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Journal of Dermatology and Dermatitis
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Review Article

Prospects for studying the role of S100 proteins in allergic and inflammatory skin diseases

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Received date: March 27 2022; **Accepted date:** April 11, 2022; **Published date:** April 20, 2022

Citation: Pyagay G.B, Sydikov A.A, Muhamedov B.I, Pyagay O.G, Ibragimova N.S, at el. (2022) Prospects for studying the role of S100 proteins in allergic and inflammatory skin diseases. *J. Dermatology and Dermatitis*. 7(2); DOI:10.31579/2578-8949/098

Abstract

The article is devoted to the review of recent discoveries in the field of the role of S100A8/A9 proteins in the pathogenesis of various diseases. It has been shown that proteins of this group play a significant role in many diseases in cardiology, oncology, inflammatory bowel diseases, etc. of various organs and systems, as a result of which they should be used as markers for determining the severity of diseases and prognosis. Therefore, the study of the expression of these proteins in allergic and inflammatory skin diseases is a promising scientific direction.

Keywords: S100A8; S100A9; calgranulin; calprotectin; inlammatory

Increased attention has recently was given to the study of proteomics. It has been shown that the number of proteins far exceeds the number of genes encoding them. Involvement of proteins in all biological processes (phosphorylation, ubiquitation, glycosylation, etc.) justifies the interest in studying them for a deeper understanding of pathogenetic mechanisms underlying various conditions. Proteomic analysis is widely used in the diagnosis of a number of disorders, including oncological diseases [4,18,19,25,26], cardiovascular pathology [9], diseases of the respiratory system [31], systemic connective tissue diseases [8,20], inflammatory and autoimmune intestinal lesions [2,10,13,15,21], etc. There have been reports about the significant role of calprotectin in the pathogenesis of Covid-19 [12], the study of which in the future will allow to adjust the treatment standards. Among the S100 family of proteins, from our point of view, the study of MRP8 and MRP14 (myeloid-related proteins) is of particular interest - S100A8 (calgranulin A) and S100A9 (calgranulin B), respectively. These proteins are the products of myeloid differentiation of cells, mainly exist as heterodimers S100A8/A9 (calprotectin) due to the fact that homodimers are unstable forms. They are widely expressed in neutrophils, keratinocytes, phagocytes. Also, they have antimicrobial effects, broad biological activity on inflammatory processes, and therefore, have diagnostic and prognostic value.

Thus, G.V. Kokurina et al. [14] suggest the widespread adoption of proteomic technologies as prognostic markers for squamous cell carcinomas of the head and neck. For the purpose of early diagnosis, as well as the prognosis of the sensitivity of tumors to chemotherapeutic drugs, it is proposed to identify proteins, among which the proteins of the S100 family are mentioned, in particular S100A8/A9. Martin Boettcher et al. [2] indicate that a disruption of the expression of S100 proteins is observed in several types of cancer. For example, the expression of S100A8 in leukemic blasts predicts poor survival in patients with acute myeloblastic leukemia. It is also known that the stem cells niche of the bone marrow can serve as a protection in hematological malignant diseases and the study of the interaction between leukemic cells and the surrounding mesenchymal stromal cells has shown that leukemic cells can change their environment in their favor. Studies have revealed that AML cells with a high content of S100A8/A9 were characterized by elevated surface levels of maturation markers (such as CD14 and CD11b) as well as metabolically altered important transporters (glucose, fats and amino acids), which causes high chemoresistance of S100A8/A9HIGH cells. The authors demonstrated that the regulation of S100A8/A9 induced by the bone marrow stroma in AML cells activates the Jak/STAT pathway through soluble factors [3,4]. Youyi Chen et al. [7] claimed that the binding of S100A8/A9 to the melanoma cell adhesion molecule (MCAM) leads to the migration of melanoma cells into the lung tissue. In this case, the activation of protein kinase (MAP3K8) by mitogen occurs, which leads to strong activation of the ETV4 transcription factor and subsequent induction of matrix metalloproteinase-25 (MMP25), and finally, to the induction of lung melanoma metastases. Zhao J. Lyu et al. [18] having studied the problem of bladder cancer indicate a significant molecular heterogeneity of this disease due to various molecular changes, which causes large differences in the response to treatment of urothelial carcinoma (UC). Analysis of sequencing data of patients with UC revealed recurrent somatic mutations in the ZNF83 gene in 18% of

