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Role of S100 in immunity.

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Abstract

S100 are acidic proteins with a molecular weight range of 10-12 KDa that firstly recognized in 1965. They are mostly able to form homodimer and/or heterodimer molecules and considered useful biomarkers for different diseases especially those of inflammatory and autoimmune in nature. The proteins of S100 are mostly coded for by closely linked genes inside a region on the long arm of human chromosome 1 (1q21.3) and have a specific tissue or cell typespecific expression pattern. The S100 proteins can be grouped under the superfamily of EF-hand (a helix-loop-helix structural domain or motif) calciumbinding proteins because they show dual calcium-binding domains; N-terminal S100-specific EF-hand and a C-terminal canonical EF-hand. Diverse intracellular and extracellular functions have been linked to S100 proteins and through which they impact various cellular processes; including, apoptosis, proliferation, migration, energy metabolism, differentiation, calcium ions homeostasis and inflammation. They are also able to interact with various cellular receptors enabling S100 proteins to modulate innate and adaptive immune response with some influence on cell migration and chemotaxis, as well as tissue modeling, growth and repair. Based on these functions, S100 proteins are regarded as alarmins playing significant role in etiology and pathogenesis of juvenile autoimmune and autoinflammatory diseases. A dysregulation of S100 proteins has also been described and represented a prominent factor in pathogenesis and development of various diseases; for instance Alzheimer disease, RA and cancer in general 14. One group of S100 proteins is calgranulins, which comprises A (S100A8), B (S100A9) and C (S100A12) calgranulins.

Keywords: Lung cancer, Bronchoalveolar lavage fluid, YKL40, KRT5, Early diagnosis.

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Introduction

S100A8 and S100A9 are known as MRP8 and MRP14 (Myeloid Related Proteins 8 and 14, respectively) due to their particular high level in myelogenous cells (monocytes and granulocytes). However, the expression of both proteins is also inducible in activated cells under inflammatory conditions; for instance, keratinocytes, epithelial cells, and osteoclast [1]. The S100A8 and S100A9 form heterodimeric complexes (called calprotectins) under high extracellular calcium concentrations, and represent their dominant forms in the majority of biological processes [2]. The intracellular role of calprotectins has not been well-defined, although they constitute about 40% of neutrophils and 5% of monocyte cytosolic proteins. However, the intracellular function depends on a calcium-dependent interaction with cytoskeletal component; such as actin filaments, keratin and microtubule [3]. Further and due to their abundance in the cytosol of phagocytes, it has been presented that calprotectins play critical roles in various cellular processes that include motility and danger signaling, and their interactions modulate the activity of target proteins [4]

Materials and Methods

A further important member of calgranulins is S100A12 that is classified under the calcium binding proteins of S100 family. It functions as a proinflammatory cytokine-like protein, which is first isolated and described in human in 1995 main cellular source of S100A12 is neutrophil granulocytes and macrophages [5]. A lower level of expression has been described in monocytes, while epithelial and dendritic cells have also shown to express S100A12 but at the early stages of differentiation. However, as this alarmin is granulocyte-specific, it is suggested to consider it as an activity indicator of these cells [6]. Several pleiotropic properties are described for S100A12; pro-inflammatory effects, chemotaxis and intracellular signaling cascade activation that leads to production of inflammatory cytokine and oxidative stress induction. The pro-inflammatory effects of S100A12 are mediated through interaction with receptor for advanced glycation end products (RAGE) and TLR-4 [7]. The interaction with RAGE activates inflammatory cells; such as macrophages and lymphocytes, while induction of monocyte activation occurs through interaction with TLR-4. The interaction of S100A12 in both cases triggers the activation of nuclear factorkappa B (NF-κB). Such reactions enhances the target

cells to produce proinflammatory cytokines (IL-1β and TNF-α) and molecules of adhesion; such as Vascular Cell Adhesion Molecule-1 (VCAM-1) and Intercellular Adhesion Molecule-1 (ICAM-1) [8].

Results and Discussion

S100A8 and S100A9 and inflammation

The S100A8 and S100A9 are also shown to be produced in various inflammatory diseases. They act as alarmins that account for the bulk of inflammatory reactions in different cells; for instance, lymphocytes, phagocytes, endothelial cells and osteoclasts [9]. It has also been noticed that myeloid cells can excrete S100A8 and S100A9 proteins into the extracellular compartment through two mechanisms; passive and active. The passive release mostly occurs due to damage to affected tissues through necrosis or *via* extracellular traps of neutrophils. On the contrary, the active synthesis of S100A8/S100A9 complexes during inflammatory processes is dominated by activated phagocytes in a specific energy-dependent process that is triggered by their contact with endothelial cells 15 during the process of inflammation. Therefore, calprotectins are suggested to have a role in the inflammatory processes, and their significance in diagnosis, pathogenesis and monitoring of rheumatic disorders has gained an important attention in recent years [10]. As shown in Figure 1, different cells are influenced by the extracellular S100A8/S100A9 complex; such as T cells, mononuclear cells (including macrophages), neutrophils and dendritic cells, in which pro-inflammatory and anti-inflammatory responses are induced (Figure 1) [11].

