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S100A8 and S100A9 in inflammation and cancer

*Christoffer Gebhardt, Julia Németh, Peter Angel *, Jochen Hess*

Division of Signal Transduction and Growth Control, German Cancer Research Center, D-69120 Heidelberg, Germany

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Abbreviations:
DMBA, 7,12-dimethylbenz(a) anthracene
TPA, 12-O-tetradecanoylphorbol-13-acetate
SCC, squamous cell carcinoma
AP-1, activator protein-1
NF-κB, nuclear factor-κB
JNK, Jun N-terminal kinase
AGEs, advanced glycation end-products
RAGE, receptor of advanced glycation end-products

ABSTRACT

Calprotectin (S100A8/A9), a heterodimer of the two calcium-binding proteins S100A8 and S100A9, was originally discovered as immunogenic protein expressed and secreted by neutrophils. Subsequently, it has emerged as important pro-inflammatory mediator in acute and chronic inflammation. More recently, increased S100A8 and S100A9 levels were also detected in various human cancers, presenting abundant expression in neoplastic tumor cells as well as infiltrating immune cells. Although, many possible functions have been proposed for S100A8/A9, its biological role still remains to be defined. Altogether, its expression and potential cytokine-like function in inflammation and in cancer suggests that S100A8/A9 may play a key role in inflammation-associated cancer.

1. Introduction

During the past decade, cancer research has generated a complex picture of dynamic genetic and epigenetic changes within the genome of transformed cells influencing the expression and function of numerous proto-oncogenes and tumor suppressor genes implicated in regulatory circuits governing cell proliferation, differentiation, and homeostasis. Emerging evidence indicates that tumorigenesis is a multistage process bearing analogy to classical evolution and leading to progressive conversion of normal cells into cancer cells. Hanahan and Weinberg suggested that the vast majority of cancer cell genotypes is the consequence of six essential alterations in cell physiology that result in malignant growth including self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion

* *Corresponding author at*: Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany. Tel.: +49 6221 425570; fax: +49 6221 424554.
E-mail address: p.angel@dkfz.de (P. Angel).
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of programmed cell death, unlimited replication potential, sustained angiogenesis, and tissue invasion/metastasis [1]. In addition, solid cancers are not only autonomous masses of transformed tumor cells, but also consist of multiple cell types including adjacent fibroblasts and epithelial cells, innate and adaptive immune cells, as well as cells from the blood and lymphatic vasculature, which create a tumor-specific microenvironment. Recent studies on mouse tumor models and numerous clinical observations have provided new insights in the molecular mechanisms of communication between tumor and stromal cells and in the role of soluble factors and direct cell–cell adhesion during each stage of cancer development [2–7].

Chemically induced skin carcinogenesis represents one of the best-established *in vivo* models to study the multistage nature of tumor development and to design novel therapeutic concepts for human epithelial neoplasia [8,9]. This tumor model is generated first by single application with the mutagen 7,12-dimethylbenz(a)anthracene (DMBA), which leads to frequent HA-Ras mutations of initiated keratinocytes. Tumor promotion is achieved by repeated subsequent treatment with phorbolesters, such as 12-O-tetradecanoylphorbol-13-acetate (TPA) resulting in benign papillomas, some of which spontaneously progress into malignant squamous cell carcinomas (SCC). Compelling experimental evidence argues for an important contribution of gene regulatory networks controlled by the transcription factor AP-1 in neoplastic transformation of keratinocytes and skin cancer development. AP-1 is mainly composed of Jun and Fos protein dimers and mediates gene transcription in response to many physiological and pathological stimuli, including cytokines, growth factors, stress signals, bacterial and viral infections, as well as oncogenic stimuli [10,11]. Studies in genetically modified mice and in cell culture models have highlighted a crucial role for AP-1 in numerous cellular events, such as proliferation, differentiation, and survival, which are involved in normal development and neoplastic transformation [12]. The requirement of AP-1-mediated gene transcription that leads to tumor promotion in response to TPA has been extensively studied in the mouse epidermal JB6 model [13,14]. Moreover, detailed analysis of genetically modified mice with impaired JNK/AP-1 function revealed that changes in the gene regulatory network depending on JNK signaling and AP-1 activity are key features of multistage skin carcinogenesis *in vivo* [15–18]. NF-κB is another important transcription factor that has been identified as an essential player in neoplastic transformation of keratinocytes [13,14]. NF-κB collectively describes a family of dimeric transcription factors consisting

