Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

S100A4 (S100 calcium binding protein A4)

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Published in Atlas Database: March 2011

Online updated version : http://AtlasGeneticsOncology.org/Genes/S100A4ID42192ch1q21.html
DOI: 10.4267/2042/46036

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 (profilaggrin)-IVL (involucrin)-LOR (loricrin)-S100A9-S100A12-S100A8-S100A7-S100A6-S100A5-S100A4-S100A3-S100A2-S100A13-S100A1-1qtel.
S100beta is located on 21q22.3 (Schäfer et al., 1995; Marenholz et al., 1996; Mischke et al., 1996).

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.

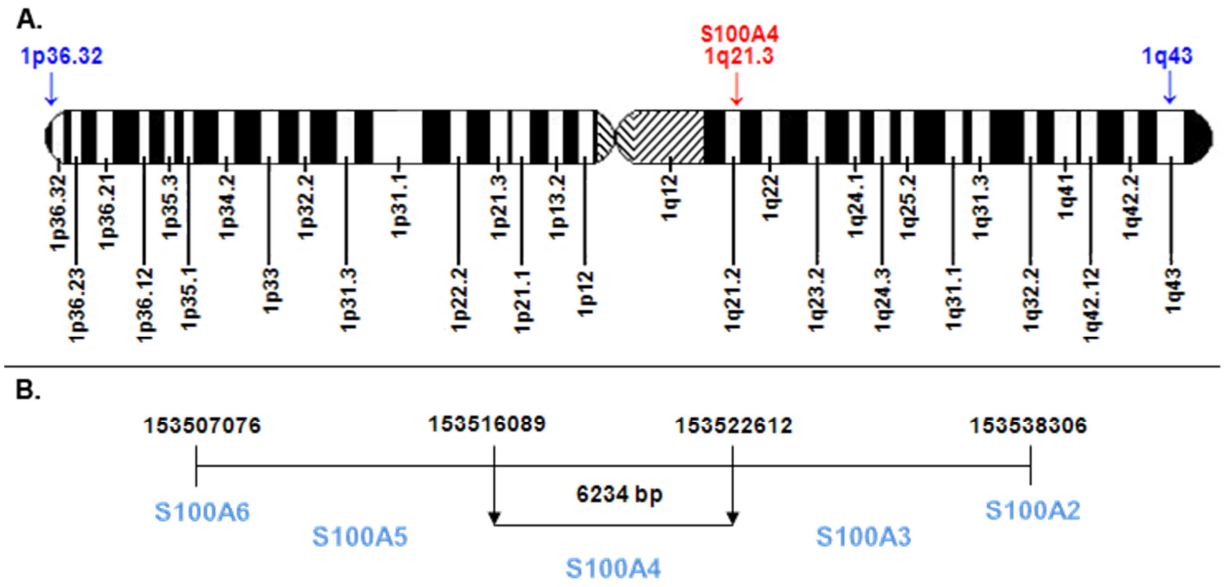

Figure 1. A. Chromosome 1 ideogram showing the location of S100A4 based on National Library of Medicine Handbook. **B.** The position of S100A4 is based on Entrez Gene ID 6275 (not drawn to scale).

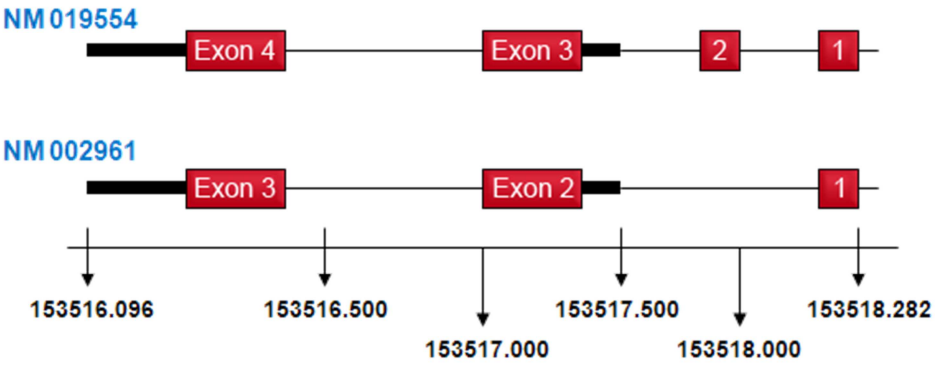

Figure 2. Not drawn to scale.

1 macplekald vmvstfhkys gkegdkfkln kselkelltr elpsflgkrt deaafqklms

61 nldsnrdnev dfqeycvfls ciammcneff egfpdkqprk k

Figure 3. Sequence.

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.

