

Gene Section

Review

S100A2 (S100 calcium binding protein A2)

Christopher J Scarlett, Andrew V Biankin

Cancer Research Program, Garvan Institute of Medical Research, 384 Victoria St Darlinghurst, NSW 2010, Australia (CJS, AVB)

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Identity

Other names: CAN19, MGC111539, S100L

HGNC (Hugo): S100A2

Location: 1q21.3

DNA/RNA

Description

The nucleotide sequence and genomic organization of the S100A2 gene was originally described by Wicki et al. (1997), using a normal and a tumorigenic breast epithelial cell line. The structure of S100A2 was originally deduced by the analysis of cDNA from a positive genomic clone from an EMBL-3 SP6/T7 human female peripheral blood leukocyte genomic library (Clontech, no. HL 1111j). The human S100A2 gene is located next to the S100A4 locus on chromosome 1q21.3 within a cluster of S100 genes (Wolf et al., 2011), and part of the epidermal differentiation complex (Wolf et al., 2011). The S100A2 gene spans a total region of 4723 bp (NM_005978.3) consisting of three exons. The three-exon-structure contains the coding sequence within exons two and three, reflecting the common

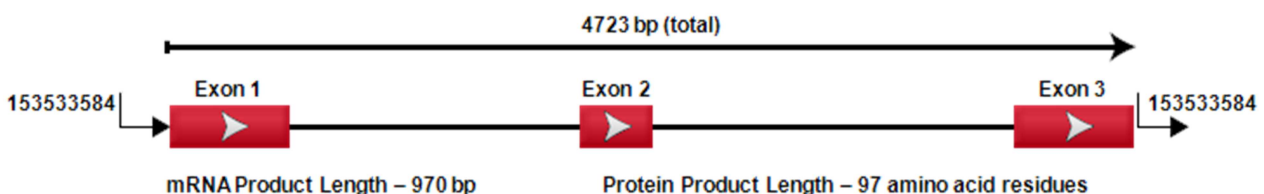
composition of S100 genes. Exon 1 is untranslated, exon 2 codes for the N-terminal 47 amino acids and exon 3 codes for the C-terminal 50 amino acids.

The S100A2 gene has a total length of 4723 bp and seven splice variants, which can be categorized into five variants with protein product and two transcripts without an open-reading frame. Four of the variants contain the three-exon structure with the coding sequences in exon 2 and exon 3, while also sharing identical protein sequences only differing in their untranslated 5' region (Wolf et al., 2011).

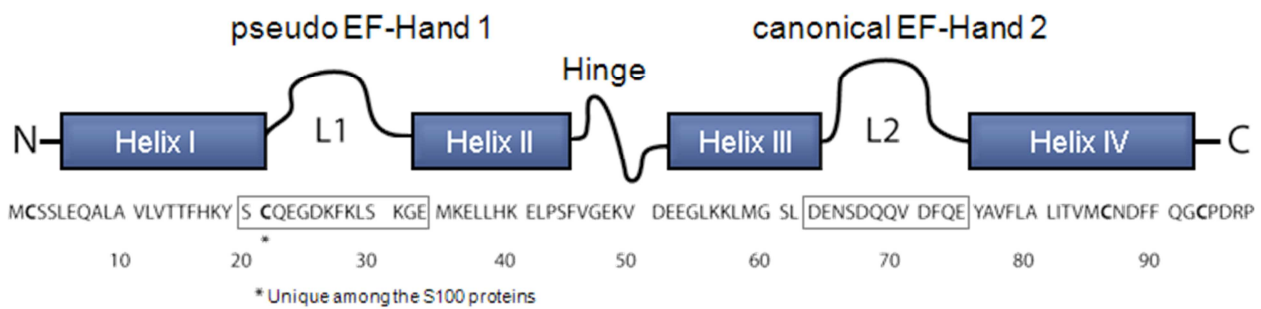
Transcription

The S100A2 mRNA product length, including the polyadenylate stretch, is 970 bp (NM_005978.3). The S100A2 gene has an open-reading frame of 294 nucleotides encoding for a protein of 97 amino acid residues with a molecular mass of 11,117 kDa (NM_005969.1; see below).

