S100 Protein Family in Rheumatological Diseases

Romatolojik Hastalıklarda S100 Protein Ailesi

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ABSTRACT

Inflammation in joint tissues is one of the causes of early mortality in rheumatological diseases. In fact, inflammation process is followed by cell infiltration, synovial tissue proliferation, cartilage and bone destruction. Therefore, various studies have been done to understand the pathogenesis and biochemical mechanisms of inflammation. Specifically, relationship between S100 protein family and inflammation in some type of rheumatologic diseases constitute the basis of this review. Scientific evidences emphasis a crucial role for S100 proteins in acute and chronic inflammatory diseases and also have been proposed as useful biomarkers of certain types of rheumatological diseases.

Keywords: S100 protein family, Inflammation, Rheumatologic Diseases

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ÖZET

Eklem dokularındaki inflamasyon, romatolojik hastalıklarda erken ölüm nedenlerinden biridir. Aslında inflamasyon sürecini hücre infiltrasyonu, sinovyal doku proliferasyonu, kıkırdak ve kemik yıkımı takip eder. Bu nedenle inflamasyonun patogenezini ve biyokimyasal mekanizmalarını anlamak için çeşitli çalışmalar yapılmıştır. Spesifik olarak, bazı romatolojik hastalıklarda S100 protein ailesi ile inflamasyon arasındaki ilişki bu derlemenin temelini oluşturmaktadır. Bilimsel kanıtlar, akut ve kronik inflamatuar hastalıklarda S100 proteinlerinin çok önemli bir rolü olduğunu göstermektedir ve ayrıca bu protein ailesinin üyeleri belirli romatolojik hastalıklarda yararlı biyobelirteçleri olarak önerilmiştirler.

Anahtar Sözcükler: S100 protein ailesi, İnflamasyon, Romatolojik Hastalıklar

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INTRODUCTION

Historical background of S100 proteins

S100 proteins were first discovered in 1965 by Blake W. Moore as a small fraction of protein isolated from bovine brain (1). The protein is named "S100" because of its high solubility in 100% of saturated ammonium sulphate at neutral pH. Subsequent experiments showed that the S100 protein fraction generates two different dimeric species consisting of either two β protomers (S100B) or one αβ heterodimer (2). Isobe et al. later stated that this S100 protein forms a dimer identified as S100A and S100B (3).

The first members of the S100 protein family are often added some suffixes according to their localization or molecular size (4). As an example; S100P (placental), S100C (cardiac or calgizzarin) and MRP8/MRP14 (myeloid-associated proteins, 8 and 14 kDa). The first genetic studies conducted in 1993 showed that six of the S100 genes cluster on human chromosome 1q21, however, S100B gene is located at 21q22 (5, 6). Based on this observation, most of the proteins have been renamed according to the physical order they occupy on the chromosome. These are named as S100A1 (formerly S100a), S100A2 (formerly S100L), S100A10 (p11) and S100A8/S100A14 (MRP8/MRP14). There are currently at least 25 known S100 family members (7). These proteins have been shown to be involved in various metabolic pathways and thus play a critical role in key cellular processes such as proliferation, apoptosis, differentiation, and inflammation (8).

Structural properties

The S100 protein family constitutes the largest subgroup among several calcium (Ca^{2+}) binding protein groups. All S100 proteins are relatively acidic and have the same basic structural properties (9). The molecular structure of S100 proteins is shown in Figure 1. S100 proteins are characterized by the EF-hand (helix-loop-helix) structural motif (10). The loop has a typical sequence of 12 amino acids surrounded by HIII and HIV helixes (Figure 1B). The N-terminal EF-hand exhibits a slightly different structure. It contains a specific sequence of 14 amino acids surrounded by HI and HII helixes (Figure 1A). This motif is characteristic for S100 proteins and is therefore often referred to as "S100 specific" or "pseudo EF-hand". Typically, the S100 protein family members form homodimers and only a few heterodimers are known, such as Moore's S100A1 / S100B protein and the S100A8/S100A9 dimer (11, 12). S100G is seen as an exception to this rule as it exists only as a monomer (13, 14). Dimerization of S100 proteins is seen as essential for their biological activity. These dimers are stabilized by Van der Waals interactions (15). Each monomer consists of two EF-el motifs and each EF-el motif consists of a Ca^{2+} binding ring surrounded by an α-helix (helix-loop-helix) (16). Generally, dimeric S100 proteins bind four Ca^{2+} ions per dimer. The S100 protein dimer interface is formed by HI and HIV helices from both monomers (Figure C, D). A compact structure of four polypeptides is formed by the combination of these dimers (17).

