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S100 Calcium-Binding Protein

► S100 Proteins

S100 Proteins

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Synonyms

S100 calcium-binding protein

S100 Protein Family Members

S100A1, S100A2, S100A3, S100A4, S100A5, S100A6, S100A7, S100A8, S100A9, S100A10, S100A11, S100A12, S100A13, S100A14, S100A15, S100A16, S100B, S100P, S100G, S100Z, trichohylin, filaggrin, filaggrin-2, cornulin, repetin

Historical Background/General: S100 Family

S100 proteins were first discovered in 1965 by Moore as a major protein fraction (0.6% of total soluble protein) isolated from bovine brain (Moore 1965). The protein was given the name S100 due to its high solubility in saturated ammonium sulfate. Later experiments showed the S100 protein fraction constituted two different dimeric species comprised of two β protomers (S100B) or an α, β heterodimer (Isobe et al. 1977). Early members of the S100 protein family were frequently given suffixes based on their localization or molecular size and included S100P (placental), S100C (cardiac or calgizzarin), p11 (11 kDa), and MRP8/MRP14 (myeloid regulatory proteins, 8 and 14 kDa). In 1993, initial genetic studies showed that six of the S100 genes were clustered on chromosome 1q21 (Engelkamp et al. 1993), a number that has expanded since. Based on this observation most of the proteins were renamed according to the physical order they occupy on the chromosome. These include S100A1 (formerly S100α), S100A2 (formerly S100L), S100A10 (p11), S100A8/S100A14 (MRP8/MRP14). A few S100 proteins are found on other chromosomes including S100B (21q21). Currently there are 27 known S100 family members: S100A1-A18, S100B, S100G, S100P, S100Z, trichohylin, filaggrin, filaggrin-2, cornulin, and repetin (Table 1).

Role of S100 Proteins in Calcium Signaling

The S100 proteins are members of the EF-hand family of calcium-binding proteins that also includes calmodulin, ► recoverin, and troponin-C. The sequence similarity between S100 family members is very high ranging from 54% for distantly related family members such as S100B and S100A14 to 76% for S100B and S100A1, which are located in close proximity on the S100 phylogenetic tree (Marenholz et al. 2004). Each S100 protomer contains between 90 and 114 residues and two calcium-binding sites. The first

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S100 Proteins, Table 1 Signaling functions of some S100 proteins

S100	Other names	Tissue(s)	Signaling function	Effectors[a]
S100A1	S100α, S100, S100A	Heart, skeletal muscle	Skeletal muscle contraction	RyR1
			Heart muscle contraction	RyR2, SERCA2a, PLB, F1-ATPase
			Neurotransmitter release	Synapsins I and II
			Tumor suppression	p53, MDM2
			(−) Differentiation	MyoD
			(+) Heat shock response	Hsp70/90, CyP40, FKBP52
			(+) Cell morphogenesis and proliferation	NDR kinase
			Ubiquitination	CacyBP/SIP
			Cytoskeletal dynamics	CapZ, MT, tubulin, F-actin, titin, GFAP, desmin, RAGE
S100A2	S100L, CaN19	Epithelial, mammary, lung, kidney, prostate, salivary, esophagus	(−) Heat shock response	HOP, CyP40, FKBP52
			(+) Tumor suppression	p53, MDM2
			Cytoskeletal dynamics	Tropomyosin
S100A3	S100E	Epidermis (hair follicles)	Differentiation and Ca^{2+} homeostasis	PAD3, S100A3 (tetramer)
S100A4	Metastasin (Mts1), fibroblast-specific protein (FSP1), 18A2 pEL98, p9Ka, 42A CAPL, calvasculin	Ubiquitous, placenta	Cytoskeletal dynamics	Myosin IIA, liprin β1, F-actin
			Tumor suppression	p53, MDM2, MetAP2, NFκB
			Inflammation	RAGE
			Cell migration	Annexin A2. MMP-2, E-cadherin
S100A5	S100D	Olfactory bulb, brain stem, spinal trigeminal tract	Inflammation	RAGE
S100A6	Calcyclin, CACY, 2A9, CABP, 5B10, PRA	Fibroblasts, epithelial, smooth muscle, brain	Cytoskeletal dynamics	Annexin A2, A6, and A11
			Heat shock response	Sgt1, HOP
			Regulation of nuclear transport	Importinα
			Tumor suppression	p53, MDM2, RAGE
			Ubiquitination	CacyBP/SIP
S100A7	Psoriasin, PSOR1	Epithelial, mammary, fetal, ear, fetal skin, fetal tongue	(+) Cell proliferation	Jab1
			Cell migration	RAGE
			Anti-microbial inflammation	RAGE
S100A8	Calgranulin A, CAGA, MRP8, P8, CGLA, MIF, NIF, L1Ag, MAC387, 60B8AG, CFAG, calprotectin	Epithelial and immune cells	Cytoskeletal dynamics	Tubulin, S100A9
			(−) Cell proliferation	CKI, CKII, S100A9, RAGE
			(−) Inflammation	NADPH oxidase, S100A9, arachidonic acid
S100A9	Calgranulin B, CAGB, MRP14, CGLB, MIF, NIF, L1Ag, MAC387, 60BAG, CFAG, calprotectin, P14	Epithelial and immune cells	Differentiation	NADPH oxidase, S100A8, RAGE
			(−) Inflammation	NADPH oxidase, S100A8, arachidonic acid
S100A10	p11, annexin II ligand, calpactin I Light polypeptide, ANX2LG, CLP11, ANX2L, p11, p10, 42 C, GP11, CAL1L	Lung, intestine, kidney	Cytoskeletal dynamics	F-actin
			Neuromodulation	5HT4, 5HT1B,
			(−) Regulation of macrophages	tPA, Plg
			Exocytosis	Annexin A2, VAMP2
			(−) Tumor suppression	RhoGAP

