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S100A12-CD36 axis: A novel player in the pathogenesis of atherosclerosis?

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ABSTRACT

S100A12 is a member of the S100 family of EF-hand calcium-binding proteins and have a variety of intracellular and extracellular activities. It exerts its proinflammatory effects by binding to the receptor for advanced glycation end products (RAGE) and Toll-like receptor 4 (TLR4). CD36 is a class B scavenger receptor that acts as a fatty acid transporter. Both S100A12 and CD36 are implicated in vascular inflammation and atherosclerosis. It has recently been demonstrated that S100A12 binds with high affinity to CD36. On the other hand, RAGE and TLR4 play a key role in the regulation of CD36 expression. These observations point to the fact that S100A12 is an interesting molecular target for the development of therapeutics. This Cytokine stimulus will focus on the possible mechanisms of S100A12-CD36 axis in the pathogenesis of atherosclerosis.

S100 protein family includes EF-hand calcium-binding proteins with a range of intracellular and extracellular activities such as cell invasion, cell proliferation, apoptosis, autoimmunity, and inflammation. S100A12 (Calgranulin C or EN-RAGE) is a proinflammatory protein expressed by human neutrophils and monocytes [1]. Unlike most S100 proteins, S100A12 is absent in the mouse genome. Interestingly, human S100A12 has a gene structure similar to murine S100A8 [2]. The human S100A12 gene is located in the S100 gene cluster on chromosome 1q21, consisting of three exons and two introns. Exons 2 and 3 contain protein coding sequences, whereas exon 1 is not translated [3]. Transcriptional regulation of the porcine S100A12 gene has been examined. The results indicated that CCAAT/enhancer-binding protein beta (C/EBPβ) and activator protein-1 (AP-1) can act as positive regulators of the S100A12 gene [4]. Elevated serum levels of S100A12 have been reported in chronic active inflammatory bowel disease, Kawasaki disease, rheumatoid arthritis, psoriatic arthritis, and glomerulonephritis. As a result, S100A12 could be a potential biomarker for some inflammatory diseases. It has been shown that proinflammatory effects of S100A12 are mediated through interaction with RAGE and TLR4 [5]. The data have revealed that S100A12 binds to the C-type domains of RAGE (C1 and C2 domains). The calcium-bound form of S100A12 binds to RAGE as a hexameric complex. This interaction leads to the activation of inflammatory cells such as macrophages and lymphocytes [6]. Furthermore, human S100A12 can induce monocyte activation and inflammatory response by interacting with TLR4 [7]. Interaction of S100A12 with its receptors triggers activation of nuclear factor-kappa B (NF-κB), resulting in production of proinflammatory cytokines and adhesion molecules such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) [5,8].

CD36 is a transmembrane glycoprotein receptor, which is a member of the class B scavenger receptor family. Several different types of cells express CD36, including monocytes/macrophages, adipocytes, platelets, cardiac myocytes, podocytes, renal tubular cells, and endothelial cells. One of the most important functions of CD36 is to bind and transport long-chain fatty acids and oxidized low-density lipoprotein (oxLDL) [9]. It has been demonstrated that CD36-oxLDL interaction is significantly involved in the pathogenesis of atherosclerosis through a number of mechanisms. These include formation of foam cells, macrophage trapping, production of cytokines, and platelet activation [10]. Moreover, CD36 and TLRs are key elements in inflammasome activation by oxLDL. Stewart et al. found that interaction of oxLDL with CD36 resulted in activation of TLR4-TLR6 heterodimer [11]. This complex (CD36-TLR4-TLR6) triggers an inflammatory response to oxLDL and also activates inflammasome by pro-IL1β transcription. In addition to CD36 cooperation with TLR4 and TLR6, intracellular cholesterol crystals formed by CD36-mediated oxLDL uptake disrupt lysosomes and activate NLRP3 inflammasome [12].

