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Role of S100 proteins in health and disease

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ABSTRACT

The S100 family of proteins contains 25 known members that share a high degree of sequence and structural similarity. However, only a limited number of family members have been characterized in depth, and the roles of other members are likely undervalued. Their importance should not be underestimated however, as S100 family members function to regulate a diverse array of cellular processes including proliferation, differentiation, inflammation, migration and/or invasion, apoptosis, Ca^{2+} homeostasis, and energy metabolism. Here we detail S100 target protein interactions that underpin the mechanistic basis to their function, and discuss potential intervention strategies targeting S100 proteins in both preclinical and clinical situations.

1. Introduction

Ca^{2+} can function as a second messenger involved in the control of an array of cellular processes ranging from muscle contraction to cell differentiation or cell death [1]. Ca^{2+} signalling and intracellular Ca^{2+} levels are regulated by several Ca^{2+} transporters and membrane channels. Importantly, Ca^{2+}-binding proteins share a common ancestor, and therefore the ability to regulate intracellular Ca^{2+} levels and many Ca^{2+}-signalling pathways [2]. These Ca^{2+} mediator proteins are characterized by an EF-hand Ca^{2+}-binding motif which transmits Ca^{2+} signals by binding to, and thereby regulating, specific target proteins in their Ca^{2+}-bound conformation [3].

Within the EF-hand superfamily the S100 proteins form the largest subfamily, with 25 currently known members comprising a set of non-ubiquitous Ca^{2+}-modulated proteins implicated in multiple intracellular and/or extracellular regulatory activities [4]. Although S100 proteins are expressed exclusively in vertebrates, each has a unique expression and distribution profile amongst different tissues and cell types. The key characteristics of each member are summarised in Table 1.

Due to the diverse range of cellular functions undertaken by S100 proteins [5] some family members have been given more than one name. These include S100A4, which is also known as calvasculin, S100A6, which is also known as calcyclin, and the dimer formed by S100A8/A9, which is known as calprotectin (Table 1). Additionally, calgranulins comprise a group of S100 proteins including S100A8 (calgranulin A), S100A9 (calgranulin B) and S100A12 (calgranulin C), which act as sensors of intracellular Ca^{2+} levels.

Various Ca^{2+}-binding proteins such as calmodulin or troponin-C only act at the intracellular level. However, other S100 proteins act both as intracellular mediators and as extracellular signalling proteins, being thereby able to regulate activities of target cells in either a paracrine or an autocrine manner [5].

2. S100 protein structure, expression, and function

2.1. Molecular structure

The S100s constitute a family of proteins where each protein is encoded by an individual gene [6]. Of the 25 human *S100* genes, 19 (group A S100 proteins) are located within chromosome 1q21. Other members (*S100A11P, S100B, S100G, S100P* and *S100Z*) map to different regions [6]. Every member of the S100 protein family has a similar molecular mass of 10–12 KDa, and they each share 25–65% similarity in their amino acid sequence. They exist as anti-parallel homo- and heterodimers, with each monomer consisting of two helix-loop-helix EF-hands (EF-1 and EF-2) connected by a hinge region and flanked by conserved hydrophobic residues at the C- and N-terminal ends [7].

In the last 15 years, 3D structures of S100 proteins have been revealed in three different forms: bound to Ca^{2+}, bound to its target protein, or in its apo (Ca^{2+}-free) form. [8,9]. These studies have revealed that upon Ca^{2+} binding, the S100 proteins experience a conformational change that allows interaction with target proteins. Furthermore, each S100 protein presents a dimeric form, in a symmetric shape. Each monomer contains two EF-hand motifs, with the N-terminal EF-hand comprising helix I, Ca^{2+}-binding site I and helix II, and the C-terminal EF-hand comprising helix III, Ca^{2+}-binding site II and helix IV. Both EF-hand motifs are separated by a flexible hinge region, or linker region [10]. Ca^{2+} binding to site I results in changes to the backbone conformation, the protein thereby acquiring a 'Ca^{2+}-ready' state.

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Table 1
S100 proteins: cell/tissue expression, function, interacting partners, and associated disease pathologies.

S100 protein	Other names	Expression	Function	Interactions	Associated pathologies	Regulation	Refs
S100A1	S100 alpha	Skeletal muscle fibres, cardiomyocytes and certain neuronal populations.	Extracell: internalized into neurons and delivered to endosomes, Golgi and lysosomes. Enhances Ca^{2+} influx in cardiomyocytes. Intracell: associates with cytoskeletal components, interacts with SR Ca^{2+}-ATPase and RyR2 in the heart, improving contractile performance.	Extracell: RAGE. Intracell: SERCA, RyR1 & 2, Fructose-bisphosphate aldolase	S100A1 deficiency results in abnormal SR Ca^{2+} content and fluxes, deterioration of cardiac performance and heart failure	Inhibitory transcription factors downstream of GPCRs and PKC	[171–173]
S100A2	S100L, CAN19	Urothelium, respiratory, gastrointestinal and squamous epithelium.	Extracell: chemotactic factor for eosinophils. Intracell: binds to p53 and potentiates tumour-suppressing activity.	Extracell: RAGE.	Downregulated in many cancers, but upregulated in others	–	[174–175]
S100A3	S100E	Hair root cells and some astrocytomas	Epithelial cell differentiation and Ca^{2+}-dependent hair cuticular barrier formation.	RARα	Involved in HCC tumorigenesis and tumour aggressiveness	–	[176–178]
S100A4	Metastasin1 (Mts1), Calvasculin	Tumour and stromal cells, myeloid cells, adipocytes, fibroblasts, immunocytes, vascular cells.	Extracell: key role in tumour cell survival and metastasis. Activates NF-κB, inducing production of pro-inflammatory cytokines and migration of neutrophils, monocytes, and macrophages. Activates ERK1/2, modulating growth and survival. Intracell: induces MMP expression and interacts with cytoskeletal proteins NMIIA, tropomyosin and actin to promote cell migration.	Extracell: RAGE, EGFR, Gαq-coupled receptor. Intracell: NMIIA, tropomyosin, actin, p53, S100A1, annexin2	Upregulated in many cancers	Upregulated by β-catenin/T-cell factor complex	[110,159,179]
S100A5	S100D	–	–	RAGE	Upregulated in bladder cancer and recurrent grade I meningiomas	–	[180]
S100A6	Calcyclin (CACY)	Epithelial cells, fibroblasts and different kinds of cancer cells	Extracell: activates RAGE and promotes apoptosis and generation of ROS. Stimulates insulin release from pancreatic islet cells. Intracell: interacts with caldesmon, calponin, tropomyosin and kinesin to modulate cell proliferation, cytoskeletal dynamics and tumorigenesis.	Extracell: RAGE	Overexpressed in AT.	–	[181]