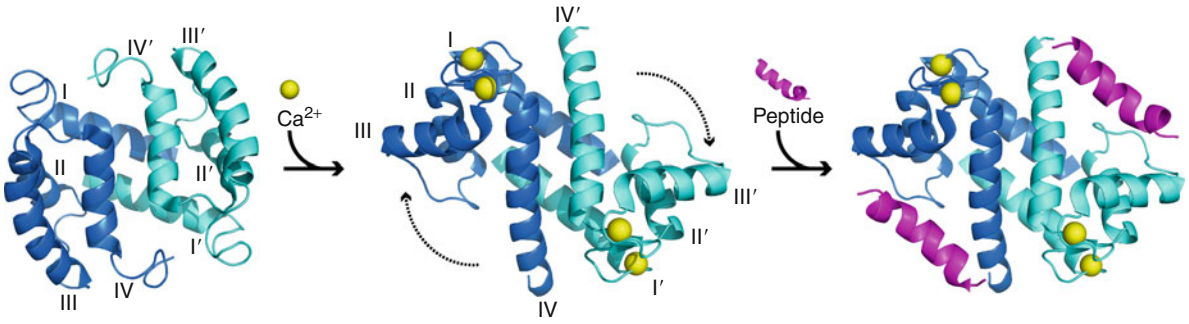
(*continued*)

Table 1 (continued)