Splice variants have been reported of only S100A4 among the S100 family. 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. 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. Splice variant with exons 1, 3, and 4 and another with exons 2 and 3, may be differentially expressed in non-malignant and malignant tissues. 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 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.NCBI sequence: NM_002961; NP_002952; NM_019554; NP_062427; UniProtKB/Swiss-Prot: P26447.

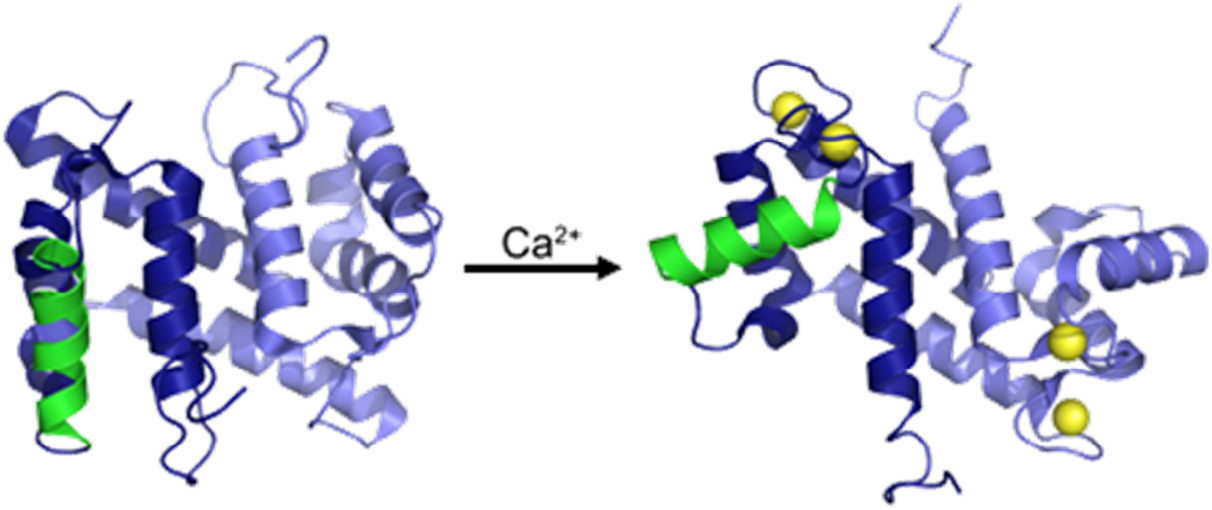

Figure 4. S100A4 undergoes a calcium-dependent conformational rearrangement that exposes the protein target binding cleft. Ribbon diagrams showing the NMR solution structure of apo-S100A4 (PDB code 1M31) and the X-ray structure of calcium-bound S100A4 (PDB code 2Q91). Following the addition of calcium (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.

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 the heavy chain of non-muscle myosin IIA, among others. These target proteins interact with specific binding domains of S100A4, which are accessible upon conformational change of the apoprotein upon Ca^{2+} binding.

Expression

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

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

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. S100A4 has been implicated in other human diseases, e.g. Crohn's disease and rheumatoid arthritis.

Localisation

S100A4 occurs extracellulary 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 as well between species. No firm functional link has been made with the site/s of localisation. 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 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 target of S100A4, which stabilises p53. 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. 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 p21waf1 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 down stream effectors, e.g. $p21^{waf}$, p16 etc. P53/stathmin signalling modulates microtubule dynamics and cell division. Furthermore, p53 and down stream 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.

