT (nuclear factor of activated T cells) transcription factor consensus binding sites; NF-kappaB related binding site (Tulchinsky et al., 1997). Much evidence is also available regarding activation of NF-kappaB by S100A4. S100A4 can activate NF-kappaB via the classical pathway mediated by MEKK/IKK β ; S100A6 and S100P also are capable of exerting pro-metastatic effects again by activating the NF-kappaB pathway. Experimentally induced expression of S100A4 is inhibited by NF-kappaB inhibitors. Aside from these, several other regulatory pathways may be identified, e.g. the Wnt/ β -catenin/TCF, HIF/HER among others, as evidenced by the established phenotypic expression induced by the gene.

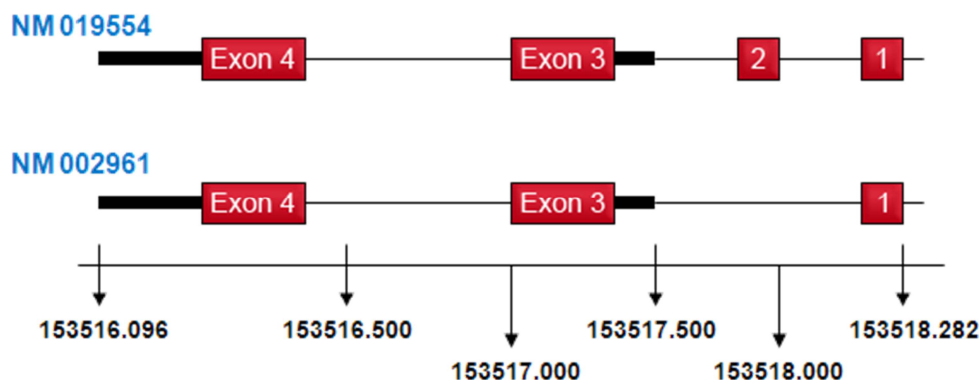


Figure 2. Based on UCSC GRCh37/hg19 Feb. 2009. Not drawn to scale.

1 macplekald vmvstfhkys gkegdkfkin kselkelltr elpsflgkrt deaafqklms
 61 nldsnrdnev dfqeycvfls ciammcneff egfpdkqprk k

Figure 3. Sequence.

S100A4 has been postulated to signal via RAGE (receptor for advanced glycation end products) which is known to activate NF-kappaB.

A composite enhancer consisting of 6 cis-elements has been identified in the first intron of murine S100A4. This interacts with Sp1 and AP-1 family members and CBF (core binding factor alpha) and KRC (zinc finger transcription factor kappa recognition component) transcription factors.

Pseudogene

None reported.

Protein

Description

Human S100A4 (also mouse and rat S100A4) contains 101 aminoacid residues and is approx 12 kDa in size. In common with most S100 family members, S100A4 is an antiparallel homodimer stabilised by noncovalent interactions between two helices from each subunit forming an X-type four-helix bundle. Each subunit has two calcium-binding EF-hands linked by the intermediate hinge region and a distinctive C-terminal extension. A pseudo-EF hand formed by helices 1 and 2 and the pseudo-EF-hand and a canonical EF-hand that are brought into proximity by a small two-stranded antiparallel beta-sheet. The hinge region and the C-terminal loop of S100 proteins are involved in target protein binding. Calcium binding produces a conformational change, which leads to the exposure of hydrophobic pocket of residues in helices 3 and 5, the hinge region and the C-terminal loop. This conformational change is required for target protein binding. S100A4 might be post-translationally modified. Charged variants conceivably resulting from post-translational changes have been described in one report, but no confirmation of these findings has been forthcoming. However, calculations from the predicted isoelectric point of S100A4 and separation of the charged variants from the major spot would suggest that two variants may have displayed 17.4 and 26.1% and a third variant with a possible highly extended form and nearly 2.6-fold increase in net negative charge. Alterations in net molecular charge of this magnitude and charge distribution can alter protein

configuration.

NCBI sequence: NM_002961; NP_002952; NM_019554; NP_062427; UniProtKB/Swiss-Prot: P26447.

Features

EF-hand domains:

EF hand 1: length 36; position 12-47,

EF hand 2: length 36; position 50-84.