S100	Other names	Tissue(s)	Signaling function	Effectors[a]
			Cell junction formation	Annexin A2, Cdc42
			Membrane receptor and channel presentation	Annexin A2, TRPV5, TRPV6, $NA_V1.8$, AHNAK, ASIC1a, TASK-1
S100A11	Calgizzarin, S100C, LN70	Smooth muscle, epidermal, Placenta, heart, lung, spleen, kidney, liver, bladder uterus	(−) Cell proliferation	Annexin A1, PLA2
			(+) Cell proliferation	RAGE
			Membrane repair	Annexin A1, annexin A2
			Tumor suppression	p53
			DNA damage response	Rad54b, nucleolin, PKCα
S100A12	Calgranulin C, CAAF1, CGRP p6, ENRAGE, calcitermin, MRP6	Immune cells	Inflammation	RAGE
			Ubiquitination	CacyBP/SIP
			Chemotaxis	GPCR
S100A13	N/A	Heart, skeletal muscle	Inflammation and angiogenesis	IL1α
			Neuroprotection and anti-necrosis	ProTα
			Mitogenesis	FGF1
S100A14	BCMP84, S100A15	Colon, thymus, kidney, liver, lung, small intestine	(+) Cell proliferation	RAGE
			(+) Apoptosis	RAGE
			Ca^{2+} homeostasis	Nucleobindin
S100A15	koebnerisin, S100A7L1, S100A7a	Epithelial, mammary	anti-microbial inflammation	GPCR
S100A16	S100F, DT1P1A7, MGC17528	Ubiquitous	(+) Cell proliferation	p53
S100B	S100β, NEF	Brain	(+) Cell survival	RAGE
			(+) Cell proliferation and (−) differentiation	FGF1
			Neuromodulation	D2R
			Cell migration	RAGE
			(−) Tumor suppression	p53, MDM2
			Cell morphogenesis and proliferation	NDR kinase
			Cytoskeletal dynamics	Annexin A6, CapZ, GFAP, MAG, MT, Caldesmon
S100P	N/A	Placenta, brain, spleen, lung	Cytoskeletal dynamics and cell migration	IQGAP1
			Inflammation	RAGE

Only S100 proteins with known signaling functions have been included in this table. Where possible (+) and (−) signs indicate the positive and negative regulation of the signaling function by the S100

[a]5-hydroxytryptamine receptor (5HT4/5HT1B), acid-sensing ion-channel-1a (ASIC1a), actin-capping protein (CapZ), c-jun activation domain binding, protein-1 (Jab1), casein kinase (CKI/CKII), cell division control protein 42 (Cdc42), cyclophillin 40 (CyP40), dopamine D2 receptor (D2R), FGF receptor-1 (FGFR1), fibroblast growth factor-1 (FGF1), G-protein coupled receptor (GPCR), glial fibrillary acidic protein (GFAP), heat shock protein (HSP), hsp70/hsp90 organizing protein (HOP), immunophilin (FKBP52), interleukin-1 (IL1α), kinesin light chain (KLC), matrix metalloproteinase-2 (MMP2), methionine aminopeptidas-2 (METAP2), microtubules (MT), mitochondrial ATPase (F1-ATPase), murine double minute (MDM2), mylein-associated glycoprotein (MAG), myogenic differentiation transciption factor (MyoD), nicotinamide adenine dinucleotide phosphate (NADPH), nuclear Dbf2-related protein kinase (NDR kinase), nuclear factor kappa-light-chain-enhancer of activated B-cells (NFκB), p38 mitogen activated protein kinase (MAPK), peptidylarginine deiminase type III (PAD3), phospholamban (PLB), phospholipase A2 (PLA2), protein kinase C (PKCα), prothymosin-α (ProTα), Ras GTPase-activating-like protein-1 (IQGAP1), receptor for advanced glycation end-products (RAGE), Rho GTPase-activating protein (RhoGAP), Ryanodine receptor (RyR1/RyR2), S100A6 binding protein/Siah 1 interacting protein (CacyBP/SIP), sarcoplasmic reticulum ATPase (SERCA2a), sodium voltage channel 1.8 (NAV1.8), synaptotagmin-1 (Syt1), tissue Plg activator (tPA), transient receptor potential channel (TRPV5/TRPV6), TWIK-related acid-sensitive K-1 (TASK-1), vesicle-associated membrane protein-2 (VAMP2), zymogen plasminogen (Plg)



S100 Proteins, Fig. 1 A general calcium-signaling mechanism for the S100 proteins. The three-dimensional structure of calcium-free S100B (*left*) comprises a symmetric dimer (*cyan, purple*) with each protomer possessing four α-helices (I-IV, I′-IV′) (Malik et al. 2008). Upon influx of calcium to the cytosol, the S100 protein binds calcium to two sites in each protomer (middle) forming the "open" conformation. In this structure, helix III (and III′) rearrange by approximately 100° compared to helix IV. This structural change exposes a shallow hydrophobic cleft used to recruit a target protein such as the N-terminus of NDR kinase (residues 72–87 shown) (*right*) that functions with S100B in regulation of cell proliferation and maintenance of cell morphology (Bhattacharya et al. 2003)