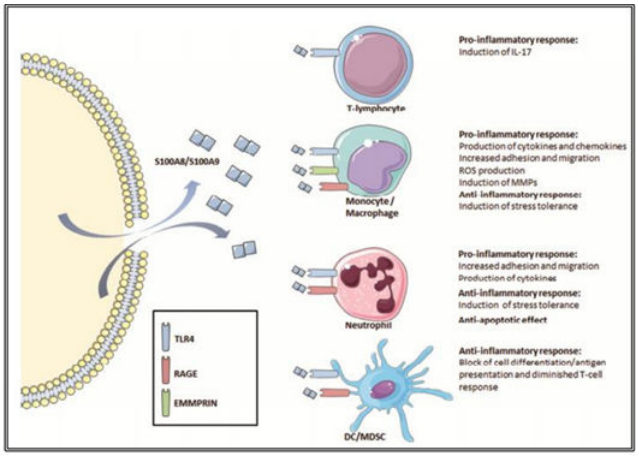

Figure 1. *Extracellular effects of S100A8\S1009 complex on T lymphocytes, monocytes, and macrophages, neutrophils and dendritic cells.*

Stimulation of neutrophils by S100A8\S1009 has been associated with an increased expression and activation of selectins and integrins, as well as initiated TLR-4-dependent pathway of neutrophil activation. In a consequence, a slow rolling of neutrophils occurs and their adhesion to endothelial cells is enhanced at site of inflammation [12]. It has been further demonstrated that survival and counts of neutrophils are regulated by exposure 16 S100A8\S00A9 proteins through their anti-apoptotic effects, which are enhanced and mediated by CD11b\CD18 and TLR-4, as well as mitogen activated protein kinase signaling pathway [13]. Similarly, monocytes are triggered by S100A8 and S100A9 to increase their adhesion to fibrinogen through enhancing the cellular expression of CD11b, and such triggering render the monocytes to be included in the process of inflammatory at induction sites [14]. A further contribution of S100A8 and S100A9 to inflammation is through their inducing effects on synthesis of chemokines, which in turn, the recruiting and migration of cells to the site of inflammation are induced and facilitated [15]. Various inflammatory triggers that lead to activate monocytes or granulocytes and their local release of S100A8/S100A9 dimers are given in Figure 2. Gene expression analyses of S100A8 stimulated monocytes have identified up-regulations in functional genes involved in enhancing inflammatory reactions; such as cell migration, leucocyte activation, and intracellular trafficking and signal transduction [16]. The development of functional auto-reactive CD8+T-cell has also been reported to be promoted by S100A8 and S100A9; an observation that suggests their role in autoimmunity [17]. Pro-regulatory inflammatory properties have been further exhibited by S100A8 and S100A9, and these properties are necessary to prevent exaggerated immune responses and tissue destruction. In laboratory animals with lipopolysaccharide-induced tolerance, S100A8 and S100A9 simulation was associated with hypo-inflammation induction in phagocytes [18]. The regulatory properties of S100A8/S100A9 have been further investigated in a mouse model of allergic contact dermatitis. Prolonged exposure to these proteins blocked the differentiation of dendritic cells and their capacity in antigen presentation, and consequently T-cell response was decreased [19]. It is widely accepted that myeloid-derived suppressor cells can suppress immune response, especially those of T-cells. In this context, it has been demonstrated that STAT-3 (signal transducer and activator of 17 transcription-3) is able to induce S100A8 and S100A9 expression on myeloid precursors. Such induction resulted in accumulation of myeloid-derived suppressor cells, which in turn caused decreased maturation of macrophages and dendritic cells (Figure 2) [20].

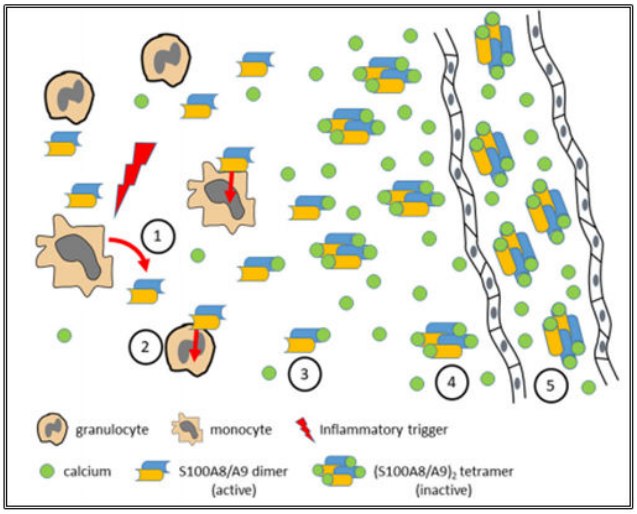

Figure 2. *Inflammatory triggers involved in activation of*

monocytes and granulocytes to release of S100A8/S100A9 dimers (1). Inflammatory response is amplified and perpetuated due to binding of S100A8/S100A9 to TLR-4 on different target cells and the (2). With increasing concentrations of calcium ions toward systemic circulation, dimers of S100A8/S100A9 bind calcium ions (3) and form tetramers [(S100A8 andS100A9)$_2$] (4), which have no inflammatory activity because TLR-4 binding site is hidden in the interface of the tetramer. In systemic circulation, high concentrations of calcium ions terminate the side-effects of systemic inflammatory via stabilization of inactive tetramers [(S100A8andS100A9)$_2$] (5), which are beneficial biomarkers in the monitoring of local disease activity [21].

