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Chronic Inflammation and S100A12/ Receptor for Advanced Glycation Endproducts Axis: A Novel Risk Factor for Cardiovascular Disease in Patients with Chronic Kidney Disease?

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1. Introduction

Atherosclerotic cardiovascular disease (CVD) is a significant cause of morbidity and mortality in patients with chronic kidney disease (CKD), particularly patients undergoing hemodialysis (HD). The death rate from CVD in patients with advanced stage CKD is 10 to 40 times higher than that in the general population (Iliou et al., 2001; Sarnak et al., 2003). A majority of patients with CKD have traditional CVD risk factors such as old age, diabetes mellitus, systolic hypertension, smoking, and dyslipidemia. However, the interventions to address these traditional risk factors have failed to decrease the risk for CVD in patients with CKD (Stenvinkel et al., 2008).

Atherosclerotic lesions develop through chronic inflammatory processes, and chronic inflammation is a common feature of CKD. In addition, the metabolic milieu during the development of renal dysfunction appears to accelerate the atherosclerotic process by decades in patients with CKD. Given these findings, many researchers have emphasized that nontraditional risk factors such as oxidative stress and advanced glycation endproducts (AGEs), in combination with their receptor (RAGE), may play an important role in the development of CVD in patients with CKD.

RAGE is a member of the immunoglobulin superfamily of cell surface molecules. Enhanced RAGE expression has been observed in peripheral blood monocytes of patients with CKD, suggesting that RAGE may amplify ligand-induced monocyte perturbation and contribute to monocyte-mediated vascular inflammation in patients with CKD. The major alteration of glycated protein in patients with CKD is decreased clearance of glycation-free adducts and their markedly increased levels in plasma. However, the change of plasma AGEs into proteins in patients with CKD is relatively modest. Therefore, ligands other than AGEs for RAGE may be more important in RAGE-mediated atherosclerosis of patients with CKD.

Several RAGE ligands, including S100 proteins, the High Mobility Group Box proteins, and amyloid fibrils, have been identified. Among them, emerging evidence indicates that S100A12 is a proinflammatory cytokine (Pietzsch and Hoppmann, 2009). In this review, we

focus on chronic inflammation, which causes atherosclerosis in patients with CKD, and highlight the role of the S100A12 protein, which is upregulated in patients with CKD.

2. CKD: An inflammatory state

The inflammatory response is not only a local process but can also be reflected systemically as it is accompanied by increases in inflammatory markers including acute phase proteins, cytokines, and adhesion molecules. In recent years, some of these markers, such as C-reactive protein (CRP), interleukin (IL-6), serum amyloid type A, tumor necrosis factor (TNF)- α , adhesion molecule, and CD40 ligands, have been evaluated for their prognostic value in normal patients as well as in patients with CVD. Numerous studies have reported an association between renal impairment and different mediators and markers of inflammation including CRP, IL-6, and TNF- α , even among patients with moderate renal impairment, suggesting that CKD is a low-grade inflammatory process (Landray et al., 2004; Stenvinkel, 2006) and peripheral polymorphonuclear leukocytes and CD14+/Cd16+ monocytes are key mediators in the process (Merino et al., 2008; Sela et al., 2005). Approximately 30–50% of predialysis, HD, and peritoneal dialysis (PD) patients have serological evidence of an activated inflammatory response (Stenvinkel, 2001). Serum CRP levels are particularly high when renal function declines to the level of end stage of renal disease. Elevated serum CRP is a strong predictor of cardiovascular mortality in patients undergoing HD (Ma et al., 1992). Thus, it is possible that inflammation could promote both atherosclerosis and cardiovascular mortality. However, the precise mechanisms that contribute to the high prevalence of inflammation in patients with CKD are not well understood.