three-dimensional structure of an S100 protein was determined for calcium-free S100A6 (Potts et al. 1995). Subsequent to this, more than 40 structures of calcium-free, calcium-bound, and S100-protein complexes have been determined. These structures have shown the S100 protomer comprises two helix-loop-helix EF-hand motifs (Fig. 1). The first EF-hand comprises a 14-residue non-canonical calcium-binding site with weak calcium affinity sandwiched between two α-helices (I, II). The second EF-hand contains helices III and IV along with a 12-residue canonical calcium-binding site that typically has a higher affinity for the metal ion. The S100 dimer is formed through interactions between helices I and IV (I′, IV′) from each protomer (Fig. 1).

Calcium signaling is propagated by an S100 protein through its calcium-binding properties. In the resting cell, intracellular calcium levels are at around 100 nM. Due to the relatively low calcium affinity of S100 proteins, they are likely found in the calcium-free or apo state at resting cellular calcium concentrations. As a result of an extracellular signal from ligand-receptor binding, stress, or injury, calcium concentrations within the cell increase about tenfold, high enough to allow an S100 protein to bind two calcium ions per S100 protomer. The binding of calcium results in a conformational change of the S100 protein. The rearrangement causes helix III of each monomer of the S100 protein to swing outward resulting in a more "open" conformation (Fig. 1). For example, in S100B helix III rotates by more than 100° in relation to helix IV, exposing several hydrophobic residues at the helix III-IV interface (Drohat et al. 1998) while other S100 proteins open to varying degrees (Malik et al. 2008). The large, flat nature of this hydrophobic patch is used to recruit a considerable number of other proteins in the cell, giving rise to varied biological responses (Bhattacharya et al. 2004). Because the S100 dimer is symmetric, the net result of the calcium-binding event is exposure of two ligand-binding sites per molecule.

S100 proteins play a role in regulation of protein phosphorylation, enzyme activities, transcription factor activation, and cytoskeletal reorganization (Donato 2001; Santamaria-Kisiel et al. 2006). For example, S100B acts to modulate the phosphorylation activity of Ndr kinase, an important cell division enzyme, through binding of the autoinhibitory region of Ndr kinase (Fig. 1) (Bhattacharya et al. 2003). This in turn causes the release of the catalytic domain allowing autophosphorylation of key Ser/Thr residues, and full activation of the kinase as a key step in the regulation of cell division. Similarly, the heterodimeric S100A8/S100A9 protein inhibits the phosphorylation activity of the enzymes Casein Kinases I and II that are involved in cell-cycle control (Murao et al. 1990). S100A1, S100A2, S100A4, S100A8, S100A10, and S100B have been shown to bind to components of the cytoskeleton including tubulin, intermediate filaments, actin, and ▶ myosin modulating the assembly of these proteins. For example, the interaction between S100B and CapZ regulates actin filament extension. Binding of CapZ inhibits S100B from associating with, and

disassembling, microtubles and intermediate filaments (Sorci et al. 2000).

In some cases, S100 proteins can bind to targets in the absence of calcium in which case expression levels, cellular localization and, ultimately, availability of the target protein control their signaling role. In one particular case, substitutions in the calcium-binding sites of S100A10 prevent it from binding calcium, yet the protein retains an "open" conformation similar to other calcium-bound S100 proteins. In an interesting turn S100A10 interacts with partner proteins such as Annexin A2, which itself is a calcium-binding protein. It is the calcium-binding properties of Annexin A2 that regulate formation of a complex with S100A10 that is proposed to bridge phospholipid membranes in fusion and repair processes (Gerke and Moss 2002).