Table 1 (*Continued*)

S100 protein	Other names	Expression	Function	Interactions	Associated pathologies	Regulation	Refs
S100A7	Psoriasin1 (PSOR1)	Keratinocytes	Extracell: signals through RAGE to activate NF-κB, inducing production of pro-inflammatory cytokines and migration of neutrophils, monocytes, and macrophages. Intracell: promotes aggressive features in breast cancer by stimulating Akt and NF-κB.	Extracell: RAGE	Overexpression induces leukocyte infiltration linked to inflammatory skin diseases such as psoriasis.	Upregulated in breast cancer by proinflammatory cytokines and in keratinocytes by IL-17, IL-22 and flagellin.	[182,183]
S100A8	Calgranulin-A (CAGA), Calprotectin 1 L1	Macrophages, dendritic cells, microvascular endothelial cells, epithelial cells and fibroblasts upon activation	Extracell: regulates inflammation. Chemotactic factor for neutrophils. Induces cell differentiation and TNF-α and IL-1β production in myeloid cells. Scavenges intracellular ROS and stabilizes NO in neutrophils, protecting from oxidative damage in inflammatory lesions. Intracell: stimulates keratinocyte differentiation and exerts anti-inflammatory effects.	Extracell: GPCR, TLR4, Scavenger receptor CD36. Intracell: telomerase	Overexpressed in inflammatory and autoimmune conditions.	Induced by pro-inflammatory stimuli, TLR agonists and oxidative stress in an IL-10-dependent manner.	[184–187]
S100A9	Calgranulin-B (CAGB), Calprotectin L1H	Monocytes, neutrophils and dendritic cells; Fibroblasts, mature macrophages, vascular endothelial cells and keratinocytes upon activation	Extracell: involved in leukocyte migration, chemotactic for neutrophils. Induces TNF-α, IL-1β, IL-6 and IL-8 in macrophages *via* NF-κB activation. Intracell: inhibits myeloid differentiation and accumulation of myeloid-derived suppressor cells *via* ROS generation, contributing to tumour growth. Regulates S100A8/S100A9 activities.	Extracell: RAGE, TLR4, Scavenger receptor CD36	Anti-inflammatory in healthy state, while oxidative stress activates its pro-inflammatory functions. Contributes to the pathogenesis of autoimmune diseases.	Upregulated by oxidative stress, corticosteroids, cytokines and growth factors.	[43,186,188],[189]

Table 1 (*Continued*)

S100 protein	Other names	Expression	Function	Interactions	Associated pathologies	Regulation	Refs
S100A8/ S100A9	Calprotectin	Monocytes, neutrophils and dendritic cells; Fibroblasts, mature macrophages, vascular endothelial cells and keratinocytes upon activation	Extracell: anti-microbial properties. Chemotactic for neutrophils. Regulates inflammation, cell proliferation, differentiation and tumour development *via* NF-κB-mediated pro-inflammatory cytokine production in monocytes and macrophages. Intracell: inhibits myeloid cell differentiation. Facilitates FA transport. Cytoplasmic Ca^{2+} sensor linking Ca^{2+} influx to phagosomal ROS production. Induces microtubule polymerization and F-actin cross-linking.	Extracell: RAGE, Scavenger receptor	Overexpression promotes resistance to TNF-α-induced apoptosis and induces malignant progression through ROS production. Mediates differentiation of psoriatic keratinocytes. Overexpressed in atherosclerotic lesions and cardiovascular events.	Regulated through an autoinhibitory process resulting in restriction of inflammation.	[67,187],[190–192]
S100A10	Calpactin-1 (CAL-1 L)	Macrophages	Regulator of cellular plasmin production: plasminogen receptor, mediates macrophage recruitment into tumour sites in response to inflammatory stimuli. Bound to annexin 2, serves as binding scaffold for pathogens and host proteins, assisting their trafficking and anchorage to the plasma membrane. Plays important roles in angiogenesis and endothelial cell function.	Annexin2, serotonin 1B receptor	Downregulated in depressive-like states. Implicated in the action of antidepressant drugs and electroconvulsive seizures due to its interaction with serotonin receptors.	Induced by EGF, TGF-α, IFN-γ, NGF, KGF, RA and thrombin, and by the oncogenes PML-RARα and Kras.	[193–196]
S100A11	S100C, Calgizzarin	Chondrocytes, luteal cells, oviductal epithelial cells	Extracell: promotes chondrocyte hypertrophic differentiation and stimulates RAGE-dependent type X collagen and IL-8 production. Intracell: When phosphorylated by PKC-α, Ca^{2+}-bound S100A11 inhibits cell growth through activation of the cell cycle modulator p21WAF1/CIP1.	Extracell: RAGE. Intracell: Nucleolin, Rad54B	Signal through RAGE to activate p38 MAPK, accelerating chondrocyte hypertrophy and matrix catabolism to promote osteoarthritis progression.	Induced/released by chondrocytes exposed to IL-1β, TNF-α, and CXCL8	[86],[197–200]

