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EDITORIAL

S100 proteins in health and disease

Jens Pietzsch

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One class of proteins that has been increasingly emerging as a potentially important group of both molecular key players and biomarkers in the etiology, progression, manifestation and therapy of various inflammatory, neurodegenerative, metabolic and neoplastic disorders is the S100 family.

S100 proteins are small, acidic, calcium-binding proteins, characterized by the presence of two calcium-binding EF-hand motifs, and found exclusively in vertebrates. The first member was identified in the bovine nervous system by Moore (1965). The name S100 was derived from the observation of the protein fraction remaining soluble after precipitation with 100% saturated ammonium sulfate at neutral pH. Subsequent studies demonstrated that this fraction contained predominantly two proteins, S100A1 and S100B. Since the first isolation and characterization of these 2 S100 proteins, at least 23 additional proteins have been assigned as members of the S100 family in humans (Marenholz et al. 2004, 2006). Twenty-one of them (S100A1–S100A18, and the multidomain proteins trichohyalin, filaggrin and repetin) are coded by genes clustered at chromosome locus 1q21, known as the epidermal differentiation complex, while the other genes belonging to the subfamilies of S100B, S100P, S100Z and S100G are, respectively, located at chromosome loci 21q22, 4p16, 5q14 and Xp22 (Santamaria-Kisiel et al. 2006).

S100 proteins form homodimer, heterodimer and even oligomeric molecular assemblies and are expressed in a tissue- and cell-specific manner, suggesting that each S100 protein may perform different functions (Donato 1999; Fritz and Heizmann 2006). Functional complexity and diversification of S100 proteins have been further achieved by differences in localization, e.g., intracellularly in cytoplasm and/or nucleus, extracellularly in various body fluid compartments, by action as autocrine or paracrine effectors, and by exhibition of different affinities toward calcium ions resulting in various degrees of conformational change and modes of interaction with a whole host of specific target proteins (Donato 1999; Leclerc et al. 2009). Moreover, several S100 proteins are known to bind to other divalent metal ions, such as magnesium, zinc and the transition metal copper with high affinity, perhaps implicating them additionally in the homeostasis of toxic metals and related pathophysiological conditions (Moroz et al. 2009). All of these result in a tremendous spectrum of pleiotropic intra- and extracellular functions. In this regard, through, e.g., inhibition of protein phosphorylation, regulation of transcriptional factors, modulation of enzyme activity and cytoskeletal dynamics, S100 proteins have been linked to vital cellular processes, including cell cycle regulation, cell growth and differentiation, transcription, cell motility and invasion, extracellular signal transduction and intercellular adhesion (Santamaria-Kisiel et al. 2006, Leclerc et al. 2009).

Among natural targets of extracellular S100 proteins, the multiligand or pattern recognition receptor for advanced glycation end products (RAGE) has gained significant importance (Hofmann et al. 1999; Leclerc et al. 2009). RAGE is a signal transduction receptor of the immunoglobulin superfamily and was first described as a receptor for end products of non-enzymatic glycation and glycoxidation of proteins (Schmidt et al. 1992). Importantly, RAGE also transduces signals stimulated by non-glycated proteins that

J. Pietzsch (✉)
Department of Radiopharmaceutical Biology,
Institute of Radiopharmacy,
Research Center Dresden-Rossendorf,
POB 510119, 01314 Dresden, Germany
e-mail: j.pietzsch@fzd.de