S100A12 has been shown to play an important role in atherosclerosis and vascular calcification (Fig. 1). Geczy and colleagues could not induce proinflammatory cytokines in human macrophages in response to recombinant S100A12 [13]. According to their previous study

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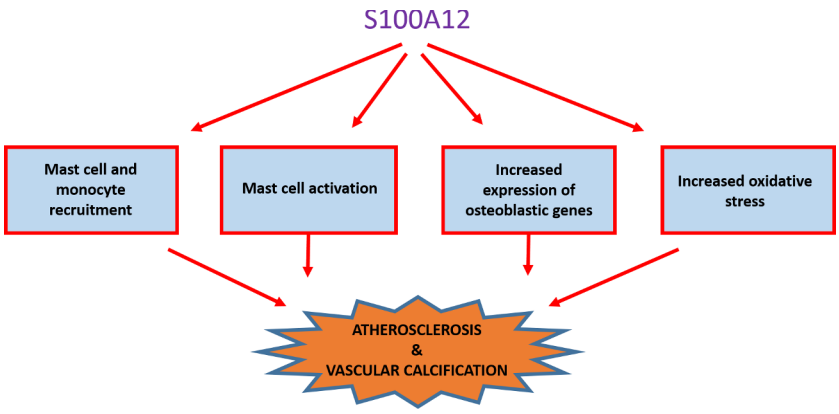

Fig. 1. The suggested role of S100A12 in atherosclerosis and vascular calcification. Chemotactic activity of S100A12 for monocytes and mast cells may play a role in their accumulation in atherosclerotic lesions. Activated mast cells can contribute to atherosclerosis by proinflammatory cytokine secretion. Additionally, expression of S100A12 in vascular smooth muscle cells (VSMC) increase osteoblastic gene expression and oxidative stress, resulting in accelerated atherosclerosis and vascular calcification.

[14], S100A12 was suggested to participate in atherosclerosis by mast cell and monocyte recruitment as well as mast cell activation. This is important because mast cells directly promote atherosclerosis by secretion of proinflammatory cytokines [15]. In another study, S100A12 was expressed in vascular smooth muscle cells (VSMC) of apolipoprotein E (ApoE)-null mice [16]. This S100A12 transgenic mouse model showed significant vascular calcification, aortic expression of osteoblastic genes, and oxidative stress. Interestingly, quinoline-3-carboxamide (ABR-215757), an antiinflammatory molecule, was able to bind S100A12 and led to decreased vascular inflammation and calcification, and smaller atherosclerotic lesions in S100A12 transgenic ApoE-null mice [17].

On the other hand, RAGE also contributes to the development of atherosclerosis. There is strong evidence to suggest that inhibition of RAGE signaling can reduce vascular inflammation and atherosclerosis. It has been suggested that RAGE can serve as a receptor for oxLDL and mediate proinflammatory responses (e.g. adhesion molecules) and oxidative stress in atherosclerosis [18,19]. It should be noted that the role of TLR4, a recently identified receptor for S100A12, is also well established in the pathogenesis of atherosclerosis, particularly in early-stage of the disease. For example, TLR4 activation is involved in the development of atherosclerosis by production of proinflammatory cytokines in arterial endothelial cells and macrophages [20]. Several S100 proteins such as S100A8, S100A9, and S100A8/S100A9 complex are considered to be endogenous danger signals that induce myeloid cells activation and proinflammatory molecules expression [21]. Similarly, another RAGE ligand, high mobility group box 1 (HMGB1), can act as an endogenous danger signal [22]. Due to similarities between human S100A12 and murine S100A8 [2], S100A12 could also be an endogenous danger signal. After release into the extracellular space, S100A12 may trigger inflammatory processes in atherosclerosis. Therefore, RAGE-S100A12 and TLR4-S100A12 interactions appears to be the main mechanism by which S100A12 exerts its pathological effects on atherosclerosis. In this context, S100A12 may participate in the pathogenesis of atherosclerosis by upregulation of proinflammatory cytokines and adhesion molecules, and generation of oxidative stress. The question is whether S100A12 can bind to other cell surface receptors and mediate negative effects on atherosclerosis. It may be answered by investigating binding of S100 proteins to CD36.