Table 1 (*Continued*)

S100 protein	Other names	Expression	Function	Interactions	Associated pathologies	Regulation	Refs
S100A12	Calgranulin-C (CAGC)	Constitutively expressed in neutrophils, monocytes and early macrophages. Induced in endothelial and epithelial cells and proinflammatory macrophages under inflammatory condition.	Extracell: Activates NF-κB, inducing production of pro-inflammatory cytokines, TNF-α, and chemokines for neutrophil, monocyte and lymphocyte recruitment. Intracell: modulates interactions between cytoskeletal elements and membranes. Inhibits aggregation of aldolase and GAPDH.	Extracell: RAGE, GPCR, Scavenger receptor. Intracell: Aldolase, Nox-1.	Expression in epithelial cells is associated with growth arrest. Overexpression causes VSMC dysfunction and aortic aneurysms, linked to leukocyte influx.	TNF-α, IL-6 and endotoxin induce its expression in monocytes/ macrophages; LPS in smooth muscle cells.	[46],[201–203]
S100A13	–	Fibroblasts, osteoblasts and melanoma cells	Involved in stress-induced release of FGF-1 and IL-1α from several cell types. Promotes its own intracellular translocation, possibly *via* RAGE signalling. Plays a key role in tumour growth, angiogenesis and metastasis.	Extracell: RAGE. Intracell: FGF-1, p40 Syt1	Overexpression associated with high intratumoral angiogenesis and poor prognosis in patients with stage I NSCLC.	Induced by FGF1 and IL-1α upon intracellular stress conditions.	[132],[204,205]
S100A14	–	Lymphocytes, epithelial cells	Extra: at low doses stimulates proliferation, at high doses stimulates apoptosis in ESCC cells *via* RAGE signalling. Intracell: may function as a cancer suppressor affecting the p53 pathway and modulating expression of MMP1, MMP2 and MMP9.	Extracell: RAGE. Intracell: p53	Ectopic overexpression promotes motility and invasiveness of ESCC cells.	Induced by EGF through p-ERK signalling pathway in breast cancer cells	[206–208]
S100A15	S100A7A	Keratinocytes in inflamed skin	Putative functional role in innate immunity, epidermal cell maturation, and epithelial tumorigenesis. Acts as chemotactic factor for monocytes and granulocytes. Acts synergistically with S100A7 in leukocyte recruitment *in vitro* and *in vivo*.	GPCR	Potential therapeutic target for various human disorders including arthritis, cancer, and AD.	Induced by LPS, IL-1β and Th-1 cytokines	[209,210]
S100A16	S100F	Astrocytes, preadipocytes	Acts as a novel adipogenesis-promoting factor, affecting negatively insulin sensitivity.	p53	Upregulated in several tumours	Increased expression in AT of diet-induced obese mice	[153],[211]

Table 1 (*Continued*)

S100 protein	Other names	Expression	Function	Interactions	Associated pathologies	Regulation	Refs
S100B	–	Astrocytes, Schwann cells, melanocytes, chondrocytes, adipocytes, skeletal myofibers, certain dendritic cell and lymphocyte populations	Extracell: Released from astrocytes, signals through RAGE. At low concentrations stimulates proliferation through ERK1/2 and NF-κB-mediated upregulation of Bcl-2. At high concentrations promotes inflammatory activities and kills neurons through ROS production. Intracell: interacts with nuclear NDR kinase and blocks recruitment of its substrates. May maintain cell proliferation with beneficial effects during development and tissue regeneration, and detrimental effects during tumorigenesis.	Extracell: RAGE, FGFR. Intracell: Tubulin, actin-binding proteins, annexin 6, Rac1, SRC kinase, NDR kinase, p53, intermediates upstream of IKKβ/NF-κB.	Involved in brain, cartilage and muscle repair, activation of astrocytes in brain damage and neurodegenerative processes, cardiomyocyte remodelling after infarction and in melanomagenesis and gliomagenesis.	NF-κB, EGF and IFN-γ regulate S100B expression in several cell types.	[212–216]
S100G	Calbindin-D9K (CABP9K)	Epithelial cells	Acts as cytosolic Ca^{2+} buffer in many tissues, resulting in modulation of Ca^{2+} adsorption.	–	–	–	[217]
S100P	S100E	Lymphocytes, epithelial cells	Extracell: mediates tumour growth and cancer cell drug resistance through RAGE signalling. Intracell: promotes transendothelial migration of tumour cells through reduction of focal adhesion sites.	Extracell: RAGE. Intracell: ezrin/radixin/moesin, IQGAP1	Overexpressed in clinically isolated tumours, associated with metastasis, drug resistance, and poor clinical outcome.	–	[218–220]
S100Z	–	Lymphocytes	–	–	Downregulated in several tumours	–	[221]

This involves a ~40° rotation of helix III to a more open structure that exposes a broad hydrophobic region including residues from helices III and IV in the C-terminal EF-hand and hinge region. This regulates protein activity by enabling the respective S100 protein to interact with many different target proteins including receptors and other S100 members [3,11].