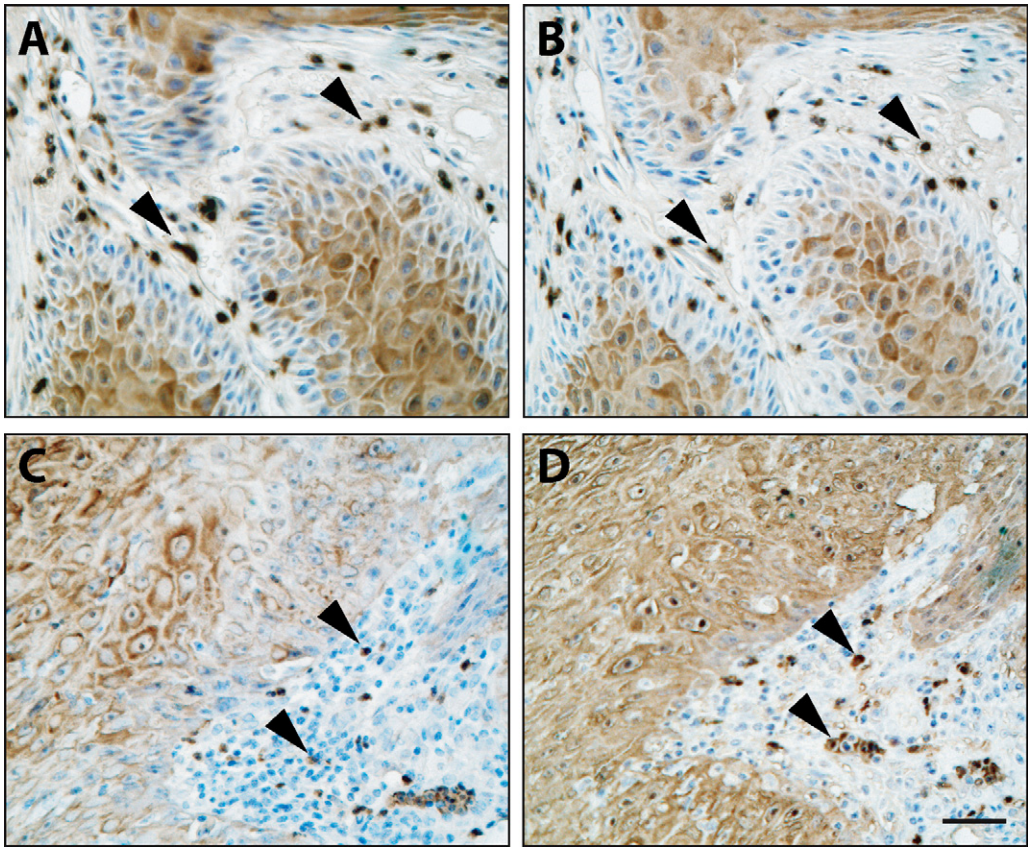

Fig. 1 – S100A8 and S100A9 expressions are restricted to different cellular compartments of mouse and human skin tumors. Representative images showing S100A8 (A and C), and S100A9 expression (B and D; stainings in brown) by immunohistochemistry on parallel tissue sections of mouse papilloma derived from the chemically induced skin carcinogenesis model (A and B) and tissue sections of human cutaneous SCC (C and D). Both proteins are strongly and coordinately expressed in tumor cells of the differentiating compartment and in distinct stromal cells (arrowheads).

of at least five Rel/NF-κB family members, p50/p105 (NF-κB1), p52/p100 (NF-κB2), c-Rel, p65 (RelA), and RelB, which form homo- and heterodimers [19,20]. Initially described and intensively studied in the context of inflammatory and innate immune responses [21], recent studies demonstrated that NF-κB regulates cell proliferation, survival, and cell migration, and is constitutively active in different types of cancer [22]. The precise role of NF-κB in tumorigenesis is still unclear as opposing effects depending on the tumor model system and its function in the development of epithelial malignancy is still under debate [23,24].