Expression and Tissue Specificity

The members of the S100 protein family are expressed in a wide variety of tissue types. Some of the S100 proteins appear to have ubiquitous expression (S100A11, S100A16) while others are expressed in only one or two specific tissue types (Table 1). The S100 proteins are typically expressed in the cytoplasm within cells but can undergo nuclear localization and even translocation to the extracellular matrix, through an unknown mechanism. Determining the expression profile for the S100 proteins is complicated due to their regulation by various cellular stimuli. For example, the expression of S100A8, S100A9, and S100A11 is altered due to infection or DNA damage. In addition, the S100 gene cluster is frequently rearranged in cancer cell types, often resulting in either increased or decreased S100 protein expression. One of the more unique and well-studied S100 proteins is S100B, which is expressed predominantly in glial cells of the brain. Recently the Dopamine D2 Receptor, which is found almost exclusively in brain tissue, was identified as a new S100B binding partner and it appears that S100B can enhance the dopamine signal (Liu et al. 2008). S100A1 is another S100 with a very specific tissue distribution. It is highly expressed in cardiac muscle cells and helps to regulate calcium cycling and contractile performance by binding to the ▶ Ryanodine Receptor (RyR) and the sarcoplasmic reticulum ATPase (SERCA2a). Interestingly, calcium-bound S100A1 competes at an overlapping binding site on the ▶ RyR with another EF-hand signaling protein calmodulin. The binding of S100A1 to ▶ RyR enhances calcium release and cell contraction in heart muscle while CaM binding results in inhibited ▶ RyR function (Treves et al. 1997).

Several S100 proteins are involved in the immune response. For example, S100A7 and S100A15 have been implicated in inflammation pathways leading to psoriasis and are highly expressed in epithelial cells. The S100A8/A9 heterodimer is expressed in immune cell types such as macrophages, neutrophils, and monocytes and are part of an inflammation pathway that is often involved in arthritis (Odink et al. 1987). For example, the expression of these proteins is regulated by transcriptional events such as the upregulation of mRNA of S100A8 and S100A9 in response to bacterial infection. Interestingly, the expression of S100A8, S100A9, and S100A7 has also been shown to be repressed by the transcription factors BRCA1 and c-▶ Myc, which are known as strong anticancer genes and appear to bind to the promoter elements of these S100 proteins. Not surprisingly, expression of the S100A7 gene has been shown to be DNA-damage inducible where it likely functions to regulate cell cycle progression.

Some S100 proteins have either been found in the extracellular matrix, or have been implicated in a signaling path through binding to the extracellular domain of the receptor for advanced glycation endproducts (RAGE). The RAGE receptor transduces extracellular stimuli leading to the activation of ▶ NF-κB and the release of proinflammatory cytokines as part of the innate immune response. Currently 12 different S100 proteins (S100A1, S100A4-S100A9, S100A11, S100A12, S100A14, S100B, S100P) have been found to interact with RAGE and elicit a variety of cellular responses. Interestingly, none of the S100 family members are expressed with signal peptides, which are normally required for transport across the cellular membrane through ER/golgi targeting. Therefore, S100 translocation is likely occurring through an alternate, but unidentified, mechanism.

Several S100 proteins experience altered localization in order to perform specific functions. For example, DNA damage (double-strand breaks and/or cell stress-calcium) results in the translocation of S100A11 to the nucleus by the nuclear transport protein nucleolin. Once in the nucleus, S100A11 competes with Sp1 for binding to nucleolin (Sakaguchi et al. 2003).

Free Sp1 results in changes in the transcription factor p21 and termination of DNA synthesis. Likewise, when a calcium signal is received, cytoplasmic S100A10 is targeted to the inner surface of the cell membrane by its binding partner Annexin A2.

S100 Proteins and Disease

Many S100 proteins and their signaling pathways are linked to a variety of diseases such as cancer (including: breast, prostate, bladder, lung, colorectal, melanomas), inflammatory conditions (including arthritis, psoriasis, Crohns/colitis), neurological disorders (including Alzheimer's, Parkinson's, schizophrenia), and cardiomyopathies.

A large number of S100 proteins are associated with cancers. Altered levels of expression of the S100 proteins have been linked to the disease and therefore are being used as biomarkers for the measurement of patient outcome. The majority of the S100 genes are located in a cluster on human chromosome 1q21, called the epidermal differentiation complex. This gene cluster is frequently rearranged in a wide array of cancers. This link between S100 proteins and cancer is likely due to the role that many of the proteins play in signaling paths involved in differentiation and proliferation of cells. In addition to their direct involvement in cancer, some of the S100 proteins are involved in cancer metastasis through their functioning in the regulation of cell motility. S100A4, S100A7, S100A12, S100B, and S100P are all involved in signaling pathways tied to cell migration and as a result are often linked to poor prognosis in cancer. S100 proteins have potential to be used as biomarkers for cancer screening. For example, overexpression of S100B correlates with reduced survival in malignant melanoma patients. Levels of S100B expression are being used in a clinical setting as a diagnostic marker for staging the melanoma, determining prognosis, evaluating treatment, and predicting relapse (Harpio and Einarsson 2004).