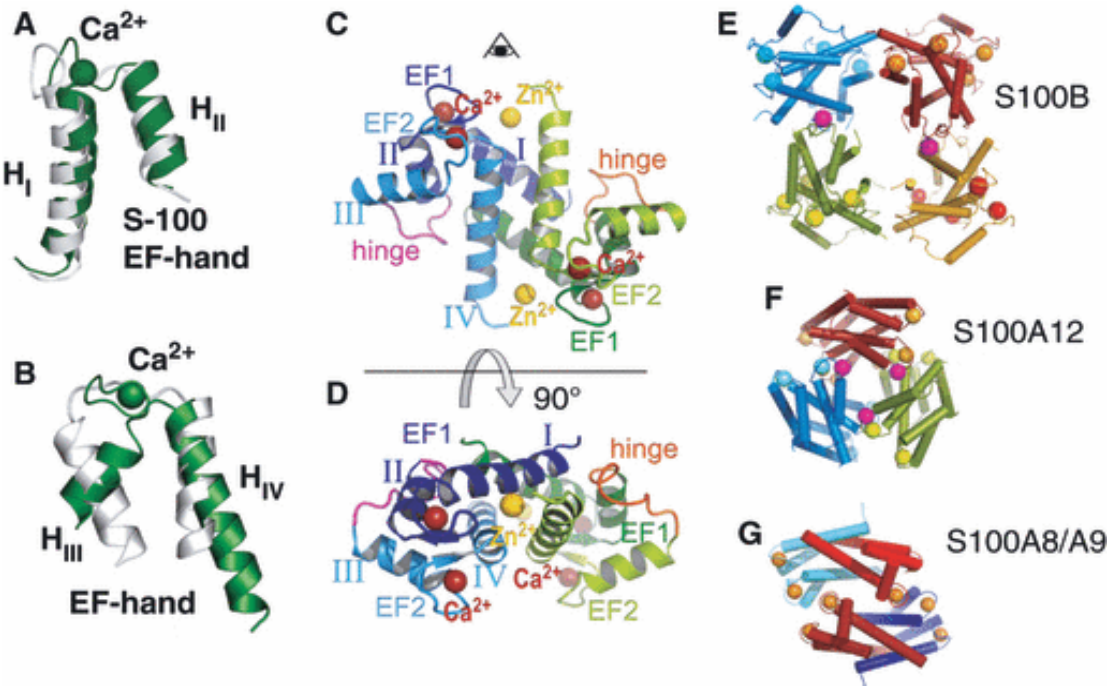

Figure 1. Molecular structure of S100 proteins (13). Calcium-induced conformational changes in EF-el motifs in S100 proteins (A, B). Structure of N-terminal, S100 specific EF-hand motif (A) and C-terminal, canonical EF-hand motif (B) in the metal-free (lighter) and Ca^{2+} bonded (darker) form of S100A6 (B). The spirals surround the EF-hand motifs (HI-HIV). Structure of Ca^{2+} and Zn^{2+} linked human S100B homodimer (C, D). The four bound Ca^{2+} ions are illustrated with red color. The two bound Zn^{2+} ions in S100B are illustrated with yellow color (E-G). Multimeric properties of S100 proteins as shown in Figure 1 E (octamer), F (hexamer) and G (tetramer).

It has been reported that S100 proteins bind to other divalent cations, but especially they bind the zinc (Zn^{2+}) ion with high affinity (18). The Zn^{2+} binding S100 proteins can be divided into two subgroups: The first group; the Cys residues, is involved in the coordination of Zn^{2+} and the second group is where Zn^{2+} is linked only through the side chains of His, Glu and Asp residues. The first group was characterized by spectroscopic analysis in combination with molecular modeling. For example S100A2 exhibits residues like presence of histidine or cysteine that are derived from different monomers, coordinated with Zn^{2+}. However, the exact mechanism of Zn^{+2} binding still unclear (13, 15, 19). For the second group; including S100A7, S100A8/A9, S100A12 and S100B, detailed structural information is available mainly by X-ray crystallography (13). S100A7, S100A12 and S100B bind two Zn^{2+} ions per homodimer at the subunit interface, which further stabilizes the dimer (16, 20, 21).