patients, which was accompanied by a poor prognosis of the UC. At the same time, the p.E293V mutation in the preserved ZNF83 region increased tumor growth and reduced apoptosis of UC cells both in vitro and in xenotransplanted mouse tumors. ZNF83-WT can mediate the inactivation of S100A8, thereby weakening transcription of S100A8, whereas the ZNF83-E293V mutation disrupts its ability to suppress transcription. Thus, the authors emphasize the importance of using ZNF83 mutation E293V for prognostic purposes as a marker of therapeutic response from NF-kb inhibitors. Sarah Minner et al. [19] having studied the clinical significance of S100A8 expression in prostate cancer, conducted immunohistochemical studies of tumor tissue microchip. It has been revealed that S100A8 immunostaining experienced in intacted prostate tissue, but was lost in 60% of prostate cancer cases. The loss of S100A8 expression correlated with advanced tumor stage, high Gleason degree, high preoperative PSA level, etc. Taking all of this into account, it was shown that the loss of S100A8 expression is associated with adverse features of the tumor and early recurrence in prostate cancer.

Ryohei Sekimoto et al. [24] conducted a study of the S100A8/A9 heterodimer complex in men with abdominal obesity and adipose tissues of mice. The correlation of serum S100A8/A9 level with visceral fat area and body mass index was determined. Similar data were obtained in obese mice in the mature fraction of adipocytes in comparison with lean mice. It has been shown that an increase in the level of the circulating S100A8/100A9 complex can be observed not only in abdominal obesity, but also in fatty and systemic tissue inflammation. Rodriguez et al. [23] report that deletion of the E-selectin gene or inhibition of the neutrophil derivative S100A9 in experiments on mice reduced inflammation in adipose tissue, reducing non-alcoholic steatohepatitis. Similar results were obtained by T. Azramezani Kopi et al. [2]. In a comparative analysis of patients with IBD and healthy people, mRNAs S100A8 and S100A9 were expressed in isolated leukocytes of the first group. Moreover, in the exacerbation phase, these indicators were significantly higher compared to the remission phase.

S100A8 differentiated patients with IBD from control group with the sensitivity and specificity of 73% and 64%, while figures for exacerbation phase of disease and remission phase amounted to 67% and 62%. As for S100A9, it distinguished IBD patients from controls with the sensitivity and specificity of 81% and 70%, and exacerbation phase of disease from remission with the sensitivity and specificity of 68% and 64%.

Juan Marta-Enguita et al. [9] claim that calprotectin (S100A8/A9) is a key protein in the regulation of inflammation and thrombosis in patients with acute ischemic stroke (AIS). During the first 24 hours in patients with AIS, it was determined in plasma, where it was detected by ELISA and in the blood clots themselves, determined by immunostaining. In subsequent studies, higher mortality was noted at three months in patients with higher calprotectin levels. Patients with high levels of S100A8/A9 had more than 4 times higher probability of death. A comprehensive assessment of these indicators with the level of CRP and NLR allows us to predict in more detail the prognosis of these patients.

Goat breast tissue, blood leukocytes and milk somatic cells were examined by F. Y. Purba in order to determine the place of production of antimicrobial peptide S100A8 [22]. mRNA expression and protein localization were studied by PCR with reverse transcription and immunohistochemistry. The level of S100A8 in milk was determined after intramammary tubing of lipopolysaccharides (LPS). This antimicrobial peptide was immunolocalized in the outermost layer of the udder nipple skin with and without LPS infusion, while in the mammary gland it was found only in leukocytes infiltrated in the alveoli after LPS infusion. In addition, S100A8 was detected in blood and milk leukocytes, and its amount in milk was greater than in blood. Thus, it is shown that the protein S100A8 is produced in leukocytes and its secretion is affected by stimulation of LPS.

Agueda Castro-Quintas et al., who examined pregnant women, report a close relationship of psychological stress with the hypothalamic-pituitary-adrenal axis, contributing to the persistent release of cortisol [5]. Chloe Taub studied women with breast cancer and revealed the relationship of psychological stress, cortisol levels with serum S100A8/A9 (evaluating it as one of the cancer markers). The authors suggest the existing psycho neuro endocrine way of their interaction, as a result of which by cognitive behavioral training, relaxation training, etc. serum levels of cortisol and S100A8/A9 were monitored for 5 weeks [26].