3. S100A12 protein

Human S100 proteins are the largest subgroup within the superfamily of EF-hand calcium-binding proteins. Currently, S100 proteins comprise a family of at least 25 low molecular weight proteins (9–14 kDa) (Santamaria-Kisiel et al., 2006). S100 proteins are characterized by the presence of two calcium-binding EF-hand motifs and display unique properties. It is thought that S100 proteins serve as a calcium trigger or sensor proteins that regulate the function and/or subcellular distribution of certain target proteins and peptides upon calcium-dependent activation. All S100 proteins, with the exception of S100G (calbindin D, 9 k), are organized as tight symmetric, antiparallel homodimers (some as heterodimers), and the noncovalent interface between the two monomers is formed mostly by hydrophobic amino acid residues. Each monomer is composed of a C-terminal, classic EF-hand, common to all EF-hand proteins, and an N-terminal, pseudo EF-hand, which has been found exclusively in the N-termini of S100 and S100-like proteins (Pietzsch and Hoppmann, 2009; Zhou et al., 2006).

In recent years, a subgroup of the S100 family (S100A12, S100A8, and S100A9) has been associated with acute/chronic inflammatory disorders (Foell et al., 2004a; Foell et al., 2004b). Human S100A12 was first described by Guignard and colleagues as a cytosolic protein, p6, in neutrophilic granulocytes and monocytes/macrophages that crossreacts with antibodies raised against S100A8 (Guignard et al., 1995). RAGE is of significant importance as a neutral target of S100A12 (Donato, 2007; Hofmann et al., 1999). Engagement of RAGE by S100A12 activates nuclear factor (NF)- κ B, a central transcription factor involved in inflammatory

events that triggers the expression of multiple gene products contributing to the inflammatory response (Hofmann et al., 1999; Yang et al., 2001).

3.1 Gene and protein structure

The cytogenetic location of S100A12 is part of the tight S100 gene cluster on human chromosome 1q21. The S100A12 gene has been mapped to 1q21.2-1q22(1q21.3) and is located between the S100A8 and S100A9 genes (Ravasi et al., 2004). The S100A12 gene has a length of approximately 4.1 kbp and consists of three exons, which are divided by two introns of 900 and 400 bp. Exon 2 contains part of the 5'-untranslated region (UTR) and exon 3 contains the 3'-UTR. The mRNA size, exclusive of the polyadenylate stretch, is 466 Bp (Acc No. NM_005621).

The protein is encoded by sequences in exons 2 (138 nucleotides) and 3 (138 nucleotides), with the two EF hand motifs of the protein separately encoded by exons 2 and 3 (Acc Nos. X98289, X98290, D83657) (Wicki et al., 1996; Yamamura et al., 1996) and a 276-bp open reading frame encoding a 92-amino acid polypeptide with a predicted molecular mass of 10,575 Da. Homologous proteins have also been found in other species such as bovine, porcine, and rabbit. Human S100A12 has 70% sequence identity with both porcine and rabbit S100A12, and 66% sequence identity with the bovine protein (Dell'Angelica et al., 1994; Hitomi et al., 1996; Nonato et al., 1997; Yang et al., 1996). Human S100A12 shares 40% identity with human S100A8 (calgranulin A; myeloid-related protein 8), and 46% identity with human S100A9 (calgranulin B; myeloid-related protein 14), respectively. The S100A12 gene is not observed in rodents. The crystal structure of calcium-bound S100A12 closely resembles structures of other members of the calgranulin subfamily, presenting as an anti-parallel homodimer of four-helix subunits (Moroz et al., 2003). At low molecular calcium concentrations, human S100A12 also forms a hexamer consisting of three symmetrically positioned calcium-bound homodimers (Moroz et al., 2003). Most of the S100 proteins have been shown in various conformational and functional states depending on the intracellular or extracellular concentrations of calcium, zinc, and copper. In both EF-hands, the calcium ion is coordinated in a pentagonal bipyramidal configuration. Generally, the dimeric S100 proteins binds four calcium ions per dimer [$\sim 10^{-4}$ to 10^{-5} M (overall Kd)], with high affinity binding [$\sim 10^{-5}$ to 10^{-7} M (Kd)] at the C-terminal canonical EF-hand motifs and low affinity binding [$\sim 10^{-3}$ to 10^{-4} M (Kd)] at the N-terminal pseudo EF-hand motifs, respectively. An additional bound calcium ion per subunit occurs in the human S100A12 hexamer structure, in addition to the two calcium ions in the EF-hands. S100A12 also binds zinc ions at a binding site formed by both subunits that is closely located at the dimer interface. Of importance, divalent copper ions may bind at the same site. Coordination of both zinc and copper ions is supported by the N-terminal residues His15 and Asp25 from one subunit and two appropriately positioned imidazoles of a His-Tyr-His-Thr-His motif comprising residues 85-89 in the C-terminus from the other subunit (Moroz et al., 2003). These cations may regulate both intracellular and extracellular functions of S100A12. Studies on S100A12 monomers isolated from porcine granulocytes demonstrate substantial regulation of S100A12 calcium-binding affinity by zinc (Dell'Angelica et al., 1994). Upon copper binding, human S100A12 dimers form close contacts possibly enabling changes in their target binding sites or forming oligomers (Moroz et al., 2003). However, the particular role of S100A12 in zinc and copper binding in normal and disease states *in vivo* remains to be elucidated.