Wicki et al. (1997) identified an enhancer element in the promoter region necessary for the transcription of the S100A2 gene. This enhancer element is active in both orientations and either upstream or downstream of the reporter gene, and is both necessary and sufficient for transcription of the gene (Wicki et al., 1997).



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The protein structure and amino acid sequence of S100A2 (human). Modified from Wolf et al., *Amino Acids*, 2011.

Protein

Note

The S100A2 gene encodes for a protein of 97 amino acid residues, with a molecular mass of 11,117 kDa (P29034; UniProtKB).

Description

S100A2 is a member of the S100 family of calcium-binding proteins. The S100A2 gene encodes for a protein of 98 amino acid residues, with a molecular mass of 11,117 kDa (P29034; UniProtKB). S100 proteins are a family of low-molecular weight (9-12 kD), calcium-binding proteins that initiate a number of cellular processes such as cell division, motility, secretion, protein synthesis, and membrane permeability through both calcium dependent and independent mechanism. Greater than twenty five different S100 proteins have so far been identified with many mapping closely together on chromosome 1q21. S100A2 calcium-binding protein is characterized by four helices, two distinct calcium-binding EF-hand motifs, a central hinge region and C- and N-terminal variable domains. S100 proteins are found in the cytoplasm as preassembled dimers. A potential role for S100 proteins in cancer originated from observations that the evolutionarily conserved gene cluster containing S100 genes on human chromosome 1q21 underwent several rearrangements during tumour development.

Expression

S100A2 appears to be tissue specific as it is expressed in many normal and tumour tissues. Expression of S100A2 occurs in normal breast, lung, kidney, prostate, skin and oral squamous cell tissue, with loss of expression observed in associated carcinomas suggesting a putative tumour suppressor role; while in some malignant tissues, such as pancreatic, esophageal, gastric, papillary and follicular thyroid, some subsets of lung cancer and non-small cell lung cancer high expression of S100A2 is associated with poor prognosis and increased metastases. Clearly, expression of S100A2 is not ubiquitous for all tissues and there is evidently an element of tissue-specific expression.

Localisation

S100A2 is primarily localised in the nucleus with translocation to the cytoplasm evident in a number of tissue types.

Function

Little is known about S100A2 function and its potential contribution as either a tumour suppressor or contributor to tumorigenesis and metastases. Upon calcium binding a conformational change occurs exposing a target protein recognition site. Once in the calcium-activated state each monomer can interact with one target protein. In this state the S100 proteins act as calcium sensors and play a role in protein phosphorylation, enzyme activation via phosphorylation, inflammation, cellular contraction and relaxation by regulating cytoskeletal constituents including actin and myosin, and nuclear transcription promoting cell proliferation and differentiation.

Homology

Close relation to S100A4 has been confirmed by sequence analysis. Both proteins share over 60% amino acid sequence identity (Glenney et al., 1989).

Mutations

Note

Mutations have not been reported.

Implicated in

Pancreatic cancer

Note

For pancreatic cancer high S100A2 expression co-segregated with a poor response to pancreatectomy. Patients with tumours that demonstrated high S100A2 expression did not have a significant survival benefit from pancreatectomy compared to biopsy alone, whereas S100A2 negative tumours did. In the subgroup of patients who had resections with clear surgical margins, those whose tumours demonstrated high, or mod/high expression of S100A2 co-segregated with a poor outcome suggesting that occult distant metastatic disease may have been present in patients with tumours

that had high S100A2 expression at the time of pancreatectomy. In a supportive study, invasive pancreatic ductal carcinoma cells were shown to express higher levels of S100A2 than did intraductal papillary mucinous neoplasms (IPMN), pancreatitis affected epithelia or normal cells, while cell lines derived from metastatic sites expressed higher levels of S100A2 than those from primary sites. This study also demonstrated that patients with high S100A2 expression had poorer overall survival. Together, these data demonstrate that S100A2 expression is a good predictor of response to pancreatectomy for pancreatic cancer and suggests that high S100A2 expression may be a marker of a metastatic phenotype (Ohuchida et al., 2007; Biankin et al., 2009; Pinese et al., 2009).