Certain S100 members have been described to bind to the same target molecules. For instance, S100A1, S100A6 and S100B interact with annexin A6 [12], while S100A1, S100A2, S100A4 and S100B bind to the tumour suppressor gene p53 [13,14]. This could be predictable given the substantial sequence similarities between most of the S100 proteins. However, there is a subtle level of discrimination that prevents arbitrary interaction of targets with any S100 protein. Structural studies of S100-target complexes have shown that S100 family members use different mechanisms for target recognition despite the similar conformational change induced by Ca^{2+} binding in all S100 family members [15–18]. Moreover, the region exposed upon Ca^{2+} binding comprises the most variable portions of the S100 sequences (hinge and C-terminal regions), which is enough to discriminate against different target proteins [10]. The distribution of hydrophobic and charged residues, together with differences in surface configurations, contribute to the specific target binding patterns described amongst S100 family members [18,19].

2.2. Expression

Members of the *S100* gene family show different patterns of both cell- and tissue-specific expression (Table 1). Moreover, expression of S100 proteins is carefully regulated in order to ensure the maintenance of immune homeostasis [20]. Calprotectin (S100A8/A9), for example, is constitutively expressed in certain immune cells including monocytes, neutrophils, and dendritic cells [21]. However, upon activation, it is also expressed in fibroblasts [22] or mature macrophages [23], amongst other types of cells. In addition, epigenetic mechanisms also play a vital role in regulating S100 gene expression, with methylation of DNA CpG islands being a common method of transcriptional repression. Accordingly, DNA hypomethylation has been reported to significantly induce expression of several members of the *S100* members in prostate and gastric cancer [24,25].

2.3. Function

S100 proteins have been implicated in the control of a wide number of intracellular and/or extracellular functions, including regulation of cell apoptosis, proliferation, differentiation, migration/invasion, energy metabolism, Ca^{2+} homeostasis, protein phosphorylation and inflammation in different cell types [5]. Some of their key regulatory functions are detailed below.

2.3.1. S100s as damage associated molecular pattern (DAMP) molecules

DAMPs play a key role in the pathogenesis of many inflammatory diseases, including rheumatoid arthritis (RA), osteoarthritis (OA) and atherosclerosis. After cell damage/stress or activation of immune cells including neutrophils and macrophages, S100 proteins are released to the extracellular space where they play a key role in the regulation of several immune and inflammatory processes [26]. They can act as DAMP molecules to activate both immune and endothelial cells by binding to toll-like receptors (TLR)s and receptors for advanced-glycation end products (RAGE) (Fig. 1).

For example, there is evidence showing that binding of calprotectin S100A8/A9 to TLR4 triggers a signalling cascade that modulates processes such as inflammation, cell proliferation, differentiation and tumour development *via* nuclear factor κB (NF-κB) activation [27]. Furthermore, S100A12 binding to RAGE has been shown to induce expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells, as well as increasing NF-κB-induced expression of proinflammatory cytokines such as tumour necrosis factor α (TNF-α) by other inflammatory cells [28]. As such, S100A12 has an essential role in the mediation of inflammation and has been described to increase atherosclerosis *in vivo* through interactions with RAGE [29,30].

Importantly, S100A4, S100A8/9, S100A11 and S100A12 have been found to be upregulated in the synovial tissue, synovial fluid, or serum of patients with RA [31–33]. Expression of S100A8/A9 was elevated in the synovium of a collagenase-induced OA mouse model [34], as well as in patients with sepsis, correlating with severity of disease [35