The analysis of gene expression profiles using microarray technology in cancer research is extensively used to measure the expression of a large set of genes during tumorigenesis and to identify potential biomarkers for tumor diagnosis and novel molecular targets for anticancer therapy. Recently, we and others have performed global gene expression analysis to define characteristic alterations of the gene regulatory network that occur within different stages of chemically induced skin carcinogenesis. These studies have revealed a comprehensive list of differentially expressed genes some of which represent novel AP-1 target genes [25–32].

2. S100A8 and S100A9 expression in cancer

Two differentially expressed genes, which exhibited a strong up-regulation in advanced stages of skin cancer in mouse and human, encode the S100 family members S100A8 and S100A9 (Fig. 1; [29,30,32]). In addition, significant alterations in the expression of other S100 members, such as S100A3, S100A6, and S100A7, were found in skin tumors suggesting a functional role of S100 proteins during promotion and/or malignant progression of epidermal skin cancer [30,33,34]. S100 proteins comprise a family of 23 different members, which are characterized by high homology, low-molecular weight, two calcium-binding EF-hands, and by tissue-specific expression [35–37]. They are of special interest in the pathogenesis of epidermal diseases, as selected S100 proteins are markedly over-expressed under cellular stress conditions, such as wound healing and inflammation-associated disorders, and are often associated with altered or abnormal pathways of epithelial cell differentiation [38,39].

Recent clinical and experimental data have suggested that changes in the expression and/or function of S100 proteins may represent a key step during cancer development. Moreover, genomic rearrangements at chromosomal region 1q21, in which most S100 genes are clustered, were frequently observed in human epithelial tumors, e.g. lung, breast, oesophagus, colorectal, and liver [40–48], as well as tumors of soft tissue and bone [49–53]. Additionally, systemic analysis for chromosomal positions of cancer-associated transcripts identified 1q21–q23 as a target region for transcriptional activation in common human epithelial malignancies [54,55]. Together with the findings on genomic levels, strong S100A8 and S100A9 up-regulation was found in breast, lung, gastric, colorectal, pancreatic, and prostate cancer [56–64], while down-regulation was detected for squamous oesophageal carcinomas [56–64]. Furthermore, altered S100A9 expression in carcinomas of glandular cell origin, e.g. breast, lung, and thyroid gland, was related to poor tumor differentiation [58,65–67].

3. Regulation of S100A8 and S100A9 transcription: the role of AP-1 and others

S100A8 and S100A9 are often co-expressed suggesting a common mechanism of transcriptional regulation [29]. *In vitro* studies with myeloid and endothelial cells revealed strong induction of transcription by numerous pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) [68,69]. Detailed analysis of proximal promoter regions of human S100A8 and S100A9 revealed common binding sites for distinct transcription factors, such as AP-1, NF-κB, and C/EBP, and Klempt et al. could identify epithelial and myeloid-specific DNA elements regulating human S100A9 gene transcription in a cell type-specific manner [70]. Recently, strong and early induction of S100A8 and S100A9 expression accompanied by histological and molecular hallmarks of inflamed psoriatic skin was demonstrated in adult mice with inducible epidermal deletion of Jun and JunB [71], suggesting that the transcription of both genes is negatively controlled by these two subunits of AP-1, at least in keratinocytes. Enhanced basal and TPA-induced S100A8 and S100A9 mRNA levels in the skin of Fos-deficient animals further support this hypothesis [29]. Yet, the regulation seems to be even more complex, since functional Fos protein is also required for inhibition of TPA-inducible S100A8 and S100A9 transcription by dexamethasone [29], which is a potent inhibitor of inflammation and TPA-induced tumor promotion in skin [72]. Detailed analysis of the molecular mechanisms controlling transcription of both genes in keratinocytes under pathological conditions is needed also taking into account other transcription factors, such as NF-κB. Remarkably, BRCA1 a potent tumor suppressor conferring genetic predisposition to breast and ovarian cancer is also a potential repressor of S100A7 as well as S100A8 and S100A9 transactivation [73].