3.2 Expression, secretion and regulation

S100 lacks a signal peptide for secretion via the Golgi-mediated pathway and some debate exists regarding whether the high levels derived from inflammatory lesions are due to active secretion or passive release as a consequence of neutrophil necrosis. S100A8/9 release correlates with loss of neutrophil viability (Voganatsi et al., 2001), suggesting that necrosis probably represents a significant extracellular source of S100. In contrast, protein kinase C activation by pro-inflammatory stimuli, $[Ca^{2+}]_i$ elevation by contact with activated endothelium (Frosch et al., 2000), and lipopolysaccharides from several bacterial species (Kido et al., 2005) cause a rapid release from neutrophils. S100A12 is constitutively expressed in neutrophils at low levels (~5% of cytosolic protein) (Guignard et al., 1995) and is expressed in myeloid cell lines (Vogl et al., 2004). We previously examined the amounts of S100A12 mRNA in cultured human THP-1 macrophages after treatment with various stimuli known to modulate atherosclerosis. First, IL-6, a proinflammatory cytokine, increased the level of S100A12 mRNA by ~2-fold in a time- and a dose-dependent fashion. The S100A12 protein was also detected in the culture medium and increased significantly after adding IL-6. Induction was abolished by pretreatment with a JAK kinase inhibitor and cycloheximide but not with an MEK kinase inhibitor. Second, pioglitazone, a thiazolidinedione, decreased the level of S100A12 mRNA by ~25% of basal in a time- and dose-dependent fashion. Pioglitazone also inhibited the induction of S100A12 mRNA by IL-6. These results indicate that S100A12 production is induced by IL-6 through de novo protein synthesis via the JAK-STAT kinase pathway and inhibited by activation of the peroxisome proliferator-activated receptor- γ (PPAR- γ) in human macrophages (Hasegawa et al., 2003). Ligand-bound PPAR- γ represses signal-dependent transcription of many inflammatory proteins (Pascual and Glass, 2006). The rapid upregulation by pro-inflammatory stimuli and repression by PPAR- γ agonists is consistent with the pro-inflammatory role of S100A12 (Goyette and Geczy, 2010). Nevertheless, further studies are needed to clarify the S100A12 regulatory mechanism.

3.3 Binding partners and function

Despite the large interest in the (patho-)physiological properties of human S100A12, knowledge of its intracellular targets is still limited. In bovine S100A12, annexin 5, aldolase, cytosolic NADP⁺-dependent isocitrate dehydrogenase, and glyceraldehyde-3-phosphate dehydrogenase show either a strict or weak calcium-dependent interaction with S100A12 (Hatakeyama et al., 2004).

The best known extracellular target protein is RAGE (Donato, 2007). RAGE is the first cell surface receptor that binds specifically to several members of the S100 protein family, including S100A12, S100A1, S100B, and S100P (Arumugam et al., 2004; Dattilo et al., 2007; Donato, 2007; Hofmann et al., 1999). The binding of S100 proteins, including calgranulins S100A6 and S100A18, is still debated (Goyette and Geczy, 2010). Engagement of the extracellular domain of the RAGE membrane by calcium-bound S100A12 activates intracellular signal cascades, including MAP kinase and NF- κ B, which induce cytokine secretion (e.g., TNF- α and IL-1 β), and expression of adhesion molecules (e.g., ICAM-1 and VCAM-1), and thereby mediate their pro-inflammatory effects on lymphocytes, endothelial cells, neutrophils, and mononuclear phagocytes (Yang et al., 2001), leading to the development of several chronic inflammation such as asthmatic lung (Yang et al., 2007), rheumatoid synovium (Yang et al., 2001), inflamed mucosa in inflammatory bowel disease (Leach et al., 2007), diabetes mellitus (Kosaki et al., 2004), and atherosclerosis (Mori et al., 2009).