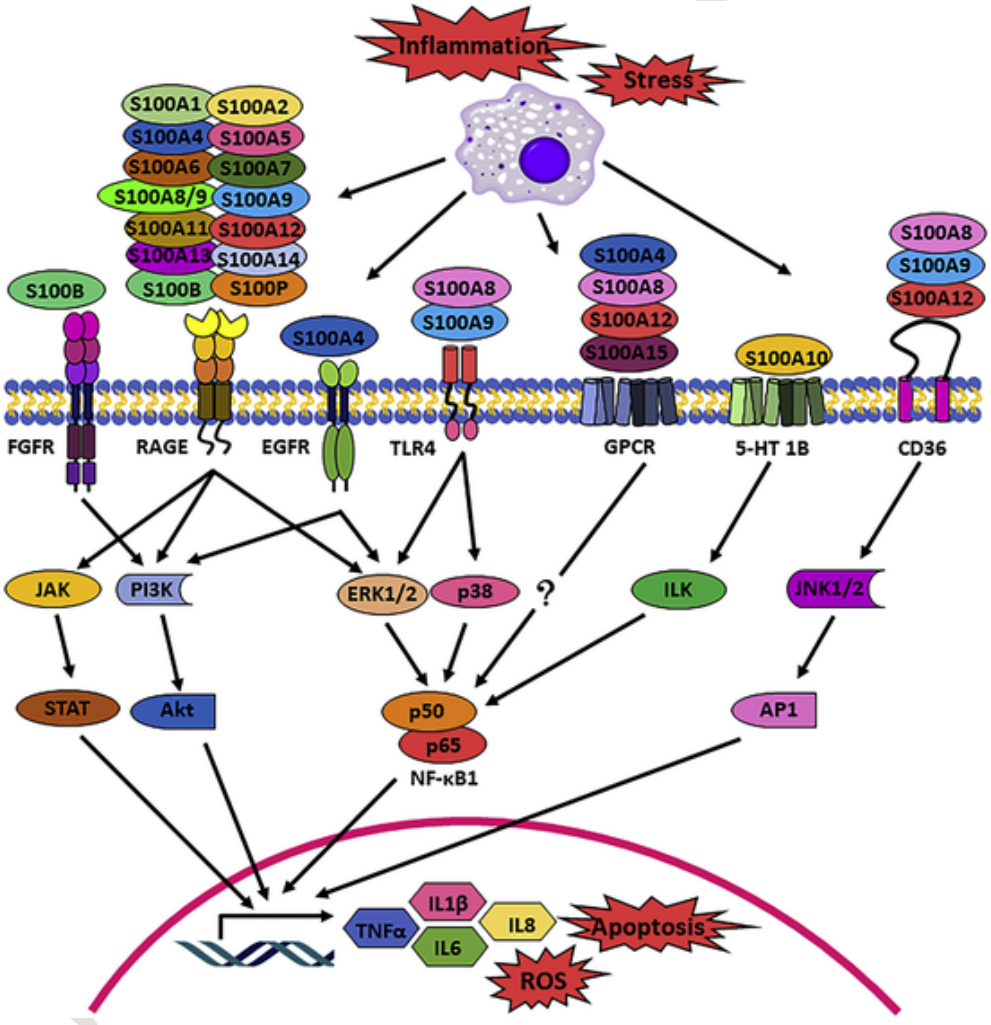

Fig. 1. Extracellular S100s signalling. S100 proteins are released from inflammatory cells including fibroblasts, macrophages, lymphocytes and neutrophils in response to inflammation and stress. They signal through a range of cell surface receptors to activate several inflammatory signalling pathways which ultimately activate transcription of proinflammatory factors including TNF-α, IL-1β, IL-6 and IL-8, as well as other mechanisms that lead to ROS formation and apoptosis. S100B signal through FGFR to activate the PI3K/PKB pathway. Most S100s signal through RAGE to activate the JAK/STAT, PI3K/PKB and ERK/NF-κB pathways. EGFR-mediated signalling can also activate the PI3K/PKB and ERK/NF-κB pathways. GPCR-mediated signalling can also activate NF-κB although the mechanism involved in unknown. S100A10 signals through the 5-HT1B receptor to activate ILK and NF-κB, while CD36-mediated signalling activates the JNK/AP1 pathway. Abbreviations: 5-HT1B5-hydroxytriptamine 1B serotonin receptor; AP1 activator protein 1; CD36 cluster of differentiation 36; EGFR epidermal growth factor receptor; ERK extracellular signalling-related kinase; FGFR fibroblast growth factor receptor; GPCR G protein coupled receptor; IL interleukin; ILK integrin-linked protein kinase; JAK Janus kinase; JNK c-Jun N-terminal kinase; NF-κB nuclear factor κB; PI3K phosphatidyl inositol 3 phosphate; PKB protein kinase B; RAGE receptor for advanced glycation end products; STAT signal transducer and activator of transcription; TLR4 toll-like receptor 4; TNF-α tumour necrosis factor alpha.

]. S100A12 levels were also found to be significantly increased in the synovial fluid of patients with OA when compared to healthy controls [36].

DAMPs also play a role in the pathogenesis of neurodegenerative diseases. S100B serum levels have been found to be closely associated to the severity of diseases such as Alzheimer's [37] and Parkinson's [38]. In addition, S100A10, which is also known as p11, increases expression of the 5-hydroxytryptamine 1B serotonin receptor (5-HT1B) in HeLa cells and brain tissue, and interestingly its expression has been shown to be decreased in rodent models of depression [39].

2.3.2. S100s in immune cell migration, invasion and differentiation

Macrophages play a vital role in tumour development and metastasis through several mechanisms including regulation of local inflammation, inhibition of anti-tumour immunological processes and stimulation of angiogenesis [40]. Macrophages are recruited by various chemoattractant molecules including chemokine ligands (CCL) 3–8 and macrophage inflammatory protein 1 alpha (MIP-1α) [41]. Importantly, increasing evidence show that several S100 proteins also contribute to leukocyte migration. For instance, as well as inducing pro-inflammatory cytokine production in macrophages through the activation of the NF-κB and p38 mitogen activated protein kinase (MAPK) pathways [42], S100A8/A9 has been seen to mediate immune cell migration [43]; S100A12 has been shown to induce the production of pro-inflammatory cytokines interleukin (IL) -6 and -8 through RAGE-dependent NF-κB activation, resulting in the recruitment of monocytes [44,45]; S100A10 has been reported to recruit macrophages to tumour sites [46]; whereas S100A8/S100A9 have been shown to signal through RAGE to mediate the effect of TNF-α on the differentiation of myeloid-derived suppressor cells [47].

3. Targeting S100 proteins in disease

3.1. S100s as biomarkers for disease

Since a number of S100 proteins can be identified in body fluids, they may be used as biomarkers to detect a specific disease, where their increased expression levels are indicative of pathological conditions [48]. As such, S100A4 has recently been reported as a novel biomarker and an important regulator of glioma stem cells, with its increased expression contributing to the appearance of a metastatic phenotype [49], as well as having been described as a marker for lupus nephritis activity, a determinant factor for the onset of the complex inflammatory autoimmune disease lupus erythematosus [50]; increased serum levels of S100A6 have been reported in patients with gastric cancer [51]; S100A7 levels have been found to be increased in cerebrospinal fluid and brain of patients with Alzheimer's disease [52]; blood levels of S100A12 are increased in patients with diabetes [30] and it has also been used as a biomarker for detection of other inflammatory disease such as systemic-onset juvenile idiopathic arthritis [53]; augmented serum levels of S100A8/A9 have been seen in individuals with obesity [54] and in patients with coronary artery diseases [55]. Importantly, S100A8/A9 has also proven to be a useful biomarker for disease activity in the management of inflammatory bowel diseases such as Crohn's disease [56], and faecal S100A8/A9 detection can be used to differentiate inflammatory bowel disease from irritable bowel syndrome [57]. Finally, recent evidence shows that S100B can be used as a monitoring and prediction tool for management of traumatic brain injury [58], while its overexpression has also been associated with certain genetic disorders such as Down syndrome [59] and even to certain mood disorders as a consequence of glial pathology [60].