Esophageal squamous cell carcinoma (ESCC)

Note

S100A2 was initially reported to be downregulated in a cohort of ESCC patients as measured by RT-PCR, with node-negative ESCC patients without S100A2 expression considered to be a high-risk group with poor survival. More recently, however, S100A2-overexpressing cancers showed a trend toward preferentially developing lymph node metastases and distant metastases, suggesting that S100A2 might be related to the progression of esophageal SCC (Kyriazanos et al., 2002; Ji et al., 2004; Imazawa et al., 2005; Cao et al., 2009).

Barrett's adenocarcinomas

Note

Expression of S100A2 mRNA and protein in Barrett's adenocarcinoma samples were performed by RT-PCR, and immunohistochemistry respectively. Frequent overexpression of S100A2 mRNA was observed in Barrett's adenocarcinomas, while overexpression of S100A2 protein was more frequently seen in well-differentiated tumours than in others. Contrary to the nuclear expression of S100A2 in normal esophageal mucosa, two thirds of Barrett's dysplasia and Barrett's adenocarcinomas that overexpressed S100A2 demonstrated stronger cytosolic staining than nuclear staining (Lee et al., 2006).

Non-small cell lung cancer (NSCLC)

Note

Many studies have been performed investigating S100A2 expression in non-small cell lung cancer (NSCLC). Increased expression of S100A2 has been demonstrated in tumour cells, with S100A2 providing valuable prognostic parameters. Patients whose tumours had positive S100A2 expression had a significantly lower overall survival and disease-specific survival rate at 5 years after surgery than did patients with negative S100A2 expression. S100A2 was overexpressed in tumours that metastasized during the course of the disease. Overexpression of S100A2 in

NSCLC cell cultures has been shown to increase transendothelial migration, corroborating the role of S100A2 in the metastatic process. High expression of S100A2 is associated with metastasis and predicts survival in early stages of NSCLC. These findings are supported by studies in a mouse model of non-small cell lung cancer (NSCLC) where NOD/SCID mice xenografted with NSCLC cells overexpressing S100A2 demonstrated significantly more metastases than vector alone transfected cells (Heighway et al., 2002; Diederichs et al., 2004; Smith et al., 2004; Wang et al., 2005; Zech et al., 2006; Bartling et al., 2007; Bulk et al., 2009; Strazisar et al., 2009a; Strazisar et al., 2009b).

Gastric cancer

Note

Early assessment of S100A2 expression in gastric cancer using serial analysis of gene expression (SAGE) revealed that over 90% of gastric tumours overexpressed S100A2 when compared to normal gastric mucosa. More recently, however, S100A2 protein expression in normal and benign gastric tissues has been reported with a loss of S100A2 expression in 52% of gastric adenocarcinomas. Loss of S100A2 expression was associated with histological differentiation, depth of invasion, lymphatic vessel invasion and lymph node metastasis. These conflicting data demonstrate the need for further studies into S100A2 expression and gastric adenocarcinomas to further elucidate the tumorigenic mechanisms underpinning gastric carcinogenesis (El-Rifai et al., 2002; Liu et al., 2008; Luo et al., 2011).

Thyroid carcinomas

Note

For thyroid carcinomas, S100A2 has been demonstrated to contribute to carcinogenic events in papillary carcinoma progression (90% positive), with S100A2 expression being one of the biological characteristics of anaplastic carcinoma (Ito et al., 2005).

Ovarian carcinomas (various subtypes) / ovarian serous papillary tumours

Note

S100A2 is highly overexpressed in the majority of ovarian carcinomas irrespective of the subtype, in particular S100A2 is overexpressed in ovarian serous papillary carcinomas compared to normal ovarian cell lines (Hough et al., 2001; Santin et al., 2004).