Lincoln H. Gomes et al. indicate to the antioxidant features of the S100A8 protein. It was revealed that recombinant S100A8 is very sensitive to the equimolar HOCl ratio, generating intermediate compounds of sulfinic and sulfonic acids and new forms of oxatiazolidinoxide/dioxide. Oxidized S100A8 was detected in the lungs of asthma patients, and also it was determined in their sputum, significantly exceeding the quantitative indicators in the control group. Studies of the oxidation of the Cys32 residue by the recombinant S100A9 monomer were weak at the same time. Oxidized Net63, Net 81 and Met94 were present in S100A9 in different ways [11]. Hence, the conditions under which activated phagocytes produce hypohalogenic acid oxidants highlight the need for a deeper study of antioxidant defense mechanisms and, in particular, the role of S100A8. Andrey V. Chernov et al. [8] note that S100A8 and S100A9 are the main induced genes in nerves after injury. The S100A8/A9 heteromer activates chemotactic genes and pathways in Schwann cells, stimulating the infiltration of myeloid cells into the nerve. Meili Wu et al. [30] revealed a significant increase in the proteins S100A8 and S100A9 in the serum of patients with multiple sclerosis and associate this with damage to the progenitor cells of oligodendrocytes with subsequent activation of microglial cells. Their stimulation increases the expression of proinflammatory cytokines interleukin 1ß (IL-1ß) and tumor necrosis factor-α (TNF-α), which exacerbate damage to oligodendrocyte progenitor cells. The authors applied the S100A8/A9 treatment for the first time and revealed activation, proliferation and migration of the BV-2 mouse microglia cell line, proving that this treatment caused cells to switch from the anti-inflammatory activated (M2) phenotype to the pro-inflammatory activated (M1) phenotype. The level of protein P65, which is a phosphorylated nuclear factor-KB (p-NF-kb), was significantly increased, the production of proinflammatory factors (IL-1β, TNF-α, MMP-9) and chemokines (CCL2, CCL3, CXCL10) were also increased in the treated BV-2 microglial cells S100A8/A9. Moreover, inhibition of phosphorylation of NF-KB P65 changed the effect of S100A8/A9 on the production of proinflammatory factors and chemokines.

Yu-Dong Xu et al. revealed the ability of S100A8 to regulate the hyperreactivity of the respiratory tract expressed by their hypercontractivity in asthma caused by an allergen [31]. Treatment with recombinant S100A8 (RS100A8) reduced this hyperreactivity of the respiratory tract in experiments on rats sensitized to eggs. S100A8 significantly reduced the level of phosphorylation of the myosin light chain in smooth muscle cells induced by acetylcholine. The authors conclude that S100A8 should be a new therapeutic target for controlling the contractility of smooth muscle in asthmatic conditions.

Gwenael Nysa et al. [20] in the study of patients with rheumatoid arthritis (RA) noticed a correlation of serum amyloid and S100 proteins (S100A8, S100A9 and S100A12) in the development of this disease. Thus, overexpression of these proteins was found in patients with RA in comparison with control group, regardless of the stage of the disease. However, the negative correlation between the isoforms of serum amyloid SAA1a and SAA1ß in the early stages of the disease indicates that regulatory mechanisms in these diseases are still unknown. Wasan W. Al-

Bassam et al. [29] studied a group of patients with juvenile idiopathic arthritis (JIA). After evaluating the serum levels of S100A8, S100A9 and S100A12, ferritin and TLR4, the authors found a significant increase in the levels of S100A9 and ferritin compared to the control data. A significant correlation of these indicators with the JIA was revealed. The sensitivity of S100A8, S100A9 and S100A12 was 63%, 70% and 61%, respectively, whereas the figures for specificity formed 60%, 66% and 60%, respectively. In a deep multivariate analysis, S100A9 and ferritin were significant predictors, especially in combination with C-reactive protein (CRP), rheumatoid factor (RF), low JADAS27.