3.2. S100s as therapeutic targets

An increasing number of studies suggest that S100 proteins could be used as potential therapeutic targets to treat a variety of diseases. S100 proteins, particularly calgranulins (S100A8, A9 and A12), play a major role in the mediation of the immune responses characteristic of a series of diseases, including inflammatory arthritis, atherosclerosis and microbial infections [61], as well as joint inflammation and cartilage degradation in patients with RA [62]. Furthermore S100A7 has been found to be abundantly expressed in psoriatic lesions or in serum from psoriatic patients [63] as well as in atomic dermatitis skin lesions, induced by pro-inflammatory factors such as TNF-α, IL-17 and IL-22 [64].

Several S100 proteins bind to TLR4 [27,33,65] and RAGE [66] (Fig. 1). Amongst them, S100A8/S100A9, whose levels are found to be elevated in the serum of patients suffering from rheumatoid arthritis and other inflammatory conditions [62], elicits most of its effects *via* these receptors [27]. Importantly, the heterodimeric form of S100A8/S100A9 can bind TLR4, whereas high extracellular Ca^{2+} concentrations induce the formation of S100A8/S100A9 tetramers [67], preventing its interaction with TLR4, thus providing an autoinhibitory mechanism for modulating S100A8/9 biological activity [68].

Substantial evidence shows that tissue and serum levels of many S100 proteins correlate with disease severity during tissue or local inflammation [5,68]. In addition, we have seen how extracellular S100 proteins can behave as DAMPs, triggering proinflammatory responses and inducing autoimmune conditions and inflammatory disorders [5,26,69]. Function-blocking antibodies directed towards receptors and ligands have been widely used as therapeutic agents for the treatment of numerous pathologies including cancers and in immune disorders [71–74]. Given the extensive evidence indicating that extracellular S100 proteins mediate inflammatory responses in many pathological conditions mostly through cell receptor signalling [62,65], the use of S100 function-blocking antibodies might therefore provide an effective therapeutic strategy to treat these conditions. Some examples of S100-neutralised activity in various diseases are described in further detail below. In addition, anti-allergic drugs have been reported to bind to S100A12, blocking downstream RAGE signalling and subsequent NF-κB activation [75].

It has been well established that elevated extracellular S100A8/S100A9 levels are closely linked to inflammatory and autoimmune diseases, including rheumatoid arthritis [76], inflammatory bowel disease [77], cystic fibrosis [78], diabetic nephropathy [79] and cardiovascular disease [80], amongst others. It has been seen that restriction of S100A8/A9 activity with the use of small-molecule inhibitors or neutralizing antibodies ameliorates pathological conditions in murine models [81]. For example, it has been seen that certain quinoline-3-carboxamides, compounds presently under study for the treatment of human autoimmune and inflammatory diseases, interact with S100A9 and the S100A8/A9 complex, thus blocking their interaction with TLR4 or RAGE and inhibiting TNF-α release *in vivo* [82]. Blockade of S100A8/A9 has also recently been seen to reduce inflammatory processes in murine models of arthritis [83]. Importantly, it has been suggested that S100A8 would be a good target against obesity-induced chronic inflammation [84]. Furthermore, it has been reported that increased S100A8/A9 expression in the tumour microenvironment is associated with the progression and aggressiveness of the disease [85,86]. In particular, it has been seen that extracellular S100A8/A9 plays a central role in the recruitment of myeloid cells, thereby promoting the formation of a pre-metastatic niche and tumour growth [87,88]. It also promotes the expression of serum amyloid 3, which recruits myeloid cells to pre-metastatic spots [89], enabling the formation of a proinflammatory environment that recruits circulating tumour cells. It has been seen that S100A8 and S100A9 neutralizing antibodies block the recruitment

of both myeloid cells and circulating tumour cells [89]. It has also been reported that peptibodies (chimeric proteins consisting of a biologically active peptide and a fragment crystallizable (Fc) domain of immunoglobulin G (IgG)) [90] directed towards S100A8 and S100A9 reduce tumour-related complications in a range of cancer models [91]. Collectively, these studies underline the potential use of S100A8 and S100A9 antibodies as therapeutic reagents, but also as diagnostic tools. In addition, S100A4 and S100B have been shown to bind to p53 tumour suppressor gene, inhibiting its phosphorylation and thereby leading to p53 down-regulation [14]. Inhibition of the S100B-p53 interaction would therefore restore the anti-tumour function of p53.

In addition to direct interaction strategies to modulate S100 proteins in disease, covalent modification has important implications for the function of S100 proteins. For example, S100A7, S100A10, and S100A11 activity is regulated through transglutaminase-dependent covalent modification [92]. In addition, several S100 proteins have been seen to be S-nitrosylated, including S100B [93], S100A1 [94] and S100A8/A9 [95]. Furthermore, the ability of S100A1 to act as a calcium receptor is thought to be regulated by S–glutathionylation [96]. Other covalent modifications such as sumoylation [97] and phosphorylation [98] of several S100 proteins have also been described. Therefore, targeting these modifications may also constitute an indirect way to modulate S100 structure or function, thus impacting upon disease pathophysiology and progression.