4. Molecular functions of S100A8 and S100A9

What is the consequence of S100A8 and S100A9 protein over-expression on epithelial cells with regard to human cancer development? Although, recent experimental studies have described the functional role of distinct S100 proteins (e.g. S100A4 and S100A7), and the biochemical pathways they target during carcinogenesis [74,75], the molecular functions of S100A8 and S100A9 on epithelial cells are currently elusive. Data from our laboratory unraveled an increase in AP-1 and NF-κB-mediated gene transcription upon simultaneous over-expression of S100A8 and S100A9 in epithelial cells, suggesting that both proteins act as a functional heterodimer (unpublished data). It is currently accepted that homo- and heterodimer formation as well as protein–protein interaction with non-S100 targets is a hallmark of S100 proteins and contribute to their functional diversification [35,36]. S100A8/A9 is the most abundant naturally occurring S100 heterodimer [76–79], and the molecular basis of the complex formation between

S100A8 and S100A9 has been defined by in yeast two-hybrid screening [80]. Generation of S100A9-deficient mice, which are healthy and display no obvious phenotype *in vivo*, allows to address the question whether heterodimer formation is a prerequisite for S100A8 protein stability, at least in some cell types, as the S100A8 protein is undetectable in bone marrow cells of these mice [81,82]. Direct interaction between different S100 members can also result in functional interference, as shown for S100A1 and S100A4 proteins [83]. In this case, S100A1 reduced S100A4-mediated cell motility, soft agar growth of a mammary tumor cell line *in vitro*, and metastasis *in vivo*. Similarly, we have observed that S100A3 co-expression inhibits AP-1 and NF-κB-dependent transcription upon S100A8 and S100A9 over-expression, which is most likely due to impaired secretion of the heterodimer (unpublished data). Although, physical or even indirect interaction between S100A3 and S100A8 or S100A9 remains to be demonstrated, it is worthwhile to note that S100A3 transcription is antagonistically regulated during chemically induced skin carcinogenesis [30].

5. S100A8/A9 and its functions as a pro-inflammatory cytokine

Originally, S100A8/A9 was discovered as an immunogenic protein expressed by neutrophils with potent anti-microbial properties referred to by its former name calprotectin [84,85]. Meanwhile, there is accumulating evidence that high S100A8/A9 levels are characteristic for inflammatory conditions and that it acts as a chemotactic molecule constitutively expressed by neutrophils, activated monocytes, and macrophages [78,86,87]. Altogether, S100A8 and S100A9 proteins contribute to approximately 40–50% of the soluble, cytosolic content of granulocytes [76,84], and S100A8/A9-positive myeloid cells are the first cells infiltrating inflammatory lesions [88,89]. Both proteins are mainly localized in the cytosol, but translocate to the cytoskeleton and membrane upon elevated intracellular calcium concentration [90]. Experimental data indicate a positive feedback mechanism according to which S100A8/A9, released by primed myeloid cells under inflammatory conditions, promotes further leukocyte recruitment [87]. The heterodimeric complex is involved in innate immunity, leukocyte adhesion, and endothelial transmigration. In addition, it also emerges as important mediator of diverse processes within chronic inflammation [78,87]. In line with these functions, elevated S100A8 and S100A9 protein levels are a hallmark of numerous pathological conditions associated with inflammation (e.g. rheumatoid arthritis, systemic lupus erythematosus, giant cell arteritis, multiple sclerosis, cystic fibrosis, chronic inflammatory bowel diseases, and psoriasis [89,91–97]). Moreover, a novel pediatric syndrome with recurrent infections, inflammation, and hyperzincaemia is also associated with excessively high S100A8/A9 plasma concentration [98,99]. Thus, it is not surprising that S100A8/A9 has been suggested as a suitable biomarker for inflammation, for monitoring disease activity as well as response to treatment [78].