An interesting fact is that some S100 proteins (S100A8/A9 protein complex) are able to bind fatty acids and CD36. S100A8/A9 complex was suggested to facilitate cellular internalization of fatty acids [23]. Most importantly, both in vivo and in vitro studies using fluorine-18-labeled S100A12 have indicated that S100A12 can interact with different scavenger receptors on macrophages and endothelial cells [24]. In a recent study, Tondera et al. used fluorescence and radiolabeling techniques to examine binding of S100A12 to CD36 [25]. Cell binding assays showed a specific S100A12-CD36 interaction that was blocked by anti-CD36 antibody. The study also revealed that S100A12, thrombospondin, and collagen have the same binding site (between amino acids 93 and 120) on CD36. However, one of the most interesting aspects of this study is that S100A12 upregulates CD36 expression and recruits CD36 to the cell membrane. These findings raise the possibility that S100A12 regulates expression and recruitment of CD36, suggesting its novel role in foam cell formation and the onset of atherosclerosis. Moreover, S100A12-CD36 axis may have different detrimental effects on atherosclerosis formation. Due to the ability of S100 proteins to bind to fatty acids, it can be hypothesized that S100A12 facilitates uptake of oxLDL through CD36. Future studies can aim to elucidate whether S100A12 have high affinity for oxLDL and fatty acids. Another possible mechanism is that S100A12-CD36 interaction leads to NF-κB activation and subsequent proinflammatory cytokine production.

There may also be a link between RAGE and CD36 expression [26]. It has been reported that RAGE knockdown is associated with an inhibition of CD36 expression. This is supported by the results of Tondera et al. [25], showing that S100A12-induced expression of CD36 is markedly increased in RAGE-expressing cells compared to cells without RAGE expression. As a result, S100A12 could have a positive regulatory effect on CD36 by binding to RAGE. In addition to effect of RAGE on CD36, TLRs have been found to downregulate CD36 on monocytes [27]. The results therefore propose that S100A12 (a TLR4 ligand) may reduce the expression of CD36 through TLR4 signaling. Taken together, these observations suggest that S100A12 can modulate CD36 expression by its other receptors.

Marsche et al. investigated the role of soluble RAGE (sRAGE), a decoy receptor for S100A12, in the uptake of LDL modified by hypochlorous acid (HOCl) [28]. They found that sRAGE can block the uptake of HOCl-LDL by CD36 due to binding to HOCl-LDL. However, this function of sRAGE may be partially attributed to inhibition of S100A12-CD36 interaction. On the other hand, blockade of the S100A12-RAGE interaction by sRAGE can downregulate CD36 and decrease the uptake of HOCl-LDL. This study may support the hypothesis that S100A12 is involved, directly or indirectly, in the uptake of oxLDL by CD36 and foam cell formation. It is well documented that sRAGE dampens atherosclerosis, suggesting a strong therapeutic candidate for vascular inflammation [29]. Among RAGE ligands, S100A12 could be a particularly suitable target for sRAGE because it is a ligand for several critical receptors (CD36, RAGE, and TLR4) implicated in atherosclerosis.

S100A12 may have a significant role in vascular inflammation through monocytes and mast cells recruitment and activation. Monocytes as important cells in the initiation and progression of atherosclerosis may release S100A12 at the site of atherosclerotic lesions. However, S100A12 ability to interact with CD36 and increase its synthesis suggest possible new roles in atherosclerosis. The focus of future research could be on S100A12-CD36 axis functions. Other RAGE ligands (e.g. HMGB1) may also act as CD36 ligands and have an impact on oxLDL internalization by macrophages and foam cell formation. Finally, S100A12 may represent a promising therapeutic target for atherosclerosis.

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