4. S100A4

Of all of the S100 family members, S100A4 is the most extensively studied. As such it is worthy of consideration in its own right. S100A4 has been given many names, including metastasin (MTS-1), PEL-98, 18A2, 42A, P9KA, CAPL, calvasculin and fibroblast-specific protein (FSP-1) [99]. The human *S100A4* gene maps to chromosome 1q21, and comprises four exons that encode a protein containing 101 amino acid residues [100]. It is ubiquitously expressed, and present both intra- and extracellularly, with intracellular levels being high both in the cytoplasm and in the nucleus [101].

S100A4 plays a significant role in many physiological functions including cell motility, adhesion, proliferation, invasion, and metastasis [102]. Intracellular S100A4 binds to proteins of the cytoskeleton including F-actin and non-muscle myosin heavy chains [103], both involved in cellular stability and/or motility [104]. By contrast, extracellular S100A4 regulates the expression of extracellular matrix (ECM)-remodelling enzymes such as MMPs, which are implicated in mediating cellular migration in various tissues [105], and can signal through membrane receptors to activate proinflammatory pathways [106].

4.1. S100A4 signalling

4.1.1. Extracellular S100A4

Under a range of pathological stimuli, a number of inflammatory cells including lymphocytes, macrophages and neutrophils upregulate expression and release of S100A4 into the extracellular space in the form of plasma membrane-derived macrovesicles [107]. Amongst the ways in which extracellular S100A4 potentially exerts its effects, it has been described to signal through several cell-membrane receptors including RAGE, epidermal growth factor receptor (EGFR), TLR4 and IL-10 receptor (IL-10R) [5,108].

RAGE is a transmembrane receptor of the immunoglobulin superfamily. Its expression is cell type- and developmental stage-specific: while it is highly expressed during embryogenesis, its expression decreases in adult life [109]. However, its expression has been seen to be increased in pathogenic environments such as inflammatory conditions [110]. For example, increased expression of RAGE and some of its ligands has been found in atherosclerotic lesions from diabetic individuals who died unexpectedly from cardiovascular problems [111]. Furthermore, numerous studies reveal that RAGE expression is low in the human kidney in physiological conditions, but that its expression is increased in kidney failure-related diseases, including diabetes [112].

As with other S100 family members, RAGE are well-established interaction partners of S100A4 [113]. In addition to inducing smooth muscle proliferation in atherosclerosis [113], it has been reported that binding of extracellular S100A4 to these receptors increases the migratory and invasive capabilities of colorectal cancer cells *via* activation of MAPK/extracellular signal-regulated kinase (ERK) and NF-κB, as well as hypoxia signalling through the hypoxia inducible transcription factor, HIF-1α, upregulation [114] (Fig. 2).

Extracellular S100A4 signalling activates several major proinflammatory pathways, including the MAPKs p38, ERK and c-Jun N-terminal kinases (JNK) [115]. This triggers leukocyte migration and recruitment during immune responses, inducing a self-amplifying pro-inflammatory cycle through the upregulation of various pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and other immune cell related factors, as well as several well-established inflammation-associated S100 proteins including S100A8 and S100A9, thereby enabling the development of an inflammatory milieu [106].

Extracellular S100A4 also triggers the activation of another key proinflammatory transcription factor, namely NF-κB [108,116]. Importantly, both NF-κB and MAPKs are main transcriptional regulators of various MMPs [117], and could therefore mediate S100A4-induced stimulation of cell migration and metastasis. The underlying mechanisms of S100A4-mediated activation of MAPKs and NF-κB have not been fully described. In chondrocytes, this process is dependent on the interaction of S100A4 with RAGE [116], whereas in primary neurons and endothelial cells, the activation of this signalling pathway appears to be RAGE-independent [118]. It has been widely demonstrated that extracellular S100A4 induces NF-κB activation in human cancer cell lines through the classical NF-κB pathway [119,120] to promote cell migration and metastasis. It has been recently proposed that S100A4 constitutes a link between cancer-related metastasis and inflammation [107]. However, very little is known about the role of S100A4 in the activation of the inflammatory processes mediated by NF-κB in many autoimmune diseases, fibrosis, and other disorders.

4.1.2. Intracellular S100A4 signalling

Intracellular S100A4 was firstly identified in tumour cells, and accordingly, extensive evidence shows that an upregulation in S100A4 intracellular levels correlates with increased tumour cell motility [121,122]. Besides tumour cells, intracellular S100A4 is expressed in normal cells and tissues, including fibroblasts and cells of the immune system [123]. For instance, it has been seen to be expressed in astrocytes, where its levels increase after injury, inducing astrocyte migration and repair responses [121]. Importantly, a model of *S100A4* (−/−) mice shows impaired recruitment of macrophages to inflammation sites *in vivo*, whereas macrophages derived from these mice showed defective chemotaxis *in vitro* [123]. Overall, these findings indicate that intracellular S100A4 plays a major role in conferring migratory capacity to cells, mainly to non-metastatic tumour cells during an epithelial to mesenchymal transition, as well as to cells of the immune system including lymphocytes, neutrophils and macrophages during the progress of the immune response [124].