Target protein interaction domains: in the active state S100A4 interacts with many target proteins e.g. p53 family proteins, HDM2, Annexin II, F-actin, tropomyosin, and heavy chain of non-muscle myosin IIA, among others. In a closed conformational state S100A4 is inactive, but the protein assumes an open conformation upon calcium binding. In the altered configuration S100A4 can interact with target proteins. These target proteins interact with specific binding domains of S100A4, which are accessible upon conformational change of the apoprotein upon Ca²⁺ binding. The Rudland/Barracough group has shown that specific mutations that inhibit self-association of S100A4 markedly reduce its metastasis promoting effects. The mutations reduce self-association and reduce the affinity of S100A4 to two target proteins viz. p53 and non-muscle myosin heavy chain isoform A. The interaction between S100A4 and target proteins can possibly also be disrupted by the packaging of S100A4 in such a way as to sequester S100A4 dimers.

Inhibition of S100A4 polymerisation by suppressing TG2 (tissue transglutaminase 2) function has resulted in the inhibition of cell migration in vitro. This is inspired by the fact that TG2 is a cross-linking protein. Treatment of cells in vitro with EGF seems to up regulate the expression of EGFR and TG2 accompanied by enhanced cell migration. S100A4 over expressing tumours not infrequently tend to be EGFR positive; so tissue transglutaminase could be promoting EGFR dimerisation and facilitate EGF/EGFR signalling.

Expression

S100A4 is distributed ubiquitously in normal tissues (Mazzucchelli, 2002).

For expression profile: Human Protein Atlas (HPA): CAB002618 and Human Protein Reference Database HPRD.

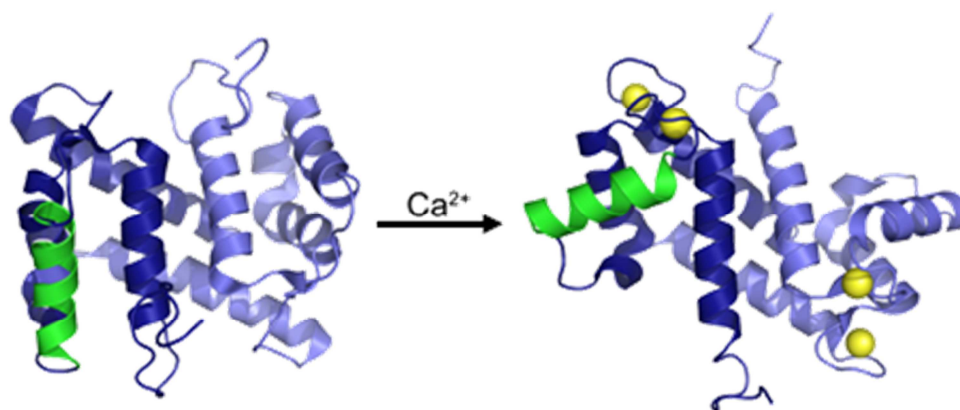


Figure 4. S100A4 undergoes a calcium-dependent conformational rearrangement that exposes the protein target binding cleft. Ribbon diagrams showing the NMR solution structure of apo-S100A4 (PDB code 1M31) and the X-ray structure of calcium-bound S100A4 (PDB code 2Q91). Following the addition of calcium (yellow spheres), helix 3 (green helix in dark blue monomer) moves to expose the target bind cleft. This conformational rearrangement is required for S100A4 binding to protein targets. The author is grateful to Anne R. Bresnick, Ph.D., Department of Biochemistry, Albert Einstein College of Medicine, Bronx, New York, for providing this illustration and the brief legend.

S100A4 occurs in many forms of human cancer, e.g. breast, colorectal, liver, lung, head and neck, ovarian, endometrial, pancreatic, renal, testicular, and prostate cancers, and melanoma; also in many cell lines of myeloid, lymphoid, lung and brain origin and cell lines derived from many forms of leukaemias. The expression of the gene is regulated by methylation. Over expression correlates with hypomethylation and the frequency of hypomethylation relates to tumour progression, e.g. in ovarian cancers. There is no implication at present that the degree of methylation is related to expression. S100A4 has been implicated in other human diseases, e.g. Crohn's disease and rheumatoid arthritis.

Localisation

S100A4 occurs extracellularly and also in cytoplasmic and nuclear location. Differential distribution has been reported between stromal components of primary and metastatic tumour. Patterns of distribution could vary between tissues and between species. No firm functional link has been made with the site/s of localisation.

Intracellular distribution is an important factor in determining genetic activity.

It may be noted here that S100A4 is often expressed in component inflammatory cells of tumour stroma. It has been postulated that interactions between the stroma and tumour cells lead to the expression of the protein and modulate its function in either or both. However, both the postulate and its potential influence in tumour progression are yet to be established.

