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Gene Section
Review

S100A1 (S100 calcium binding protein A1)

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Identity

Other names: S100; S100-alpha; S100A

HGNC (Hugo): S100A1

Location: 1q21.3

Local order: The S100A1 gene is located at the telomeric end of the 16 member S100A gene cluster on 1q21.3. The S100A1 gene is flanked by the S100A13 (centromeric) and C1orf77 (telomeric) genes.

DNA/RNA

Description

The S100A1 gene structure is highly conserved in mammals and contains three exons separated by two introns (Song and Zimmer, 1996; Zimmer et al., 1996; Kiewitz et al., 2000). The first exon encodes the 5' UTR. The second exon encodes the 5' UTR and amino terminal EF hand Ca^{2+}-binding domain. The third exon encodes the carboxy-terminal canonical EF-hand and the 3' UTR. Cis-acting DNA elements that regulate expression in skeletal muscle, neurons, glia and heart have been identified (Song and Zimmer, 1996; Kiewitz et al., 2000). S100A1 transcription in chondrocytes is regulated by the SOX trio of transcription factors, SOX5, SOX6 and SOX9 (Saito et al., 2007).

Transcription

The S100A1 protein is encoded in a 594 bp mRNA transcript. Protein products have not been verified for the five splice variants reconstructed from low abundance cDNAs (Ensembl and Aceview).

Pseudogene

None.

Protein

Description

S100A1 is a member of the S100 family of Ca^{2+}-binding proteins. S100A1 exists as a dimer of two identical monomers. Each monomer contains 94 amino acids (figure 1), has a molecular weight of 10546 Da, and contains two EF-hand Ca^{2+}-binding domains (Wright et al., 2005). The non-canonical amino terminal EF-hand contains 14 amino acids and is characteristic of S100 proteins. The carboxy terminal canonical EF-hand contains 12 amino acids and is characteristic of all S100/calmodulin/troponin superfamily members. Like other members of this superfamily, S100A1 possesses no inherent enzymatic activity and exerts its biological effects by interacting with and modulating the activity of target proteins (Zimmer et al., 2003). S100A1 undergoes an ~90 degree rotation of helix 3 upon binding calcium (figure 2), exposing a hydrophobic pocket that serves as the binding site for intracellular and extracellular proteins targets (Landar et al., 1998; Wright et al., 2009b; Zimmer and Weber, 2010). The amino acid sequence linking the two EF-hands confers family member-specific binding for some target proteins (Zimmer and Weber, 2010).

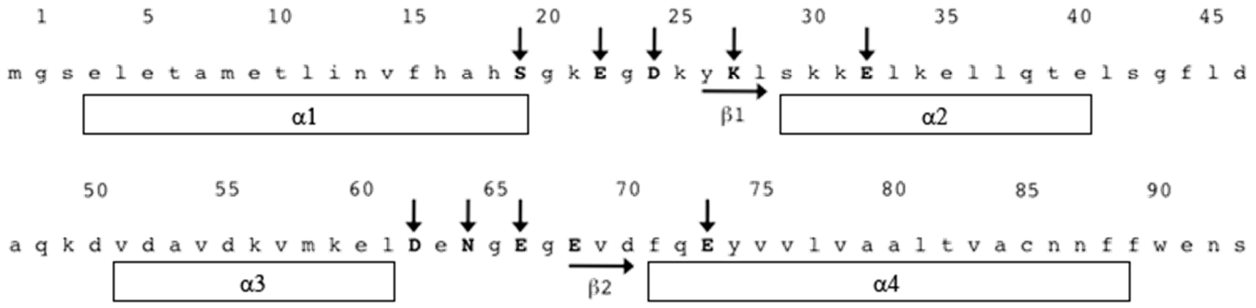

Figure 1. Amino acid sequence of the human s100A1 monomer. Residues involved in binding Ca^{2+} are shown with downward arrows. Elements of secondary structure are indicated.

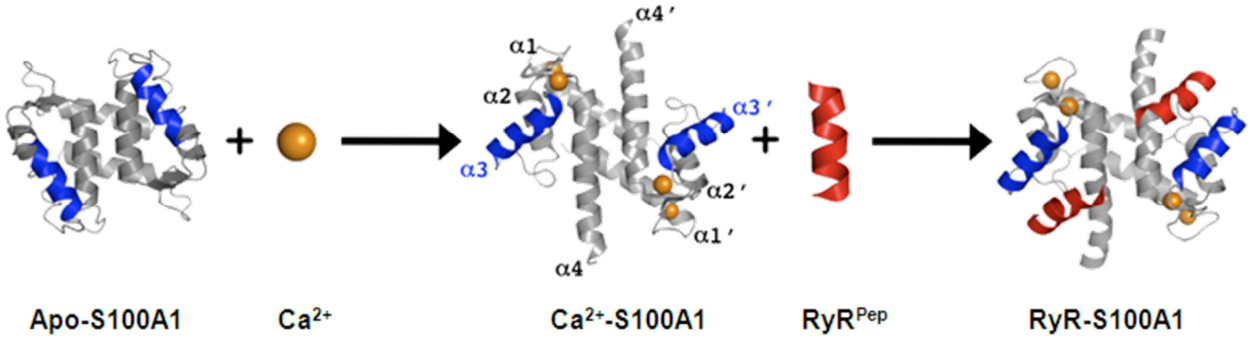

Figure 2. The conformational change of the S100A1 dimer. Upon binding Ca^{2+}, alpha-helix 3 (blue) undergoes an ~90 degree rotation, exposing a hydrophobic binding site that can interact with a variety of biological targets. Here, a peptide derived from ryanodine receptor (RyR^{Pep}; red) is shown binding to S100A1 (Wright et al., 2008).