Enhanced S100A8 and S100A9 levels in pathological conditions of chronic inflammation as well as in cancer argue for a possible role in inflammation-associated carcinogenesis. This hypothesis is supported by the fact that S100A8/A9-positive myeloid cells are detected within the tumor stroma of epithelial malignancies, such as skin, colorectal and prostate cancer (Fig. 1; [60,64]). The association between immune cells and cancer pathogenesis has been known for a long time and it was initially assumed that infiltrating leukocytes primarily represent an attempt of the host to eradicate neoplastic cells [7,100]. However, compelling experimental, clinical and epidemiological evidence suggests that a hallmark of many epithelial cancers is an underlying chronic infection accompanied by persistent and unresolved innate immune cell activation, which often predates the disease and participates in tumor initiation and promotion [7,101]. In contrast, it is important to note that innate immune cells have also been identified as key components of the stromal compartment in carcinomas arising independently of infection or chronic inflammation. How do chronically activated innate immune cells contribute to cancer development? Although this question is still largely unanswered, it is well known that immune cells produce a vast amount of cytokines, growth factors and chemokines as well as reactive oxygen species (ROS) and nitric oxide (NO) that stimulate proliferation, prevent apoptosis, induce morphogenesis, or mediate DNA damage in epithelial cells [5,7,100]. One of the key molecules mediating the inflammatory processes in tumor promotion is TNF-α [102,103]. Although, high TNF-α protein levels display an anti-tumorigenic effect by inducing necrosis, low-dose and persistent TNF-α production by tumor cells and activated innate immune cells is involved in promoting cancer growth, invasion and metastasis [103]. Several *in vivo* studies of mouse tumor models have provided direct genetic evidence for the critical role of TNF-α, its receptors (TNFR1/2) and subsequent activation of NF-κB and AP-1-dependent transcription in carcinogenesis [23,103].

Several experimental data suggest a direct link between S100A8 and S100A9 expression and inflammatory conditions in cancer. As mentioned earlier, both genes are highly upregulated in keratinocytes and infiltrating cells upon TPA treatment and during tumor promotion in chemically induced skin carcinogenesis. Additionally, it could be demonstrated that TPA-induced expression is blocked by co-treatment with the anti-inflammatory agent dexamethasone [29]. In this context, it is important to mention that TPA is a potent inducer of inflammation and that its tumor promoting activity is most likely associated with this function. *In vitro* studies showed strong induction of S100A8 and S100A9 expression in mouse microvascular endothelial cells and macrophages upon stimulation with the pro-inflammatory cytokines TNF-α and IL-1 [68,69]. Moreover, TNF-α activates S100A8 and S100A9 expression in primary keratinocytes [104]. Finally, monocytes and macrophages expressing S100A8/A9 efficiently secret TNF-α [105,106], and S100A8/A9 induces TNF-α expression in human microvascular endothelial cells [107].

6. The receptor RAGE: S100 receptor in inflammation and cancer?

S100A8 and S100A9 proteins fulfill various distinct intracellular functions and are also involved in myeloid cytoskeletal

rearrangements, cell migration, in the arachidonic acid metabolism, and in the regulation of neutrophilic NADPH-oxidase [82,95,108–111]. However, most biological functions relevant to inflammation seem to require the release of the S100A8/A9 heterodimer to the extracellular space [39,78,112]. S100A8/A9 is released from activated neutrophils as well as monocytes and has a chemotactic effect in the local micro-environment [113,114]. More recently, S100A8/A9 was also detected in non-keratinized squamous epithelia cells and could be secreted from keratinocytes in culture [39,112]. Although the exact mechanism by which S100A8/A9 crosses the cellular membrane remains to be elucidated, its secretion by human monocytes and activated granulocytes depends on intact microtubules and involves protein kinase C (PKC) activation [114,115]. This alternative secretory pathway bypasses the classical route of the endoplasmatic reticulum and the Golgi apparatus.