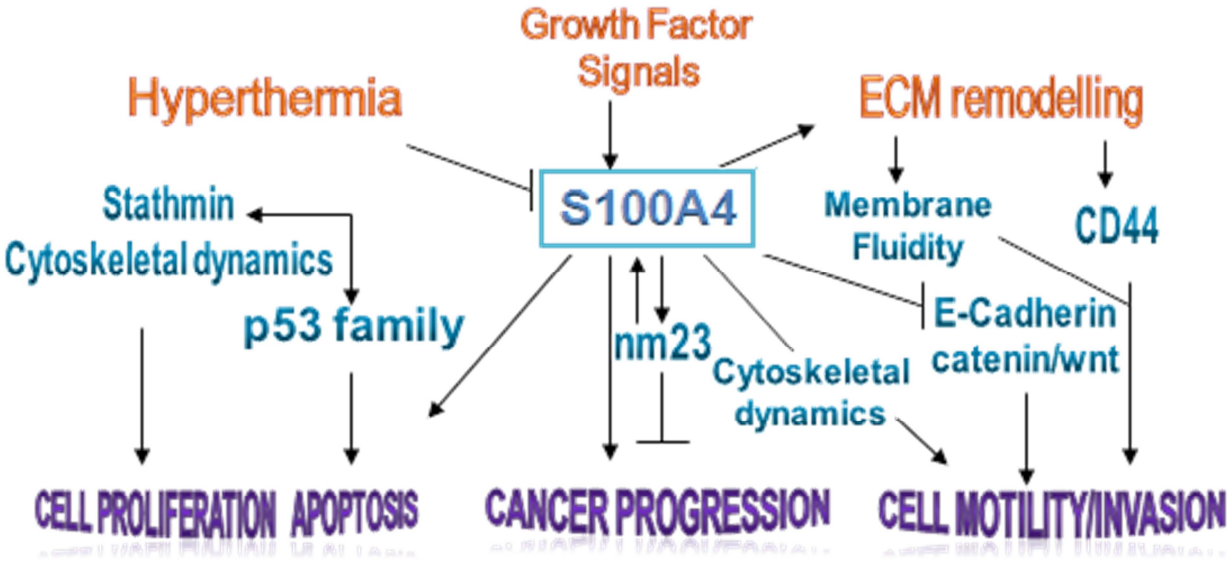

Figure 5.

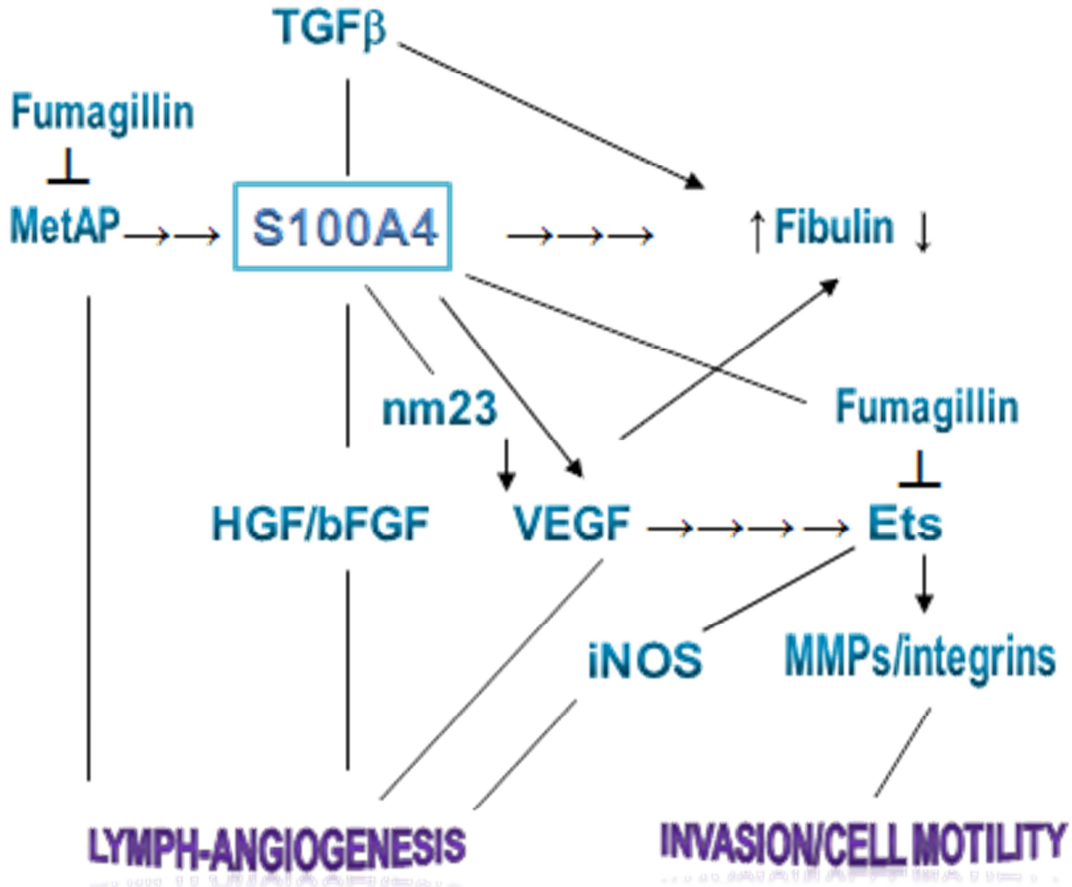

Figure 6.

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).

Invasion, motility, and intercellular adhesion. 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.

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. 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).

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, Welcome 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 dipping (placing between the lower lip and gums) has been 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).

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 seem to be able to 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 ability of breast cancer.

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, 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.

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.

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 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.

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.

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 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.

Cardio-vascular, nervous and pulmonary systems

Note

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 occurs is associated with hypertrophy induced by aortic stenosis or myocardial infarction. In vitro, recombinant S100A4 protein increases the density viable cardiac myocytes. The ERK1/ERK2 signalling system has been found to be activated in these processes.

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.

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This article should be referenced as such:

Sherbet GV. S100A4 (S100 calcium binding protein A4). Atlas Genet Cytogenet Oncol Haematol. 2011; 15(10):877-886.