The pattern of intracellular distribution of many genetic determinants has been found to be highly relevant to invasion and metastasis. Nuclear location of S100A4 was shown some while ago to

relate to aggressive tumour behaviour and poor prognosis. Translocation to the nucleus has been associated with EMT induced by TGF- β /Smad signalling. IL-induced translocation seems to require sumoylation of specific lysine residues and in this way conceivably regulating target gene expression. Expression patterns need to be explored in more than one tumour system. This might be crucial in the development of strategies of treatment targeting S100A4, especially with the postulated link of S100A4 expression with chemoresistance.

Function

S100A4 protein promotes metastasis, functions as a counter point to metastasis suppressor nm23, and is implicated in the regulation of the cell cycle, cell proliferation, motility, invasion, tubulin polymerisation, and angiogenesis. S100A4 might suppress expression of other suppressor genes e.g. PRDM2 and VASH1. PRDM2 (PR domain containing 2, with ZNF domain) is a tumour suppressor gene encoding a zinc finger protein. VASH1 (vasohibin 1) inhibits cell migration, proliferation and tumour growth and angiogenesis. S100A4 promotes metastatic spread of cancer as demonstrated by gene transfer studies. Its expression has shown clear correlation with tumour spread to lymph nodes and with prognosis.

Cell cycle, cell proliferation, tumour growth and apoptosis.

S100A4 binds to and forms complexes with p53 to regulate cell cycle progression. P53 has been confirmed as a target of S100A4, which stabilises p53. There is conclusive evidence that S100A4 binds to C-terminal regulatory region of p53. S100A4 and certain other members of the S100 family bind to TAD transactivation domain (residues 1-57) of p53.

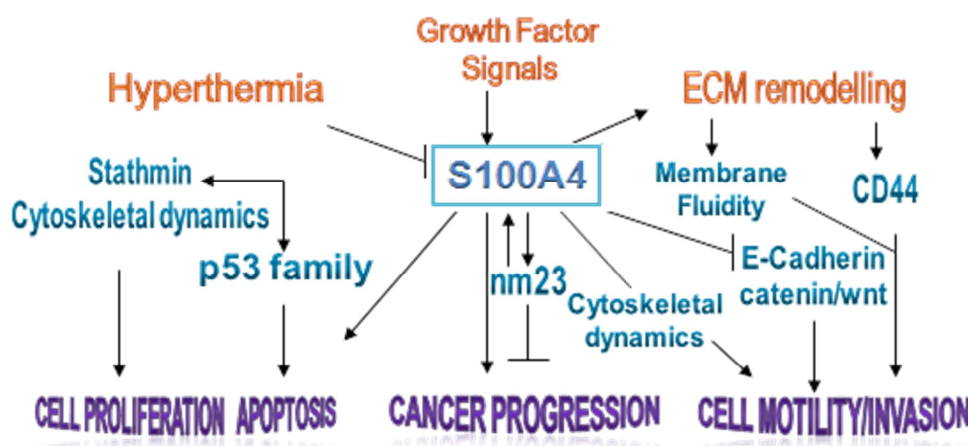


Figure 5.

They may also affect p53 function by binding to the tetramerization domain of p53 (residues 325-355) and interfering with intracellular translocation and subcellular localisation.

This interaction is suggested to be linked with p53 function. Nineteen p53 binding sites have been identified in the promoter of S100A4 (SABiosciences ChIP-qPCR Assay). S100A4 also influences waf1 ID: 139> and mdm2, a regulator of p53 function and the apoptosis family bax gene. It binds to N-terminal domain of mdm2. Signalling pathways include P53-Rb/stathmin/p53 downstream effectors, e.g. p21^{waf}, p16 etc. P53/stathmin signalling modulates microtubule dynamics and cell division. Furthermore, p53 and downstream target apoptosis family genes such as BNIP3, caspases; calpain/Fas (?) are postulated as important pathways in S100A4 signalling. Knockdown of S100A4 has been reported to lead to apoptosis. The transcription factor NF-kappaB which involved in anti-apoptosis has been implicated in S100A4 signalling.

S100A4 proliferative signalling seems to involve epidermal growth factor receptors (EGFR). EGFR expression correlates with S100A4 expression. Interactive signalling with HER2 might be postulated with the finding that S100A4 stimulates EGFR/HER2 receptor signalling and on the identification in human S100A4 promoter of an HER2 response element 1099-1487 bp up stream of the transcription start site. The interaction of S100A4 with the TGF-beta system via Smad has also been reported. S100A4 seems able to bind to the N-ter region of Smad3. TGF-beta is an important activator of epithelial mesenchymal transition leading to acquisition of invasive ability. The interaction between S100A4 and Smad thus falls in place with the metastasis-promoting function of the former. Some of these pathways are pictorially represented above (figure 5). S100A4 activates EMT via up regulation of Snail, a negative

regulator of E-cadherin. The TGF- β family receptor Activin involvement has been implicated.