are released and/or upregulated in acute and chronic inflammatory or stress responses, respectively, such as amphoterin (HMGB1) and soluble amyloid-β fibrils. Importantly, these ligands of RAGE include also a great many members of the S100 protein family, e.g., S100A1, S100A2, S100A4, S100A5, S100A6, S100A7, S100A8, S100A9, S100A11, S100A13, S100B and S100P (Leclerc et al. 2009). Membrane-anchored (full-length) RAGE is present on various cell types, including mononuclear phagocytes, tissue macrophages, cardiac myocytes, fibroblasts, epithelial cells, endothelial cells, neurons and smooth muscle cells, and is highly expressed, particularly, in lung tissue (Brett et al. 1993). Engagement of the extracellular domains of RAGE by S100 proteins activates multiple intracellular signaling pathways, including those activating the transcription factors NF-κB, AP-1 and STAT3, resulting in increased expression of proinflammatory cytokines and cellular adhesion molecules (Donato 2007, Leclerc et al. 2009). However, RAGE signaling mediated by S100 proteins is more complex and depends on the cell type, as well as the type and the concentration of the S100 ligand (Donato 2007). An important attribute of RAGE is that it is expressed at relatively low levels in homeostasis, but in situations characterized by enhanced cellular activation or stress, the expression of RAGE is strikingly enhanced. The pathobiology observed in response to RAGE activation is enhanced by accumulation of its ligands at pathologic sites, leading to further upregulation of the receptor and sustained cell activation. Consequently, ligation of S100 proteins to RAGE activates cells bearing RAGE in injured/inflamed compartments, thereby providing a crucial proinflammatory mechanism for sustained cellular perturbation and tissue injury. Hence, S100 protein interaction with RAGE has been implicated in many disorders, e.g., in the pathogenesis of type 1 and type 2 diabetes mellitus, atherosclerosis, rheumatoid arthritis, Alzheimer's disease and also in tumor outgrowth. However, considering physiological situations with various competing RAGE ligands available, which exhibit different concentrations and affinities to the receptor, the contribution of a single S100 protein to the complex overall interaction between RAGE and its ligands in several pathophysiological situations is difficult to distinguish. This situation is even more complicated by the following issues. Primarily, RAGE has been described as a non-internalizing receptor. However, recent data indicate that depending on the cell type and the type of S100 ligand, internalization/recycling of RAGE may occur (Perrone et al. 2008). Of further importance, soluble isoforms of RAGE, such as the extracellular ligand-binding region of RAGE (sRAGE) and the endogeneous secretory form of RAGE (esRAGE), respectively, influence the interaction between full-length RAGE and S100 proteins (Maillard-Lefebvre et al. 2009). These isoforms have been suggested to function as decoy or scavenger molecules abolishing both binding of ligands to membrane-anchored full-length RAGE and subsequent RAGE-mediated cell signaling, thus inhibiting, e.g., inflammatory processes (Sparvero et al. 2009; Yamagishi and Matsui 2010). On the other hand, carboxylated *N*-glycans and heparan sulfate proteoglycan on endothelial cells (Srikrishna et al. 2001; Robinson et al. 2002), carboxylated *N*-glycans on chondrocytes (van Lent et al. 2008), scavenger receptors on endothelial cells and tumor cells (Kerkhoff et al. 2001; Hoppmann et al. 2010), a putative G-protein coupled receptor on RAGE-negative mast cells (Yan et al. 2008) and Toll-like receptors (Vogl et al. 2007) are other potential cell-surface binding sites for S100 proteins, further underlining the functional complexity and diversity of this class of proteins.

Moreover, elevated protein expression and, in part, increased secretion of individual S100 family members are associated with a number of human pathologies, including atherogenesis, cardiomyopathies, cancer, neurodegeneration and chronic inflammatory conditions (Goyette et al. 2009; Kraus et al. 2009, Salama et al. 2008, Donato et al. 2009, Srikrishna and Freeze 2009). Exemplarily, some S100 proteins are linked directly to the innate immune system and have been characterized as endogeneous damage-associated molecular pattern molecules (DAMPs or alarmins): most prominently, the calgranulins S100A8, S100A9 and S100A12, and, furthermore, S100A7 and S100A15. These S100 members are released to extracellular compartments in response to cell damage, infection or inflammation, and function as proinflammatory danger signals (Perera et al. 2010; Wolf et al. 2008). Other S100 proteins, such as S100A2, play both oncogenic and antitumor roles, depending on the cancer type being investigated (Salama et al. 2008). Some of them, e.g., S100A4 and S100P, are released by tumor cells into the microenvironment and are likely to promote tumorigenic processes, tumor invasion and metastasis (Missiaglia et al. 2004).

In this regard, the clarification of the adequacy of the intended use of S100 proteins, ideally those secreted into body fluids, as biomarkers or surrogate markers, which are amenable to the design of non-invasive clinical tests, is of utmost importance. Such biomarkers that could aid or improve the diagnosis of disease, the discrimination of several inflammatory conditions or the correct staging of cancer, as well as indicate patient prognosis or the most appropriate therapeutic regimes, would fit into the frequently discussed model of personalized medicine. The fact that several S100 proteins are known to fulfill these requirements make them particularly strong biomarker candidates, not only in inflammatory or neoplastic disorders. As more specific reagents for individual S100 proteins are being generated, their potential diagnostic and prognostic usage will increase substantially. Very recently,

several groups contributed to the current debate on the use of extracellular S100 proteins in plasma, urine and other compartments as biomarkers in a panoply of common and rare disorders, e.g., in patients with familial Mediterranean fever (S100A12; Kallinich et al. 2010), inflammatory joint diseases (S100A8, S100A9 and S100A12; Baillet et al. 2010), mood disorders (S100B; Schroeter et al. 2010), traumatic head injury (S100B; Hallén et al. 2010), bladder adenocarcinoma (S100P; Raspollini et al. 2010) and lung squamous cell carcinoma (S100A4; Tsuna et al. 2009). This continuing debate also highlights the complex levels of both cell and tissue regulatory specificity and functional diversity of the S100 proteins. Given these associations, S100 proteins are increasingly regarded as attractive targets for study and receive more and more attention as possible targets for therapeutic intervention.