Breast cancer

Note

S100A2 expression in normal mammary epithelium is usually high, with loss of S100A2 associated with the development of malignant breast carcinoma. Studies have revealed that loss of S100A2 expression is not associated with early carcinogenesis from normal

mammary epithelium to benign hyperplasia. These experiments provided early evidence that S100A2 repression in tumour cells may be mediated by site-specific methylation. Interestingly, recent investigations have demonstrated that the highly invasive basal breast cancers express significantly higher levels of S100A2 than non-basal breast malignancies (Wicki et al., 1997; Liu et al., 2000; McKiernan et al., 2011).

Oral squamous cell carcinoma (OSCC) / laryngeal squamous cell carcinoma (LSCC)

Note

Recent data has emerged surrounding the potential antitumour role of S100A2 in squamous cell carcinomas, partly via reduced expression of COX-2. For oral squamous cell carcinomas (OSCC) a higher rate of late cervical metastasis has been shown in patients with S100A2-negative tumours than those with S100A2-positive tumours, indicating that patients with stage I or II invasive OSCC without S100A2 expression should be considered a high-risk group for late cervical metastasis (poor overall survival). Loss of nuclear S100A2 may also serve as an independent prognostic marker for early-stage oral cancer patients at high risk of recurrence. A more aggressive treatment modality and intensive follow-up may be recommended for the patients with reduced expression of S100A2 in tumour cell nuclei. In laryngeal squamous cell carcinoma, a correlation was found between S100A2 tumour positivity and longer relapse-free and overall survival (Lauriola et al., 2000; Suzuki et al., 2005; Tsai et al., 2005; Tsai et al., 2006; Almadori et al., 2009).

Bladder cancer

Note

Conflicting data has emerged concerning S100A2 expression in bladder cancers. Overexpression of S100A2 mRNA has been demonstrated in bladder cancers using RT-PCR, however a study investigating S100A2 expression at the protein level demonstrated that S100A2 expression was significantly decreased in the bladder cancer specimens compared with the controls. The loss of expression of S100A2 and increased expression of another calcium binding protein, S100A4, were associated with muscle invasion with alterations in expression also associated with a greater risk of disease progression and a decreased chance of cancer-specific survival (Matsumoto et al., 2007; Yao et al., 2007).

Squamous cell carcinoma of the head and neck (SCCHN)

Note

In oral cancer cells the Ca²⁺ and cell cycle-dependent p53-S100A2 interaction might modulate proliferation, while for squamous cell carcinomas of the head and neck (SCCHN) it has been postulated that S100A2 may

play a role in the metastasis of SCCHN, however most tumours expressed S100A2 but lymph node metastases showed a pattern of reduced staining for S100A2 compared with primary tumours (Mueller et al., 2005; Zhang et al., 2007).

Lung adenocarcinoma / lung squamous cell carcinoma (LSCC)

Note

Expression of S100A2 is reportedly downregulated in some lung squamous cell carcinomas, with S100A2 positivity being a favourable prognostic indicator in patients with p53-negative tumours (Feng et al., 2001; Shen et al., 2002; Matsubara et al., 2005).

Prostate cancer

Note

S100A2 expression was observed in the basal cells of non-malignant epithelium, while absent S100A2 expression was demonstrated in a cohort of 41 prostate cancer specimens, potentially due to promoter hypermethylation. In benign conditions such as benign prostate hyperplasia and prostatitis, high levels of S100A2 are observed with a progressive loss of S100A2 expression occurring with increasing tumour grade and metastases indicating that loss of S100A2 may be an important event during progression of prostate cancer. More recently, high S100A2 protein expression was observed in a cohort of benign prostatic hyperplasia, with little or no expression in prostate cancer cells, while a concomitant increase of S100A4 expression was observed in prostate cancer cells. These data suggest that the analysis of both S100A2 and S100A4 expression in prostatic tissues may be a useful prognostic indicator for prostate cancer (Gupta et al., 2003; Rehman et al., 2005; Kwon et al., 2010).

Malignant melanoma

Note

For malignant melanoma, loss of S100A2 gene expression may be an early event in the development of melanoma. All nevi showed moderate to high expression levels of S100A2, while the expression levels were low in cell lines established from primary melanomas and metastases did not express S100A2 mRNA (Maeldansmo et al., 1997).

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