Invasion, motility, and intercellular adhesion.

One of the targets of S100A4 involved in cell motility is myosin filaments. Myosin II consists of two heavy chains (MHC) with globular domains which interact with F-actin. The tail domains of heavy chains form a coiled-coil tail that participates in the assembly of myosin filaments. Wrapped round the neck region of each heavy chain are the essential and the regulatory light chains. Phosphorylation of the regulatory light chain and also of MHC plays an important part in the assembly of myosin II monomers into filaments. S100A4 inhibits CK2-mediated phosphorylation of MHC, inhibits the assembly of myosin monomers into filaments. The affinity of S100A4 for the myosin-IIA can be reduced by CK2-mediated phosphorylation. S100A4 destabilises MHCIIA filaments phosphorylated by PKC and inhibits the assembly of monomers. PKC and CK2 can phosphorylate distinct serine residues but yet be additive in their effect. The outcome is that S100A4 promotes dissociation of the filaments and prevents self assembly of monomers resulting in enhanced migration. Thus S100A4 seems to provide a mechanistic link between the actomyosin cytoskeletal and migration.

Signalling systems include modulation of cytoskeletal dynamics; cadherin/catenin complex cytoskeletal linkage and significantly a TCF, a component of the canonical Wnt signalling system, binding site has been identified in the S100A4 promoter and S100A4 directly binds heterodimeric beta-catenin/TCF complexes; CD44/cytoskeletal linkage; ECM associated proteolytic enzyme system/ECM remodelling, affects tubulin polymerisation. S100A4 and tumour suppressor nm23 exert opposite effects on tubulin dynamics. Two C-terminal lysine residues are required for enhanced motility and invasion and interaction with

target proteins. The connective tissue growth factor (CTGF) has been reported to up regulate S100A4 expression and inhibition of S100A4 blocks CTGF-induced cell motility.

S100A4 seems to function via the MMP/TIMP system in promoting invasion as well as induction of angiogenesis. S100A4 is over expressed in invasive glioma cell lines together with down regulation of TIMP-2, indicating a close linkup of S100A4 with the MMP system in the promotion of invasion.

Angiogenesis signalling occurs via activation of MMP/TIMP; activation of angiogenic factors VEGF/endothelial cell proliferation; MetAP2/p53-mediated inhibition of endothelial cell proliferation. S100A4 stimulates angiogenic signalling in breast cancer. An indirect link is suggested by the inhibition of S100A4 by Interferon-gamma which might inhibit angiogenesis by down regulating VEGF expression. Hypoxia is a major regulator of angiogenesis. HIF-1 α (hypoxia-inducible factor-1 α) is a transcription regulator in hypoxia. It can activate VEGF to induce angiogenesis and TGF- α and promotes cell survival. Exposure to hypoxia has been correlated with reduced methylation of the hypoxia response element in S100A4's promoter region and enhanced HIF binding to the promoter and increased transcription of the gene together with increased cell proliferation and invasion. Given that HIF also promotes VEGF expression one can see a potential two pronged approach to control tumour growth with HIF inhibition. Some clinical studies are underway to study the effects of Sorafenib-mediated inhibition of HIF-1 α and VEGF. In laboratory studies Sorafenib has been

found to reduce tumour growth and tumour associated microvessel density.

Osteopontin was identified as a metastasis-associated protein some time ago. Many strands of evidence suggest that osteopontin is an intermediary in S100A4 signalling pathway. In breast cancer expression of osteopontin in the background of S100A4 has generally correlated with poor patient survival.

Osteopontin is associated with several activated NF-kappaB pathways. S100A4 induces the expression and secretion of osteopontin in some osteosarcoma cell lines in an NF-kappaB-dependent fashion. Inhibition of osteopontin inhibits tumour development and angiogenesis; inhibition of both might result in synergistic suppression of tumour progression.

Shown below are the potential pathways of S100A4 signalling in cell motility/invasion and angiogenesis, emphasising the possibility that S100A4 seems able to influence many significant systems leading to angiogenesis.

Homology

Sequence homology to protein from Pan troglodytes (Chimpanzee) (Gene ID: 457320; Protein NCBI RefSeq: XP_001138744.1).

Bos taurus (Bovine) (Gene ID: 282343).

Canis lupus familiaris (Gene ID: 403787; NCBI reference sequence: NP_001003161.1; protein: NP_777020.1).

Sequence homology 93% to murine S100A4 (Entrez Gene ID 20198; NP_035441).