Expression

S100 proteins are expressed exclusively in higher chordates in a cell-type and tissue-specific manner (Zimmer et al., 1995; Zimmer et al., 2005). It is the unique complement of S100 family members expressed in individual cells that allows cells to transduce changes in calcium levels into unique biological responses. While there are species-specific differences in S100A1 levels, all species exhibit intermediate to high levels of S100A1 in heart, skeletal muscle, smooth muscle, skin, brain, adipose and kidney (Kato et al., 1986; Zimmer and Van Eldik, 1987; Zimmer et al., 1991; Zimmer et al., 1995; Zimmer et al., 2005; Song and Zimmer, 1996; Kiewitz et al., 2000). Lung, liver, spleen, intestine, testis, thyroid gland, salivary gland, pancreas, ovary, placenta and prostate also contain detectable levels of S100A1 protein/mRNA.

Localisation

In non-muscle cells, S100A1 is located in the perinuclear cytoplasm. In muscle cells, S100A1 co-localizes with the sarcolemma, sarcoplasmic reticulum and mitochondria. Extracellular forms of S100A1 have also been detected (Most et al., 2003; Hernández-Ochoa et al., 2009).

Function

Like other S100 proteins, S100A1 has been implicated in a variety of biological and cellular processes. S100A1 mediates the suppression of chondrocyte differentiation (Saito et al., 2007). In the nervous system, S100A1 modulates innate fear and exploration of novel stimuli (Ackermann et al., 2006). In neuronal cells, S100A1 regulates cell proliferation, dendrite formation, intracellular calcium levels, microtubule stability, and amyloid precursor protein levels (Zimmer et al., 1995; Zimmer et al., 2005). In ganglion neurons, exogenous S100A1 increases sympathetic output by enhancing L-type calcium channel currents in a PKA-dependent manner (Hernández-Ochoa et al., 2009). In the heart, S100A1 regulation of the ryanodine receptor, SERCA pump and phospholamban alters Ca^{2+} handling; regulation of titin alters contractile performance; and regulation F1-ATPase alters mitochondrial energy metabolism (Rohde et al., 2010). In skeletal muscle, S100A1 interaction with the ryanodine receptor modulates excitation contraction coupling (Prosser et al., 2008; Wright et al, 2008). In endothelial cells, S100A1 moldulates calcium levels and nitric oxide production (Pleger et al., 2008). Additional S100A1 target proteins include the RAGE receptor, aldolase, annexin A6, the actin-capping protein CAPZA1, desmin, glial fibrillary acidic protein, the 43 kD gap junction protein (GJA1), heat shock proteins, immunophilins (CyP40 and FKBP52) phosphoglucomutase, glycogen phosphorylase kinase, tubulin, the calcyclin binding protein, and other S100s (S100A3, S100A4, S100B, S100P) (Wright et al, 2009b). Two structures of S100A1-target complexes

have been characterized using NMR (Wright et al., 2008; Wright et al., 2009a).

Homology

Species comparisons
Human - Chimpanzee: 100%
Human - Cow: 99%
Human - Canine: 98%
Human - Rat: 94%
Human - Mouse: 94%
Other S100 family members
Human S100A1 - Human S100A4: 51%
Human S100A1 - Human S100A5: 46%
Human S100A1 - Human S100A7: 24%
Human S100A1 - Human S100A10: 48%
Human S100A1 - Human S100A13: 41%
Human S100A1 - Human S100B: 60%
Human S100A1 - Human S100P: 56%

Mutations

Note

No disease-associated mutations in the S100A1 gene have been reported.

Implicated in

Melanoma

Note

Like other S100 proteins, S100A1 displays altered expression patterns in melanomas. Expression is increased in malignant, relative to benign, melanocytic tumors (Sviatoha et al., 2010) and has been proposed as a possible melanoma biomarker (Nonaka et al., 2008).

Renal cell carcinoma

Note

It has also been observed that renal cell carcinoma is accompanied by increased expression of S100A1 (Teratani et al., 2002). As with melanoma, S100A1 has been proposed as a marker to differentiate between renal cell carcinoma subtypes (Keijser et al., 2006; Li et al., 2007; Yusenko et al., 2009).

Lung cancer

Note

Genomic changes in the S100A1 gene have been reported in lung cancer (Jiang et al., 2010).

Alzheimer's disease

Note

There is evidence suggesting that S100A1 could be involved in Alzheimer's disease (Zimmer et al., 2005). PC12 cells not expressing S100A1 are more resistant to $Abeta_{25-32}$-induced cell death. Such cells also display a stabilization of intracellular calcium levels similar to that observed in other systems displaying increased resistance to Abeta-induced cell death. These observations suggest that S100A1 antagonists could hinder the progression of Alzheimer's disease.

Heart disease

Note

The importance of S100A1 in cardiac function was hypothesized in light of two early observations - that S100A1 levels are diminished in cardiac tissues from patients with end stage heart failure (Remppis et al., 1996), but increase during pulmonary hypertension leading to myocardial hypertrophy (Ehlermann et al., 2000). S100A1 is now known to modulate excitation-contraction coupling through interactions with the ryanodine receptor, competing for the same binding site occupied by calmodulin (Prosser et al., 2008; Wright et al., 2008). Furthermore, over-expression of S100A1 delays myocardial remodeling, improves contractile performance, and increases survival in response to myocardial infarction (Kraus et al., 2009; Rohde et al., 2010). This protein is now the subject of gene-therapy studies for treating chronic heart failure (Pleger et al., 2007).

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