Christoph Kessel et al. [15] studied the level of 50 biomarkers in the blood serum of patients with Crohn's disease and ulcerative colitis. 9 cyto- and chemokines, including S100A8/A9, were the most sensitive in the group of patients with relapse outbreaks, which, according to the authors, will optimize individual therapy to maintain remission. Siwen Wang et al. [28] pointed to the great potential of the S100A8/A9 heterodimer as a biomarker in inflammatory diseases, claiming that this protein is expressed in neutrophils and monocytes as a Ca2+ sensor, participating in arachidonic acid metabolism and cytoskeletal rearrangement. The release of S100A8/A9 during inflammation leads to the attraction of leukocytes and induces the secretion of cytokines, as a result of which, in addition to the diagnostic role, it should also be a therapeutic target. Blockade of S100A8/A9 activity with the help of low molecular weight inhibitors in experiments on mice improved their pathological condition, which may be a justification for expanding their use in therapeutic practice. Yu Fujita et al. [10] experimentally showed in mice that the loss of ubiquitin ligase E3 RNF5 in intestinal epithelial cells leads to increased secretion of S100A8 which induces CD4+ in the mucosa, leading to pro-inflammatory reactions of Th1. Administration of antibodies neutralizing S100A8 to mice treated with dextran sodium sulfate (DSS) weakens the development of acute colitis and increases survival. In addition, an inverse correlation of RNF5 and S100A8 protein was found in intestinal epithelial cells in patients with inflammatory bowel diseases. Similar data are reported by Kohki Okada et al. in experiments on rats treated with Dextran Sodium Sulfate (DSS) or in combination with tacrolimus (TMR) [21]. Biomarkers of inflammation such as CRP and inflammatory cytokines were measured by enzyme immunoassay (ELISA). In doing so, CRP and some inflammatory cytokines did not correlate with r-S100A8/A9, but the deterioration of the rectal epithelium structure was not as serious as when using TMR. It was determined that the level of r-S100A8/A9 in the blood serum varies depending on the severity of experimental UC. In experiments on dogs with chronic inflammatory enteropathies (CIE), the levels of S100A8/A9 and S100A12 in blood serum and feces were analyzed to determine the activity of mononuclear cells of the intestinal mucosa. Biopsied areas of intestinal tissues were subjected to histopathological and immunological assessment for the presence of S100A8/A9 and S100A12. Cells S100A8/A9 and S100A12 were identified in all segments of the gastrointestinal tract with predominant localization in its own plate.

The pandemic of a new coronavirus infection and the important role in the pathogenesis of the immune system disease causes interest in studying the proteins of the S100 family and their role in inflammatory processes. Guo et al. [12] discovered a reliable induction of alarmin S100A8 by coronavirus infection, studying macaques and mice infected with SARS-CoV-2, as well as in people infected with this virus. It is notable that the authors using a specific inhibitor S100A8/A9 - paniquimod achieved almost 100% survival rate in mice, as it contributed to a significant reduction in viral load and saved from pneumonia.

This analysis of the literature indicates a high interest in calprotectin and its constituent calgranulins, on the part of scientists from different fields for diagnostic, prognostic purposes, and also as a target for improving therapeutic results. A logical continuation, in our opinion, would be an in-depth study of these proteins in the pathogenesis of dermatological diseases, especially inflammatory and allergic skin conditions, which make up a significant proportion of the overall incidence in dermatology.

Qingling Zhu et al. [33] studied the level of 100A8/A9 and inflammatory factors, including TLR4, nuclear transcription factors (NF-kb) and tumor necrosis factor-α (TNF-α) in brown Norwegian rats with mild food allergies. For this purpose, rats of the experimental group were sensitized to ovalbumin and, by assessing the level of specific serum IgE (OVA-IgE), a successful model of food allergy was established in comparison with the control group. Analysis of the results of the level of all inflammatory factors at certain intervals showed a significant increase in their values, by 21,28,35 and 42 days, and there was a positive correlation between serum levels of 100A8/A9 and cytokines associated with inflammation. It should be noted that higher levels of 100A8/A9 were observed earlier than TLR4 and TNF-α, which indicates the interaction of immune and inflammatory factors in food allergies.