This volume is intended to familiarize and to concern the readers of this journal and all the scientific community with this promising field of interdisciplinary research. Therefore, a selected panel of authors were enlisted, many of whom participated as speakers in the workshop dedicated to this subject at the 11th ICAAP conference held in Vienna, 3–7 August 2009.[1] We hope that these proceedings will provide further insights into the family of S100 proteins, encourage researchers in the field of biomedical sciences to think about novel diagnostic and therapeutic approaches in their specific areas and possibly instigate a novel discussion forum in this emerging field.

The first part of this issue is essentially concerned with basic biochemical, biological and methodological aspects of S100 research. Moroz et al. (2010) summarize the present knowledge on zinc binding by S100 proteins. While the importance of modulation of the function of the S100 family of EF-hand proteins by calcium is well established, a substantial proportion is also regulated by zinc or copper. The authors in this review article clearly illustrate that some members appear most unlikely to be regulated by calcium, since they lack the appropriate amino acids and/or the architecture to coordinate calcium ions in one, or both, of the EF-hands. They also point out that in the extracellular space, precision regulation by calcium is improbable for any S100 protein because the concentration of calcium is already high. Therefore, investigation of a range of zinc-binding members of the S100 family and the role of zinc/calcium crosstalk in their function will shed more light on common features and differences as to how they propagate their signals. This will also provide valuable information relevant to the treatment of numerous S100-related pathologies.

[1] All manuscripts in this special issue were subjected to external peer reviewing according to the policy of this journal.

The importance of two intracellular target proteins of S100A6, the CacyBP/SIP protein (S100A6-binding protein and Siah-1 interacting protein) and the co-chaperone protein Sgt1, for fundamental physiological processes such as ubiquitination, proliferation, differentiation, tumorigenesis, cytoskeletal rearrangement or regulation of transcription is discussed by Filipek et al. (Schneider and Filipek 2010; Prus and Filipek 2010). In a review article, they explain the interrelation between overexpression/upregulation of CacyBP/SIP and cell differentiation, e.g., of neuronal cells, and on the other hand its possible association with tumorigenic processes or multidrug resistance. In a second original article, they show that the heat shock-induced nuclear translocation of Sgt1, a protein involved in many processes including those important for cell survival, depends on the calcium-bound form of S100A6.

The review article by Wolf et al. (2010a) highlights the distinct expression, regulation, functions and mechanisms of action in normal and diseased tissues of two S100 proteins that are highly homologous, S100A7 (psoriasin) and S100A15 (koebnerisin). By focusing on processes of epithelial maturation, immunity, inflammation and tumorigenesis, it becomes apparent that a more detailed understanding of the distinct functional roles and synergistic action of both proteins will be crucial for developing novel therapeutic interventions, e.g., in psoriasis and chronic atopic eczema.

The review article by Sakaguchi and Huh focuses on the intracellular and extracellular functions of S100A11 (Sakaguchi and Huh 2010). They exemplify that a single S100 protein can exhibit pleiotropic functions in one single type of cell. The discussed findings, mainly obtained from studying normal human keratinocytes, indicate that S100A11 plays a dual role in growth regulation: by activating growth suppressive pathways when acting intracellularly, and by being growth promotive when binding extracellularly to RAGE and activating the RAGE-signaling cascades.

The specific association of S100 RAGE interaction with pathophysiological processes resulted in a growing interest in RAGE as a target for diagnostic and therapeutic approaches. A particular challenge in discriminating the different contributions of RAGE and other multiligand receptor pathways to the overall metabolic fate and action of the 'multireceptor' S100 ligands in vivo will be the development and use of appropriate tracer approaches. In this regard, an original article by Wolf et al. (2010b) reports a novel radiotracer methodology using recombinant human S100A4 as potential probe for molecular imaging and functional characterization of S100 RAGE interaction by means of small animal positron emission tomography (PET). In this work, PET imaging of fluorine-18 labeled S100A4 administered to rats indicates that it co-localizes

with RAGE. However, experiments in vitro and in vivo suggest that S100A4 also interacts with other receptors, e.g., scavenger receptors. The authors compare the present data on radiolabeled S100A4 to other fluorine-18 labeled S100 RAGE ligands developed by the same group and, furthermore, critically discuss the potential use of this methodology to both delineate functional expression and differentiate multiligand interaction of RAGE under normal and pathophysiological conditions in rodent models of disease.