S100A8/A9 action as a secreted protein complex requires the presence of cell surface structures on target cells that trigger intracellular signaling cascades. *In vitro* studies demonstrated interaction of S100A8/A9 with heparan sulfate proteoglycans and carboxylated glycans [116,117]. Moreover, the molecules CD36 and RAGE (receptor of advanced glycation end products) are two other putative receptors for S100A8/A9 (Fig. 2; [87,118,119]). In support of that, S100B and S100A12 signaling *via* RAGE has been implicated in a novel inflammatory axis [120,121], and recent reports have demonstrated a functional interaction between S100P and RAGE in pancreatic cancer cell lines [122,123]. Moreover, co-expression of several S100 proteins and RAGE has been found in prostate, breast, and lung tumor tissue [64,124]. The close structural relationship of the S100 proteins raises the possibility that RAGE may interact with multiple, maybe even all, S100 proteins released from distinct cell types [119,125]. It is still a matter of debate whether the other putative S100-binding surface molecules act independently from RAGE or as co-receptors enhancing the affinity of the RAGE for its S100 ligands.

RAGE is a multiligand receptor of the immunoglobulin superfamily that interacts not only with S100 proteins but also with a broad spectrum of other ligands, including advanced

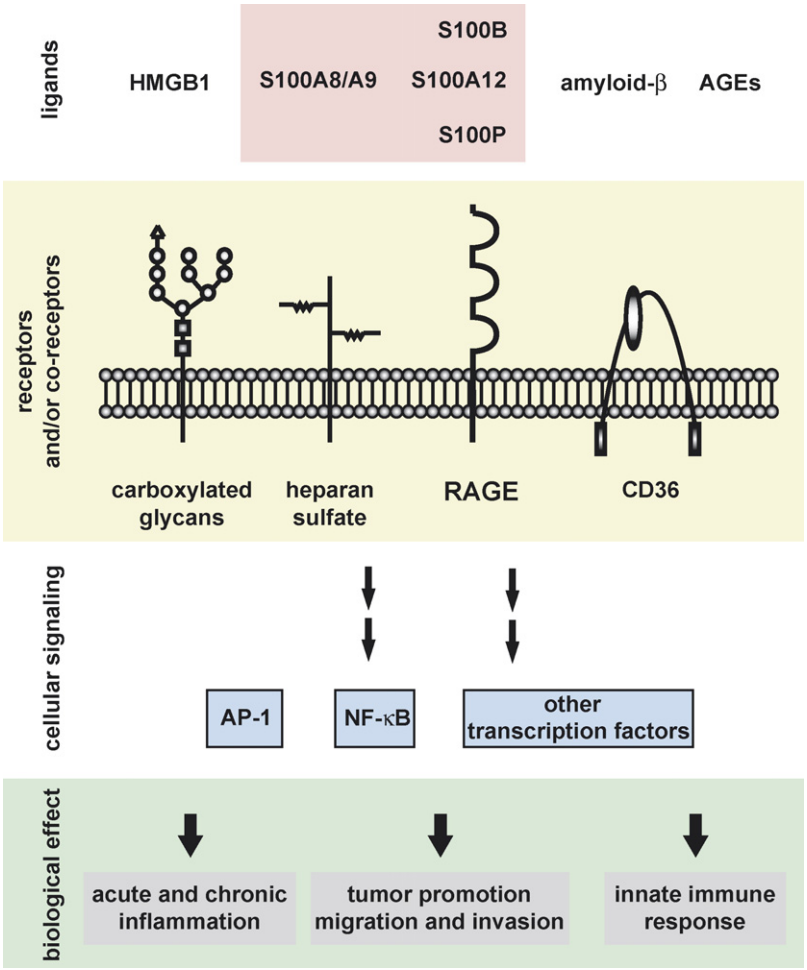

Fig. 2 – Model of a novel activation network in inflammation and cancer. The S100A8/A9 heterodimer and other extracellular molecules such as S100A12, S100B, S100P, HMGB1, amyloid-β, and AGEs (advanced glycation end-products) interact with distinct cellular surface molecules such as RAGE (receptor for advanced glycation end-products), heparan sulfate, carboxylated glycans, and CD36. This interaction is thought to initiate signaling cascades leading to the activation of transcription factors AP-1, NF-κB, and others, thereby establishing biological effects resulting in acute and chronic inflammation, tumor promotion and progression, and innate immune response.