Thus, Young-Sook Lee et al. [17] in 2008 studied the functional role of S100A8 in X-ray irradiated keratinocytes on cell cycles and the process of apoptosis. It was revealed that X-ray radiation induced the expression of S100A8 in the mouse epidermis. It was revealed that overexpression of S100A8 initiated by recombinant adenovirus transduction led to increased cell proliferation compared to the control group, thereby the authors claim that there is a mechanism of overexpression of S100A8 protecting against excessive apoptosis caused by X-ray radiation. Andreas Voss et al. [27] studied the effect of S100A8/A9 on the proliferation and differentiation of creatinocytes and revealed the mechanism of stimulation of this heterodimer on NADPH oxidase in keratinocytes, which in turn increases the activation of NFjB, which plays a vital role in the balance of epidermal growth and differentiation. S100A8/A9 positive HaCaT cells are usually present in cells with reduced division rate and greater expression of the markers of differentiation of involucrin and phyllagrin. Moreover, positive S100A8/A9 cells also have better cell survival compared to mutant cells, as a result of which it is suggested that S100A8/A9 mediated growth arrest may affect the consequences of tissue remodeling and repair.

Arby Abtin et al. [1] determined antimicrobial properties of the heterodimeric S100A8/A9 complex in keratinocytes. Cultures of gram-negative bacteria activated the expression of S100A8 and S100A9. To identify molecular patterns associated with pathogens responsible for the regulation of S100A8 and S100A9, keratinocytes were stimulated by Toll-like receptor ligands (TLRs) and quantitative real-time PCR analysis was performed. An increase in the expression of S100A8 and S100A9 mRNA by the TLR5–flagellin ligand was determined. It was observed that RNA-mediated suppression of TLR5 expression suppressed the ability of keratinocytes to regulate the expression of S100A8 and S100A9 mRNAs in response to E.Coli supernatant. Consequently, according to the authors, bacterial flagellin regulates S100A8 and S100A9 in keratinocytes through a TLR5-dependent mechanism.

Zhong et al. [32] conducted immunohistochemical studies of the skin revealed high expression in the epidermis in the area of hypertrophic and keloid scars. The observed reduced hydration in these areas leads to the activation of fibroblasts in the joint culture of keratinocytes and fibroblasts. The RNA interference of keratinocytes with a decrease in S100A8/A9 is unable to activate fibroblasts. Pretreatment of TLR4 receptors and glycation end-product receptors with pharmacological blockers S100A8/A9 inhibits fibroblast activation induced by recombinant proteins S100A8/A9, which ultimately leads to an increase in scarring processes in the scar model in the rabbit ear experiment. Thus, in order to prevent excessive scarring, the heterodimer S100A8/A9 is considered as a target.

Mun Jeong Kim et al. [16] in order to determine the connection between cytokine expression and skin barrier protein with calcium binding proteins S100A8 and S100A9 in human keratinocyte HaCaT cells, patients with atopic dermatitis (AD) were studied. After treatment with S100A8/A9 with various inhibitors specific to these signaling proteins, the expression level of keratinocytes was investigated. Activation of the mitogen-activated protein kinase (AMPK) pathway and nuclear factor (NF-kb) were evaluated using Western blotting and an NF-kb activity test. The levels of IL-6, IL-8 and monocytic chemoattractant protein increased after treatment with S100A8 and S100A9. This increase was blocked by specific inhibitors of signaling pathways, including Toll-like receptor 4 inhibitor (TLR-4i), rottlerin, PD98059, SB203580 and BAY-11-7085. Phosphorylation of ERK and P38 MAPK was blocked by TLR4i and rottlerin. In addition, S100A8 and S100A9 reduced the expression of phyllagrin and loricrin.

V.V. Sobolev et al. [25] having detected an increase in the expression level of S100A8 in psoriasis-affected skin compared to unaffected skin, treated patients with low-intensity radiation with a wavelength of 1.27 microns. The biopsied areas after irradiation were examined by real-time PCR. A significant decrease in the expression of the S100A8 gene was revealed, which may be an indicator of the effectiveness of psoriasis treatment at the molecular level.

Thus, the data of the scientific literature convincingly demonstrate the relevance of further research in this direction. A deeper understanding of the role of S100 family proteins in the development of allergic and inflammatory skin diseases, such as toxidermy (food, drug genesis), will allow predicting the development of these diseases, as well as optimizing therapeutic tactics.

Conflict of interest disclosure

The authors declare no conflict of interest.

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DOI: 10.31579/2578-8949/098