In the second part of this issue, articles have been included to provide a selection of novel aspects of S100 biology related to non-neoplastic diseases. The review article by Goyette and Geczy focuses on new aspects of extracellular roles of the S100 calgranulin subfamily (Goyette and Geczy 2010). The members of this subfamily, S100A8, S100A9 and S100A12, are specifically linked to innate immune functions by their predominant expression in cells of myeloid origin. There is evidence that these phagocyte-specific S100 proteins are actively secreted via an alternative pathway bypassing the classical Golgi route, a mode of secretion that is typical for factors that play a role in cell homeostasis as intracellular molecules, but turn into proinflammatory danger signals after release into extracellular compartments due to cell damage, infections, autoimmune tissue destruction or inflammation. However, the authors of this article point out that the calgranulins may play pleiotropic roles and also fulfill often overlooked, protective functions. They propose that oxidative modifications, proteolytic cleavage to release active peptides, zinc binding and complex formation may be the key factors in functional diversity of calgranulins. Receptor-mediated functions may be governed by glycosylation of the receptors and requirements for co-receptors and/or co-stimuli. They conclude that deeper understanding of the consequences of these modifications to calgranulin function and the receptors mediating these effects may explain some of the seemingly incongruent functions proposed for these proteins.

The review article by Tsoporis et al. (2010) summarizes disease-related effects of S100B with emphasis placed on cardiovascular processes. In this regard, the important role of S100B in negative intrinsic regulation of aortic smooth muscle cell proliferation, cardiac myocyte hypertrophy and, via RAGE ligation, apoptosis is highlighted. The intracellular, and extracellular, roles of S100B are, besides their implication in brain injury or neurodegenerative pathologies, also attractive therapeutic targets for the treatment of both cardiac and vascular disease.

The articles selected for the third part of this issue cover the role of S100 proteins in cancerogenesis that is under extensive investigation. Paradoxically, some S100 proteins appear to play both oncogenic and anti-tumor roles. This substantially depends on the cancer type being investigated. The review article by Wolf et al. (2010c) summarizes some important biochemical characteristics of S100A2 and highlights its controversial role in the etiology, progression and prognosis of neoplastic disorders. On the one hand, S100A2 acts as a tumor suppressor in some tumor entities and, on the other hand, as a tumor promotor, however, by mechanisms that are still poorly understood. The different patterns of S100A2 expression in distinct tumor types might be explained by the control through multiple factors with effects varying from tumor entity to tumor entity. However, controversy still exists about the role and clinical significance of S100A2 in the progression, invasion, metastasis and therapy of tumors.

Berge et al. focus on metastasis as a complex cascade of events involving a finely tuned interplay between malignant cells and multiple host factors. In a review article, they summarize the findings showing S100A4 to be a key player in the transition from benign tumor growth to malignancy (Berge and Mælandsmo 2010). However, the exact molecular function or mechanism by which S100A4 exerts its putative metastasis-promoting effects has not been fully elucidated, but there is increasing evidence that direct interaction and/or reciprocal influence between S100A4 and the tumor suppressor protein p53 is of potential importance. In this regard, an original article by the same group reports on the first observation of S100A4 and p53 coexpression in individual primary colorectal carcinoma cells, with nuclear co-localization as a particularly interesting feature. Although experimental manipulation of S100A4 and p53 expression did not show evidence for reciprocal regulation in the isogenic colorectal carcinoma cell line HCT116, a role for direct or indirect interaction between S100A4 and p53 cannot be excluded (Berge et al. 2010).

Two further review articles deal with the role of S100P in tumorigenesis (Gibadulinova et al. 2010; Arumugam and Logsdon 2010). By focusing on transcriptional regulation of S100P in cancer, the first article discusses recent studies that implicate, besides DNA hypomethylation, bone morphogenic protein and non-steroidal anti-inflammatory drugs in the control of S100P expression during tumor progression. Functional analysis of S100P promoter identified SMAD, STAT/CREB and SP/KLF binding sites as key regulatory elements participating in the transcriptional activation of S100P in cancer cells. Moreover, the expression of S100P seems to be upregulated by the activation of glucocorticoid receptor suggesting that S100P could play a role in therapy resistance mediated by glucocorticoids in solid tumors. The second article summarizes the existing literature strongly supporting the significant role of S100P RAGE interaction during the development and progression of different cancers. In this

regard, therapeutical implications of, particularly, blocking the S100P RAGE interaction, e.g., by sRAGE, are discussed.

Finally, the sessions at the 11th ICAAP conference included more presentations on the subject of S100 proteins in health and disease (see the abstract book published in vol 37, Suppl 1, 2009 of this journal) illustrating the widespread interest of scientists in this aspect of protein research.

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