Sequence homology 91% to rat protein (Entrez Gene ID 24615; NP_036750).

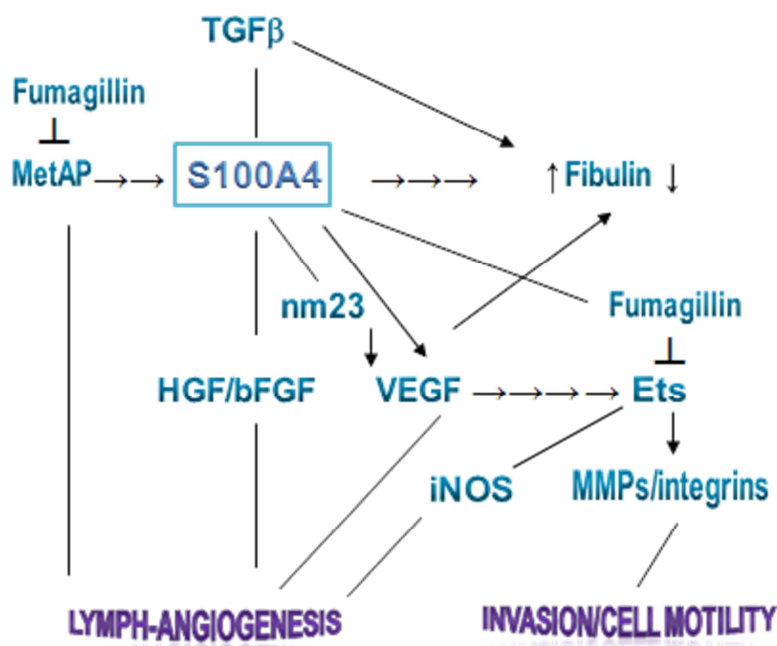


Figure 6.

Mutations

Note

Many SNPs have been identified; 7 shown in NCBI and 26 in Applied Biosystems data source. The NCBI Entrez SNP database lists 19 submissions.

Chromosomal rearrangements

The locus 1q21 is a hotspot for chromosomal rearrangements, microdeletions and duplications; significance uncertain and there are no clear implications for metastasis. No translocations leading to hybrid S100A4 have been recorded.

There are 11 common and 1 rare fragile sites on chromosome 1. The common FRA1F occurs in 1q21. Chromosome 1 is prone to sister chromatid recombination (SCR) and >70% SCRs occur at the fragile sites or in the same band as the fragile sites, but no link with S100A4 established.

Germinal

None reported.

Somatic

No simple mutations, gene fusions, or structural variants detected in breast and colorectal carcinomas and in gliomas (Cosmic: Catalogue Of Somatic Mutations In Cancer, Wellcome Trust Sanger Institute).

No mutations have been found coding regions in human, canine and feline S100A4. Mutating phenylalanine 72 to alanine reduces functional effectiveness. Toombak (tobacco rich in tobacco-specific nitrosamine) dipping (placing between the lower lip and gums) has been indirectly linked with S100A4 mutations in oral squamous cell carcinoma, but mutations have been described also in non-dippers. The carcinoma from dippers had 4 mutations (one transition, 3 transversions) and non-snuff-dippers showed 3 mutations each (one transition, 2 transversions). The suggestion is that S100A4 mutations could be complementing the effects of more frequent mutations of p53 and p21^{waf1}.

Implicated in

General notes on association with human cancer

Note

S100A4 has been implicated in the progression and prognosis of several forms of human cancer, e.g. breast, colorectal, gastric, pancreatic and bladder cancer, SCLC and oesophageal squamous cell carcinoma, among others. Poor prognosis associated with high S100A4 expression is accompanied by clear signs of disease progression, e.g. high histological and clinical grades and involvement of lymph nodes.

Also indicative of poor prognosis is high S100A4 expression coupled with reduced E-cadherin expression in pancreatic, oral squamous cell carcinoma and in melanoma. S100A4 expression is inversely related with expression of metastasis suppressor nm23 and with prognosis of breast cancer.

Cytogenetics

No cytogenetic data are available.

Abnormal protein

No fusion proteins or hybrid genes involving S100A4 are known.

Breast cancer

Note

Both tumour and serum levels are reportedly enhanced in breast cancer patients. S100A4 expression is inversely related to that of the metastasis suppressor nm23 in breast cancers. Tumour levels might correlate with proliferative state and shown to be linked with p53 dysfunction. S100A4 proliferative signalling seems to involve epidermal growth factor receptors (EGFR). Breast cancers that are high S100A4s expressers tend to be oestrogen (ER)/progesterone receptor (PR) negative.