The metal binding properties of S100 proteins have an essential effect as the modulators of the conformation, folding, oligomerization of their structure and finally effect their activities. As stated above, S100 proteins are able to bind different metal ions including Ca^{2+} and Zn^{2+}. In the Ca^{2+} free state, both EF-hand helix in each monomer adopt an antiparallel conformation that masks the target protein interaction site. When the Ca^{2+} ion binds, the C-terminal end undergoes a large conformational change (Figure 1B). HIII helix, by making a 90° degree movement, allow the structure to exposure of a large hydrophobic cleft that mediates the target recognition. Meanwhile, the N-terminal EF-hand shows a minor structural change (Figure 1 A, B). This conformational change involves the residues of the hinge region, helix HIII and C-terminal, regions that exhibit the greatest variation in amino acid sequence throughout the S100 family.

Helix HI and HIV hardly move during Ca^{2+} binding, maintaining the dimeric state of the S100 proteins. Residue invariance and conserved spatial arrangement of helices at the dimer interface form the main basis of heterodimer formation. In the absence of Ca^{2+} ions, the EF-hand region is available to bind Na^{+} or Mg^{2+} ions. In fact; the affinity of this region for Mg^{2+} ions are very low and only have a small effect on Ca^{2+} binding (13). A study showed that calprotectin (CP), a S100A8/S100A9 oligomer, can also bind iron (Fe^{2+}) (22).

Interestingly, although S100 protein family members share high sequence similarities and exhibit similar folding behavior, they differ in shape and charge (23, 24). Effects of S100 proteins on a wide variety of target proteins may be explained by the fact that each S100 family member has different expression profiles from each other, as well as specific target binding regions that differ in the hinge region and C-terminal extension (10, 24).

Expression and regulation

So far, S100 proteins have only been detected in vertebrates (23). In humans, genes of the S100A subfamily cluster on chromosome 1q21, while genes of other S100 members are located on chromosomes 21q22 (S100B), Xp22 (S100G), 4p16 (S100P), and 5q13 (S100Z) (25, 26). Generally, a S100 gene consists of three exons and two introns; exon 1 is not translated, exon 2 and exon 3 encode EF-hand structures (27).

Contrary to Moore's initial hypothesis that S100 proteins are expressed only in the nervous system, later it has been shown that; members of the S100 protein family have been expressed in a variety of tissues. However, each S100 protein family member appears to have a specific expression pattern and these expression levels vary between each cell type. For example, S100A9 is expressed in immune cells, while S100A3 is found mainly in hair cuticular cells. (28, 29). Some S100 proteins are also expressed in a cell cycle dependent manner. For example, while S100A2 expression is almost absent in G0 phase, its expression increases in early G1 and S phase in epithelial cells (30).

The clustered genes of the S100A subfamily on chromosome 1q21 are part of the epidermal differentiation complex (EDC) and are therefore regulated by the transcription factors (eg, Klfch, Grhls, Arnt) (31). However, cell-specific expression of these genes indicates that other factors such as epigenetic mechanisms (DNA methylation) also play a role in the regulation of the S100 genes. Although these epigenetic changes are not yet fully understood, it is assumed that the S100 genes, among others, are silenced by the methylation of cytosine within CpG pairs of regulatory regions (27). In addition, it appears that the expression of some S100 protein family members is regulated by microRNA (miRNA). Thus, Choe et al. demonstrated that S100A4 is negatively controlled by miRNA-124 (32). Recently, Wen et al. described S100B down-regulation by miR-135b in cerebral palsy rat models (33). Various studies have showed that extracellular stimuli such as growth factors and cytokines, as well as intracellular signaling cascades, may affect S100 protein levels (34). Since the S100 proteins lack the structural sequence for the classical ER/Golgi secretion pathway, a potential active secretion mechanism is not fully understood (35).

Functions

S100 proteins have both intracellular and extracellular functions; mainly in proliferation, differentiation, apoptosis and migration of cells, also Ca^{2+} homeostasis and inflammation process; by affecting various target cells (8, 36).

Intracellular functions of S100 proteins include calcium homeostasis, regulation of enzyme activity and protein phosphorylation, cytoskeletal components, and transcriptional factors. Ca^{2+} is involved in almost every cellular process, and high Ca^{2+} concentrations lead to cell death; therefore tight regulation of Ca^{2+} levels is essential (37). S100 proteins maintain cellular Ca^{2+} homeostasis not only by binding free intracellular Ca^{2+} to the plasma membrane but also transporting Ca^{2+} through the plasma membrane. It also interacts with transmembrane proteins such as plasma membrane Ca^{2+}-transporting ATPase 1b (PMCA1b), transient receptor potential vanilloid subfamily member 6 (TRPV6) and Na^{+}/Ca^{2+} exchanger (NCX1) (36). The prominent example is S100A1, as it interacts with the sarcoplasmic reticulum ATPase (SERCA2a) and cardiac ryanodin receptor 2 (RyR2), which enhances systolic release and diastolic uptake of Ca^{2+}, modulating the contractile performance of cardiomyocytes (38). Also, the S100 family of proteins is associated with the inflammation process and the immune response. S100A8, S100A9 and S100A12 exhibit the characteristics of damage associated molecular patterns (DAMPs), also named as alarmin (39, 40). DAMPs are danger signals released by damaged, infected or dying cells, and they trigger an inflammatory response (41).