glycation end-products (AGEs), high mobility group box 1 (HMGB1; also known as amphoterin), amyloid-β peptide [121,126,127]. All of those ligands comprise β-sheet structures and fibrils (Fig. 2; [119,121,125,128–131]). Structural analysis of receptor–ligand interaction indicated that RAGE recognizes three-dimensional structures rather than specific amino acid sequences, and therefore, RAGE could be considered as a pattern recognition receptor [128]. RAGE is composed of three immunoglobulin-like regions (one V-type and two C-type domains), a short transmembrane domain, and a 48 amino acids cytoplasmic tail [132,133]. Whereas, the cytoplasmic tail is required for intracellular signaling, the V-type domain is responsible for ligand binding. Activation of the RAGE axis has been shown to be a key event in inflammatory conditions and studies with RAGE-deficient mice have confirmed its role in functional innate immune responses and chronic inflammation [121,134,135]. It has been demonstrated that RAGE acts as an endothelial adhesion receptor promoting leukocyte recruitment to inflamed environments, which seems to require direct interaction of RAGE with the β2-integrin Mac-1 [134]. Interestingly, this interaction was reinforced by S100B protein. Although, *in vitro* studies suggested that S100A8/A9 regulates transendothelial migration of myeloid cells by increasing ICAM-1 binding to Mac-1 [136,137], one may argue that S100A8/A9 release by myeloid cells also increases the RAGE–Mac-1 interaction and that both mechanisms support recruitment of cell types relevant in inflammatory conditions and disorders.

Multiple pathways downstream of RAGE have been identified (e.g. activation of Ras, MAP kinases (ERK, p38, and JNK), PI3K, Rho GTPases, NF-κB, and JAK/STAT [119,128]), but the proximal signaling components, which probably binds to the cytosolic tail of the receptor to initiate signaling events have not been characterized, yet. The diversity of signaling cascades identified in RAGE-mediated cellular responses implies that different RAGE ligands might induce distinct pathways in a cell-type specific manner, and thereby add a further level of complexity to the RAGE network. Interestingly, RAGE-mediated NF-κB activation is of prolonged time course, which appears to overwrite endogenous autoregulatory feedback loops. Due to its ability to sustain cellular activation, RAGE can convert a transient pro-inflammatory response into sustained cellular dysfunction [128].

In adults RAGE protein levels are absent or low in most tissues, whereas, the presence of its ligands seems to trigger receptor expression. Thus, RAGE function seems to be largely mediated by the expression or accumulation of its ligands under pathological conditions. In the context of cancer, elevated expression levels of RAGE and its ligands have been detected in a growing number of tumor types. In contrast, its down-regulation has been proposed as a critical step in lung tumor formation [138]. Nevertheless, the lung is one of the few exceptions where RAGE is highly expressed in adults and may be involved in cell differentiation. Taguchi et al. have demonstrated that in the presence of an excess of its ligand HMGB1, RAGE expression in glioma cells drives tumor growth and metastasis *in vivo*, as well cell growth, migration, and invasion *in vitro* [139]. Moreover, they observed suppression of phorbolester-induced papilloma formation in v-HA-Ras transgenic mice using sRAGE, the soluble form of RAGE. It is important to note that sRAGE has an impact on some aspects of immune responses even in the absence of functional RAGE [128], leading to the hypothesis that beneficial effects of sRAGE in mouse disease models are not solely the result of preventing ligand engagement of the cell surface RAGE. Therefore, it will be a major challenge to investigate the process of skin carcinogenesis in RAGE-deficient animals. Although highly increased levels of the RAGE ligand HMGB1 were detected in papillomas [139], an important contribution of phorbolester-induced S100 proteins in this tumor model has to be considered.

7. Conclusion and outlook

Recent evidence suggests that S100A8/A9 and its potential receptor RAGE are not exclusively involved in the acute and the chronic state of inflammation. The expression pattern of S100A8/A9 in epithelial tumor cells and in the stromal compartment, its up-regulation in various types of tumors as well as its regulation *via* a putative tumor-promoting feed-forward loop indicate a functional role of S100–RAGE interaction in inflammation-associated cancer. Further studies are needed to elucidate the *in vivo* relevance of S100–RAGE interaction and to assess its suitability as a potential novel target for pharmaceutical interference in epithelial malignancies in order to tackle both the inflammatory and the tumor component.

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