Given that ER/PR expression is inversely related to the expression of epidermal growth factor receptors, ER/PR status together with S100A4/nm23 expression status could provide significant leads to the prediction of prognosis. S100A4 signalling could interact with HER2 function; this is suggested by the finding that S100A4 stimulates EGFR/HER2.

Up regulated expression was associated with increased tumour angiogenesis and this would be expected to contribute to the invasive spread of breast cancer.

Of some interest is the suggestion that phosphosulindac might target and induce apoptosis of breast cancer stem cells.

Prognosis

S100A4 may be regarded as an independent predictor of prognosis.

Colorectal cancer

Note

Primary cancers show enhanced S100A4 expression and associated with metastatic disease in the lymph nodes.

Up regulation of its expression has been correlated with enhanced invasion and nodal dissemination. Nuclear expression has been reported to be a prognostic indicator.

As in the case of breast cancer there are indications that S100A4 might interact with and abrogate p53 function. The implied association with aggressive

disease is underscored by the emergence of correlated expression of S100A4 with the extracellular matrix metalloproteinase inducer CD147/Basigin/EMMPRIN but a causal link is yet to be established. One should note in this context that S100A9 can also bind CD147.

Efforts are being made to inhibit Wnt/ β -catenin mediated targeting of S100A4 using sulindac.

Bladder cancer

Note

Higher expression S100A4 has been observed and this might be associated with muscle invasion.

Prognosis

High expression has been related to decreased survival.

Oesophageal squamous cell carcinoma

Note

S100A4 expression levels negatively corresponded with E-cadherin expression in ESCCs patients with metastatic disease. In vitro studies of migration of cells with experimentally enhanced S100A4 expression have lent support to the perceived relationship. Transfection of gall bladder carcinoma cell lines E-cadherin has led to the suppression of S100A4.

Ovarian cancer

Note

The expression of nuclear S100A4 expression is associated with more aggressive disease in primary carcinoma where the level of expression has been reported to be higher in solid tumours than in effusions.

Lung cancer

Note

Higher expression of S100A4 has been encountered in squamous cell but not adenocarcinoma of the lung.

Prognosis

A large study of the expression levels has revealed S100A4 to be significantly predictive of survival in squamous cell but not adenocarcinoma of the lung. S100A4 was significantly associated with patients' poor prognosis in lung squamous cell carcinoma but not lung adenocarcinoma.

Pancreatic cancer

Note

S100A4 up regulation might be accompanied by reduced E-cadherin expression. This inverse relationship has also been encountered in melanoma and oral squamous cell carcinoma cell lines. This might generate an additive effect on tumour aggression.

Perineural invasion has been associated with enhanced S100A4 expression. Worthy of note is that perineural invasion is a feature linked with tumour spread and poor prognosis and its correlation with S100A4 might have implications for disease management.

Prognosis

Some preliminary evidence is available indicating that S100A4 expression levels relate to shorter overall survival of patients with pancreatic cancer.

Gastric cancer

Note

Higher expression of S100A4 has been noted in gastric cancer and correlated with the presence of the tumour in lymph node and the occurrence of distant metastases, and with poor prognosis. Consistent with the situation in certain other forms of cancer, in gastric cancer S100A4 levels inversely relate to E-cadherin expression. Indeed, down regulation of E-cadherin has been found to occur in parallel with hypomethylation of S100A4.

Melanoma

Note

A marked inverse relationship has been described between S100A4 and E-cadherin in these tumours.

Gliomas

Note

S100A4 is over expressed in invasive glioma cell lines together with down regulation of TIMP-2, indicating a close linkup of S100A4 with the MMP system in the promotion of invasion. This ability to induce angiogenesis and metastatic dissemination could be complemented and indeed augmented by its postulated ability to enhance endothelial permeability. Occludin is a transmembrane tight-junction protein essential for maintaining integrity of both epithelia and endothelia. S100A4 is said to reduce occludin expression and could compromise in this way the integrity of the vascular endothelium. This might enhance endothelial permeability. Indeed the ability of tumours to form metastatic deposits in the brain has been attributed to possible dysfunction of the blood brain barrier. If future work provides substantive evidence for this, this might have potential implication for the management of metastatic disease. But then it ought to be recognised here that gliomas do not normally metastasise to extracranial sites. Glioma cell lines do over express S100A4, but there is little information concerning the tumours. S100A8 and S100A9 have been implicated to impede diapedesis with up regulated expression of the adhesion proteins ICAM-1 and VCAM-1. S100A4 and A9 can form heterodimers in vivo and the heterodimers carry features that resemble S100A9 homodimers in

respect of the ability to bind pro-inflammatory receptors. It is not known if S100A4 and A9 heterodimers and A9 homodimers differ with regard to effects on endothelial permeability.