DAMPs play a key role in the pathogenesis of many inflammatory diseases, including rheumatoid arthritis (RA), osteoarthritis (OA), and atherosclerosis. After cell damage/stress or activation of immune cells, including neutrophils and macrophages, S100 proteins are released into the extracellular space where they play a key role in the regulation of various immune and inflammatory processes (42). S100A8/A9 and S100A12 can be released from neutrophils with active release of neutrophilic DNA content in a process called neutrophil extracellular netlike structures (NET-osis), and NET-derived S100A8/A9 can promote IL-1 expression.

Most of the extracellular S100 proteins can act as DAMP molecules to activate both immune and endothelial cells by binding to receptor for advanced glycation end products (RAGE) and Toll-like receptor 4 (TLR4). The binding of S100A9 and S100A12 to these receptors stimulates NF-κB signaling, resulting in up-regulated expressions of cytokines and proinflammatory factors such as IL-1β or TNFα (42, 43). In addition; S100A7, S100A8, S100A9 and S100A15 have been shown to have chemotactic properties that attract neutrophils and lymphocytes (30, 43). S100A7, S100A12 and S100A15 also support the initial immune response by reducing the survival of pathogens such as Escherichia coli (E. coli) (30).

In the literature; controversial data is found about the cellular receptors related to calgranulins. Previously; it has been reported that both S100A8/A9 and S100A12 bind to RAGE and the later hexameric form is reported to be a RAGE ligand. Recent studies have been suggested that RAGE ligation with S100A12 triggers a pro-inflammatory cascade in microvascular endothelial cells, macrophages, and lymphocytes, resulting in NF-κB activation. It is suggested that this triggers further RAGE expression, increasing inflammation and thus activating a feed-forward cycle that may result as a severe inflammation response (9, 44). However, most studies indicate that S100A8/A9 and S100A12 promote inflammatory signaling through TLR4 (42, 45-47). It is assumed that TLR4 binding is mediated by S100A8, which is a part of the S100A8/A9 complex. On the other hand; S100A12 should be arranged in a hexameric quaternary structure in order to bind TLR4, expressed in human monocytes (44). It has been reported that TLR4 signaling by S100A8/A9 and S100A12 may induce pro-inflammatory cytokine expression by myeloid and lymphoid cells and promote myeloid cell migration (44).

Over expression of S100A8/A9 and S100A12 appears to be associated with some autoinflammatory diseases (44).

Clinical Relationship of S100 Proteins

Since S100 proteins can be identified in body fluids, increased expression levels are indicative of pathological conditions and are used as biomarkers to detect a particular disease (48). Many S100 proteins and their signaling pathways are linked to numerous pathological conditions and diseases such as cancer (breast, prostate, bladder, lung, colorectal, melanomas etc.), inflammatory diseases (such as arthritis, psoriasis, Crohn), neurological disorders (such as Alzheimer, Amyotrophic Lateral Sclerosis, Parkinson, schizophrenia) and cardiomyopathies. Disregulation of these proteins can have serious consequences. Therefore, several studies have shown that they are promising markers for diagnosis and possible new treatment goals (44, 48, 49).

S100 Proteins in Autoinflammatory Diseases

Although, S100 proteins are not only specific for autoinflammatory processes; but in some autoinflammatory disorders the over expression of proinflammatory cytokines provides a sterile inflammatory environment that triggers the expression of calgranulins (S100A8 (Calgranulin A), S100A9 (Calgranulin B) and S100A12 (Calgranulin C)), resulting in the maintenance of the disease activity. Moreover, these proteins may also detect the subclinical inflammation and monitoring the immunological remission (9, 50).

Significantly elevated levels of S100 proteins are a hallmark of systemic juvenile idiopathic arthritis (sJIA), Familial Mediterranean Fever (FMF) and inflammatory diseases associated with proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1), such as pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome or PSTPIP1-associated with myeloid-related proteinemia inflammatory (PAMI) syndrome and differentiate these conditions from other infectious or autoinflammatory conditions (9). In contrast, S100 levels are lower in cryopyrine-associated periodic syndromes (CAPS) or periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome and are within the normal range of pro-inflammatory levels.