Several S100 proteins alter the activity of the tumor suppressor protein, ▶ p53 (Salama et al. 2008). Some S100 proteins, such as S100A4 and S100B, inhibit the phosphorylation of ▶ p53 by binding to its C-terminus. This leads to a decrease in its transcriptional activity and inhibition of its tumor-suppressor function. Alternatively, other S100 proteins, such as S100A2, have been found to upregulate ▶ p53 activity and increase the expression of pro-apoptotic genes. S100A4 overexpression has been linked to several cancers including bladder, breast, thyroid, lung, prostate, and colorectal cancers. S100A4 plays role in the metastasis of cancer cells by potentially altering cell motility through its interactions with F-actin and ▶ myosin and increasing invasiveness through the regulation of matrix metalloproteinase (MMP) activity. S100A7 is overexpressed in breast, bladder, and skin tumors and its elevated levels indicate poor prognosis and reduced survival. Enhancement of breast cancer cell survival mechanisms through an interaction of S100A7 with Jab1 has been shown. S100A8 and S100A9 form a heterodimer and together are upregulated in gastric, prostate, and colorectal cancers. In prostate tumor cells, S100A8/A9 were found to induce activation of the ▶ NF-κB pathway and cause phosphorylation of ▶ MAP Kinase through an extracellular interaction with RAGE. In some cases, S100 overexpression is related to tumor suppression rather than promotion. For example, S100A2 is expressed in the prostate, but is downregulated in prostate cancer. Similar observations have been found in breast cancer, with normal mammary epithelial cells expressing S100A2 but not tumor cells. Overexpression of S100A11 has been linked to tumor suppression in bladder and renal carcinomas.

S100B is found in the cells of the brain and has been linked to a number of neurological disorders such as Alzheimer's disease (AD). In the example of AD, S100B protein is found to be overexpressed in the astrocytes of affected individuals. Similarly, patients with schizophrenia also have increased serum concentrations of S100B protein. S100B has been shown to interact with the Dopamine D2 Receptor and can increase receptor signaling. The D2-Receptor is involved in neuromodulation and is closely tied to the above-mentioned disorders.

Downregulation of S100A1 results in a diseased heart and can lead to heart failure. S100A1 binds calcium during the calcium oscillations of heart cells increasing the contractile performance of the cardiomyocytes. The use of S100A1 gene therapy for the treatment of heart failure is approaching clinical trial stages. Keratinocytes overexpress S100A7 in the skin disorder, psoriasis. S100A8/S100A9 are secreted by neutrophils and play a role in inflammatory diseases such as inflammatory arthritis.

The S100A10/Annexin A2 complex controls the recruitment and function of ion channels including CFTR in cystic fibrosis.

Summary

First discovered in the brain, the S100 proteins are expressed in a wide variety of tissues. There are a large number of S100 family members and each has multiple binding partners and functions. The members of the S100 protein family are EF-hand calcium-binding proteins, which utilize calcium to propagate a response through a signaling pathway. Binding of calcium to the S100 protein causes a structural rearrangement, exposing a target-binding surface. This surface in most S100 proteins is large and can accommodate multiple targets, sometimes at the same time. Target binding results in a range of responses from inflammation and cytoskeletal reorganization to control of cell growth and tumor suppression. Altered expression of S100 proteins has been found in a number of human cancers and these proteins are becoming recognized as important signaling molecules in this disease. In addition, some S100 proteins such as S100B, are linked to neurological diseases including Parkinson's, Alzheimer's, and schizophrenia. Future research focusing on the in vivo identification of new target proteins will help expand the knowledge of S100 signaling pathways and the mechanisms these proteins use to recruit molecules. This in turn may allow some of the S100 proteins to become valuable pharmacological targets.

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S12

► RPN8