Crohn's disease (a form of irritable bowel disease)

Note

S100A4 expression is increased in structure fibroblasts of fibrostenosing Crohn's disease promoting intestinal fibroblast migration.

Rheumatoid arthritis

Note

Increase S100A4 mRNA found in proliferating synovial fibroblasts. Also protein expression up regulated in rheumatoid arthritis synovial tissues and linked with joint invasion. IL-7 and S100A4 occurs in cartilage osteoarthritis and can lead to increased MMP-13 production by chondrocytes. The JAK/STAT/RAGE signalling has been implicated here.

Psoriasis

Note

Many S100 proteins are found in the dermis. S100A4 is up regulated in the dermis and colossal release of the protein has been reported. Enhanced stabilisation of p53 near cells expressing S100A4 has been noticed. It appears to affect cell proliferation and induce angiogenesis. Suppression of S100A4 using antibodies seems to suppress vascularisation of psoriatic skin xenografts, together with diminution of both number and size of blood vessels. There are no suggestions of co-operative or interactive function of S100A4 with S100A7 (Psoriasin).

Cardio-vascular, nervous and pulmonary systems

Note

The focus in this review is on the role of S100A4 in the disease process. Indeed, S100A4 is expressed in normal as well as in pathological conditions, subserves several physiological functions such as regulating macrophage motility, and participates in fibrosis and tissue remodeling in several diseased and damaged states, e.g. fibrosis of the kidney and loss of renal function, cardiac fibrosis, tissue repair and regeneration and wound healing; central nervous system injury, and pulmonary vascular disease.

S100A4 may be involved in disorders of these systems, but data currently available are somewhat fragmentary. Both S100A4 mRNA and protein are said to be up regulated in the hypertrophic hearts. Up regulation is associated with hypertrophy induced by aortic stenosis or myocardial infarction. In vitro, recombinant S100A4 protein increases the

number of viable cardiac myocytes. The ERK1/ERK2 signalling system has been found to be activated in these processes.

Two putative neurotropic motifs have been identified in S100A4 and neuroprotective function has been attributed to the protein.

S100A4 might be associated with PAH (pulmonary arterial hypertension) and putatively linked with 17 β -oestradiol modulated S100A4/RAGE signalling. A clinical trial is underway at present to study S100A4 as a marker in PAH treatment (NCT01305252).

Breakpoints

Note

A 1q21 breakpoint was described some time ago in renal cell carcinoma (RCC)-associated (X;1)(p11;q21) translocation. This has been mapped to the S100 gene cluster, but its link with S100A4 is uncertain. No translocations involving S100A4 have been recorded. No fusion proteins or hybrid genes involving S100A4 are known.

There are 11 common and 1 rare fragile sites on chromosome 1. The common FRA1F occurs in 1q21. Chromosome 1 is prone to sister chromatid recombination (SCR) and >70% SCRs occur at the fragile sites or in the same band as the fragile sites, but no link with S100A4 has been established.

To be noted

Note

S100A4 expression has been linked with chemoresistance, but the mechanisms involved remain to be elucidated. Whether this occurs via engagement of RAGE by S100A4 and activation of RAGE signalling leading up to chemoresistance is an avenue yet to be explored.

S100A4 activates interacting and multi-functional signalling systems, including EMT signalling systems such as Wnt/ β -catenin, NF- κ B, and E-cadherin among others, highly relevant in the context of cancer. Mediation of its function by osteopontin and potential function of S100 family proteins to act as RAGE ligands are important considerations. These would make S100A4 an eminently valuable chemotherapeutic target. Some downstream effectors of the S100A4 pathways might also lend themselves as targets of interest.

The diversity of biological effects flowing from the inappropriate expression of S100A4 and interactions of S100A4 signalling with several systems which modulate biological response would merit investigations into suppressing S100A4 expression as a possible therapeutic approach. S100A4 function is allied with growth factor and steroid hormone receptors and osteopontin which is itself subject to regulation by Wnt, NF- κ B

among others, so here is ample provision of options available for therapeutic studies. Also the perceived link up between EMT and S100A4 expression affords fresh avenues of approach.

The antihelminth drug Niclosamide which targets the Wnt/ β -catenin pathway can suppress S100A4 expression with parallel inhibition of cell proliferation, migration, promotion of apoptosis, and metastatic spread in vitro and xenograft tumour models.