As a result, it has been proposed that S100 proteins are related with the disease activity but not useful for the differential diagnosis of autoinflammatory conditions from infectious diseases. Moreover, S100 proteins known to reflect the degree of inflammation more than acute phase proteins (51, 52).

FMF is an autoinflammatory syndrome associated with the activation of phagocytic cells and the excessive secretion of IL-1β. Mutations in domains of pyrin proteins are the genetic basis of FMF, leading to the activation of proinflammatory pathway through IL-1β production (51).

Extremely high levels of S100A12 in FMF, unlike other autoinflammatory diseases, indicate that S100A12 proteins released from mainly neutrophils and this may play a role in the pathogenesis of the attack period of this disease. S100A8/A9 localizes in the cytoskeleton and has exhibit a tubulin dependent release rather than a Golgi independent process (53). Colchicine blocks tubulin-dependent processes at the molecular level and is therefore a possible alternative secretion inhibitor (9).

Juvenile Idiopathic Arthritis (JIA) is a chronic disease characterized by persistent joint inflammation. Various studies have reported that S100A8/A9 and S100A12 levels are related with the disease activity and determine the severity of inflammation in patients with JIA (54, 55). However, the exact pathogenic mechanisms in JIA are still elusive. Several studies have reported controversial results dependent the evidence of the relationship between S100 proteins and disease activity (52). The association between the S100 proteins family and certain types of rheumatologic diseases are listed in Table 1. Further studies of the predictive and potential effect of the S100 proteins should be performed in larger cohort studies.

Table 1. The association between the S100 proteins family and certain types of rheumatologic diseases

S100 Proteins	Disease	References
S100A4	RA	(65)
S100A8, S100A9 and S100A12	JIA	(66)
S100A8/A9) and S100A12	sJIA	(51, 52)
S100A8/A9	Synovitis-associated pain	(67)
S100A8/A9	RA, JIA, spondyloarthritis	(51, 68)
S100A11	OA	(68)
S100A12	SLE	(69, 70)
S100A12	Kawasaki disease	(71-73)
S100A8/A9 and S100A12	FMF	(74)
S100A8/A9	PAPA, PAMI	(75)
S100A8/A9, S100A12	PFAPA	(76)

FMF: Familial Mediterranean Fever; JIA: Juvenile idiopathic arthritis; OA: Osteo arthritis; PAMI: PSTPIP1-associated myeloid-related proteinemia inflammatory syndrome; PFAPA: Periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome; PAPA: pyoderma gangrenosum and acne syndrome; RA: Rheumatoid arthritis; sJIA: Systemic juvenile idiopathic arthritis; SLE: Systemic lupus erythematosus.

Use as a biomarker

In order to use S100 proteins or cytokines as available biomarkers they should predict the initial diagnosis, accurately reflect the disease activity, and easily applicable for analysis with high reproducibility (9). Autoinflammatory disorders are a heterogeneous group of diseases with variable progression and response to different treatment strategies depends on the individuals (54-59). Because of this heterogeneity, better biomarkers should be required involving among the all aspects of patient care. Assessment of disease activity is currently based on a combination of clinical evaluation (e.g. Auto-Inflammatory Disease Activity Index-AIDAI) and routine laboratory parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum amyloid A (SAA). However, these parameters have little predictive value for the prognosis. (9).

Serum levels of S100 proteins have been proven as a useful biochemical marker that reflects the disease activity (9, 56, 60).

Laboratory Assay Methods

ELISA (Enzyme Linked Immunosorbent Assay) is commonly used for detecting S100 proteins in serum and plasma, for clinical diagnosis (61). It has been also reported that S100 proteins can be detected by various analytical methods such as immunoradiometric assay (IRMA), western blot, mass spectroscopy (MS), polymerase chain reaction (PCR) and electrochemiluminence (62-64). Assays for the detection of S100A8/A9 and S100A12 are commercially available. However, it is not feasible to precisely compare the performance of all these tests (9).

CONCLUSION

The S100 protein family are considered as sensitive biomarkers for inflammation process in a wide range of diseases. These proteins have been used not only for the monitorization of subclinic period of the disease. Although, some of these proteins have been already used in several autoinflammatory diseases like systemic JIA; further studies should be required for widely clinical use among autoinflammatory disorders.

Conflict of interest

No conflict of interest was declared by the authors.

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