S100A8 and S100A9 and autoimmune disease

Based on the aforementioned presentations, both inflammatory and anti-inflammatory functions are ascribed to S100A8 and S100A9 or their heterodimer complex. With respect to inflammatory functions, it has been demonstrated that the synovial sub-lining layer of psoriatic arthritis patients 18 show an intense expression of S100A8 and S100A9, and accordingly the importance of both proteins in mediating migration of leukocytes across the endothelium was suggested. Such up-regulation was observed in serum, synovial fluid and psoriatic arthritis plaques of patients [22]. Further investigators considered S100A8 and S100A9 as potentially more sensitive biomarkers for disease activity in rheumatoid diseases than the conventional inflammatory parameters; such as ESR and C-Reactive Protein (CRP), because they directly reflect the status of inflammation in synovium of patients [23,24]. In further rheumatic diseases (ankylosing spondylitis, Sjögren's syndrome and Still's disease), alterations of S100A8/S100A9 level have been positively associated with disease activity[25]. In JIA, S100A8 and S100A9 have been under intensive investigation, and their serum levels were positively correlated with other inflammatory parameters (ESR and CRP) [26]. Their synovial fluid levels in the inflamed joints were reported to be higher than those in serum. In addition, S100A8/S100A9 complex has been augmented to be important biomarker for diagnosing systemic JIA [27]. Compared to healthy children or patients with systemic infections (autoinflammatory chronic infantile neurological cutaneous and auricular syndrome), levels of S100A8/S100A9 complex were significantly elevated in sera of patients with systemic active JIA [28]. The serum level of these proteins has also been used to detect the sub-clinical inflammatory activity in systemic JIA. Moreover, S100A8/S100A9 levels predicted JIA relapse after therapy withdrawal in patients [21]. It has been further suggested that S100A8 and S100A9 proteins are important biomarkers for forecasting the disease process and predicting the JIA remission [29]. Although much of the presented concern has considered the proinflammatory functions of S100A8 and S100A9, it has also been found that the complex of both proteins shows anti-inflammatory effects under specific 19 conditions in order to avoid tissue damage due to progressed inflammation. Such effects are modulated by the production of mediators that have proinflammatory influences; such as cytokines, chemokines, reactive oxygen species and nitric oxide [30].

Role of S100A12 in arthritis

The produced mediators from the reactions of S100A12 with RAGE and TLR-4 have been implicated in the pathogenesis of inflammatory conditions, and therefore, S100A12 is suggested to plays a crucial role in immune response participating in recruitment of inflammatory cells [1]. Recent investigations suggested that the protein S100A12 could be of a significant importance in evaluating and assessing the clinical profile of different inflammatory disorders. Overexpression of S100A12 in inflamed tissues has been demonstrated in patients with psoriatic arthritis, RA and inflammatory bowel diseases. Serum level of S100A12 has also been considered as a biomarker of disease activity in children with Kawasaki disease [6]. Accordingly, serum levels of S100A12 have emerged as a significant biomarker of rheumatic diseases. It has been demonstrated that S100A12 showed an increased expression in the synovial fluids of patients with RA and psoriatic arthritis, but not in osteoarthritis, which is a non-inflammatory disease. It has been further presented that S100A12 serum levels were higher in RA patients than in healthy controls [31]. Moreover, elevated levels 21 of S100A12 protein were detected in both the synovial fluid and serum of RA patients with the erosive forms of disease compared to non-erosive RA. Thus, S100A12 has been suggested to be significantly associated with inflammation and bone erosion in RA patients [32,33]. Among JIA patients, the investigation-based data suggest that S100A12 is up-regulated and it can be considered as a useful biomarker of the disease. It has been demonstrated that synovial fluid level of S100A12 was 10-folds higher than in serum of JIA patients. The authors also suggested that S100A12 is a potential reliable marker of joint inflammation [34]. Furthermore, serum levels of S100A12 were significantly higher in JIA patients with active disease compared to children with stable remission. Serum levels of S100A12 were also elevated in JIA patients who were exacerbated within six months after assessments. Similar findings were in JIA patients who did not maintain remission for two years [35-36].

Conclusion

The S100A12 was further considered as the best assigned biomarker for prognosing JIA flares. A correlation with response to therapy has also been presented, and JIA patients with a good response to methotrexate and TNF inhibitors had elevated baseline levels of S100A12 compared to therapy-refractory children. In addition, S100A12 levels measured at the time of withdrawal in JIA patients predicted the flare development better than S100A8/S100A9, while measuring S100A12 and high-sensitivity CRP had a better prediction potential.

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