Xanthohumol is a prenylflavonoid antioxidant, derived from the female flowers of the hops plant (*Humulus lupulus*). It was identified to possess anticancer properties some while ago. Recent work has shown its ability to suppress cell proliferation, invasion and tumour progression. The flavonoid has been found to inhibit proliferation and invasion in many breast cancer cell lines, including the triple negative breast cancers MDA-MB-231 cells. It induces apoptosis and might be functioning by inhibiting Akt and NF- κ B activation. The postulated suppression of tumour progression by Xanthohumol is based on assays purportedly resembling intravasation of tumour emboli through defects in the endothelial barrier, so needs much further scrutiny. It would be necessary to perform in vivo studies, ethically undesirable they might be, and ascertain these claims by using stringent criteria to evaluate intravasation of tumour cells and formation of metastases.

It may be noted here that Xanthohumol is said to inhibit cell motility and EMT activation and this is accompanied by inhibition of S100A4 among other determinants. Also of interest is that Xanthohumol induces apoptosis which is caspase-mediated and requires Annexin I. This might be of particular interest since S100A4 as well as other S100A proteins bind to and regulate the function of many target proteins which include annexins. Disruption of Annexin/S100A11 alters the phenotypic behaviour. Annexins display divergent effects on cell proliferation, apoptosis and invasion. The effects may relate to whether the specific S100A is a tumour promoter or suppressor. It would be needless iteration that further investigation is warranted. A clinical study of its pharmacokinetics has been undertaken (NCT01367431).

Phenanthrenes are a class of compounds originally obtained from various members of Orchidaceae and described to possess cytotoxic, antimicrobial and anti-inflammatory activity. They may be therapeutically important in preventing metastasis by inhibiting the interaction of S100A4 with its target molecules (see Bresnick AR patent WO2011146101 A1).

The induction of motility response to S100A4 seems to be mediated by Rho signalling. Rho, Rac and Cdc42 are most prominent players in cytoskeletal reorganization and modulation of cell

motility. Of this RhoA has been linked with membrane ruffling and cell motility. Recently S100A4 has been shown to bind to Rhotekin, a RhoA interacting scaffold protein, via the RBD (Rho binding domain), but Rho and S100A4 seem to bind to different residues of RBD. The Rho-Rhotekin-S100A4 complex generates the invasive phenotype. At the practical level it is worthy of note and future pursuit that Paclitaxel at low doses well below therapeutic levels has been shown to inhibit S100A4 in the nuclear compartment and in parallel reduce cell migration and invasion in vitro of human cholangiocarcinoma cells in a Rho-GTPase mediated manner.

Membrane bound mucins such as MUC16 (CA125) and MUC2, MUC4, MUC13 have been associated with cancer malignancy. MUC16 is associated with the formation of peritoneal metastases in ovarian cancer. MUCs 2 and 13 are over expressed in pancreatic cancer. MUC4 is overexpressed in oesophageal, lung and colon cancer. Its expression correlates with progression of pancreatic cancer. Experimental suppression of MUC4 in oesophageal cancer cells by shRNA reduces S100A4 expression and reduces cell proliferation and tumorigenic ability as compared with MUC4 expressing parent cells.

The causal linkup is not established; however being integral membrane glycoproteins possibly they anchor S100A4 to the cell membrane and interferes with activation of S100A4 signalling pathways. Growth factors are known to induce phosphorylation of the cytoplasmic domain of MUC1 and activate nuclear localization of MUC1 and β -catenin and participate in growth factor signalling.

Little is known about the involvement of the immune system in relation to S100A4 function, but there are indications that it may be recruited to NK cell immune synapses and possibly contribute to immune synapse formation. Whether S100A4 participates in restraining NK lytic function or promotes the formation and function of inhibitory synapses is uncertain. The cytoplasmic Src kinases regulate the activating or inhibitory pathways and it has been suggested S100A4 might be capable of influencing the operation of these pathways. CTLs and NK cells induce apoptosis via the pore forming protein perforin and granzyme B pathway. S100A4 may not be involved in this apoptosis pathway, but could be involved in the FasL pathway.

The non-steroidal anti-inflammatory agent sulindac has been found to interfere with Wnt signalling. The β -catenin/TCF transcription complex targets and regulates S100A4. Using an in vivo model involving intrasplenic xenografting of colon cancer cells, sulindac has been shown to down regulate S100A4 promoter activity and expression together with inhibition of Wnt/ β -catenin signalling.

Phosphosulindac is said to target breast CSCs in vitro and induce apoptosis.

Sulindac is currently being investigated in clinical trial on advanced stage IV colorectal cancer (NCT01856322).

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