3.4 Association of plasma S100A12 level with atherosclerotic CVD in CKD

In 2009, we were the first to report that plasma S100A12 levels in 72 patients undergoing HD had mean levels 2.3-fold higher than those in control subjects. Furthermore, maximum carotid artery intima-media thickness correlated positively with plasma S100A12 levels in patients with HD, suggesting that plasma S100A12 levels are associated with atherosclerosis as a complication of CKD in patients undergoing HD (Mori et al., 2009). We also found that plasma S100A12 levels were elevated in patients undergoing PD (~2-fold), and in a high group of the peritoneal equilibrium test, suggesting the influence of chronic inflammation (Uchiyama-Tanaka et al., 2007). Consequently, a larger cross-sectional dataset of 550 patients undergoing HD at our affiliated hospital was analyzed to assess the relationship between plasma S100A12 levels and the presence of CVD (Shiotsu et al., 2011). We found that plasma S100A12 levels in patients undergoing HD with a history of CVD were significantly higher than those in patients with no history of CVD. Furthermore, plasma S100A12 level was identified as an independent factor associated with the prevalence of CVD, and higher plasma S100A12 levels were associated with an increased risk for CVD. These results suggest that plasma S100A12 protein may be a novel predictor of CVD events in patients undergoing HD. This finding was compatible with a report by another group (Nakashima et al., 2011) that conducted a prospective study including 184 patients undergoing prevalent HD. Plasma concentrations of S100A12 and sRAGE were studied in relation to risk profile and mortality after a median follow-up period of 41 months. The results showed that S100A12 and sRAGE levels were significantly elevated in patients undergoing HD compared with those in healthy controls. S100A12 had a strong positive correlation with CRP and IL-6, whereas sRAGE was negatively associated with CRP. S100A12, but not sRAGE, was independently and positively associated with clinical CVD. Further adjustment for inflammation made the predictive value of S100A12 disappear for all-cause mortality, but it still persisted for CVD-related mortality. In another population, the expression of RAGE and S100A12 in peripheral blood mononuclear cells (PBMCs) of subjects with pre-mature coronary artery disease (CAD) for the first time without CKD and diabetes were reported (Mahajan et al., 2009). Semi-quantitative RT-PCR was performed to determine RAGE and S100A12 transcriptional expression in PBMCs. Increased expression of RAGE and EN-RAGE in non-diabetic patients with pre-mature CAD was observed, suggesting a significant contribution of enhanced S100A12 expression in PBMCs to CAD pathophysiology.

4. Conclusion

Circulating S100A12 is elevated in patients with CKD and is associated with CVD events and CVD-related mortality, which is partly explained by its links to inflammation. Further studies are apparently needed from a therapeutic point of view. It is likely that a modification in uremic state affects S100A12 expression in neutrophils and/or monocytes. The identification of "activated" leucocytes and interventions by targeted therapy for such a leucocyte population may be beneficial to prevent CVD in patients with CKD.

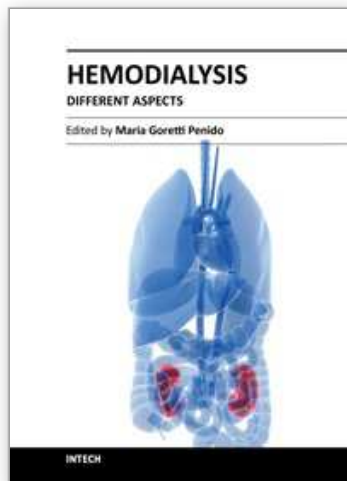
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