One of the mechanisms through which this intracellular S100A4 upregulation is thought to take place is through TGF-β-induced expression [125]. Secretion of proinflammatory cytokines and other factors such as TGF-β by activated immune cells and fibroblasts signal through the SMAD2/SMAD3 pathway to induce expression of intracellular S100A4, which is then able to interact with cytoskeleton–associated target molecules such as acto-myosin filaments, tropomyosin or non-muscle myosin heavy chain IIA (NMIIA) (Fig. 2). This interaction destabilises the myosin II assembly, promoting its dissociation and remodelling, ul-

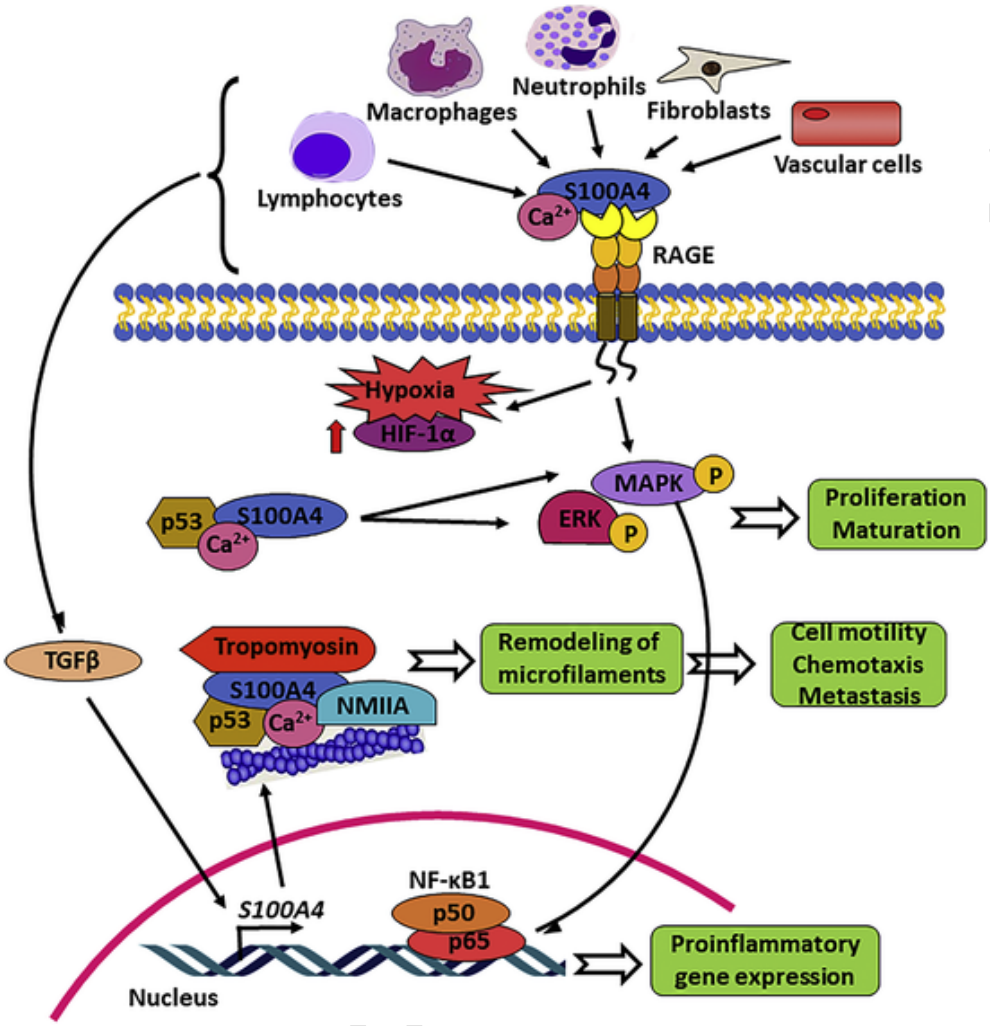

Fig. 2. RAGE-mediated S100A4 signalling. Extracellular S100A4, released from fibroblasts, macrophages, lymphocytes, neutrophils, vascular cells, and other bone marrow derived cells, signals through RAGE, leading to increased phosphorylation of MAPKs and subsequent activation of NF-κB, inducing expression of pro-inflammatory genes. On the other hand, TGF-β secreted from immune cells induces intracellular expression of *S100A4*, which is then able to interact with a number of target molecules, including NMIIA, tropomyosin, p53, and actin, to form complexes that facilitate the remodelling of microtubes and microfilaments to enhance cell motility and chemotaxis, as well as contributing to the infiltration of fibroblasts, immune cells and vascular cells into the affected region. In addition, binding of intracellular S100A4 to p53 promotes cell proliferation and collagen expression *via* MAPK activation and phosphorylation of ERK. Finally, extracellular S100A4 signalling through RAGE can also activate hypoxia signalling through upregulation of HIF-1α. Abbreviations: ERK extracellular signalling-related kinase; HIF-1α hypoxia inducible factor 1α; MAPK mitogen-activated protein kinases; NF-κB nuclear factor κB; NMIIA non-muscle myosin IIA; RAGE receptor for advanced glycation end products; TGF-β transforming growth factor β.

timately resulting in enhanced migration [126]. In the case of fibroblasts and immune cells, this enhanced migration allows subsequent infiltration into the affected regions, inducing the release of inflammatory factors and thereby contributing to the aggravation of pathological processes [127]. Additionally, intracellular S100A4 is also able to bind to p53. This interaction inhibits p53 phosphorylation and subsequent activation, thereby modulating transcription of cell cycle-regulating genes, and consequently stimulating apoptosis [124]. Importantly, intracellular interactions of S100A4 with the mentioned cytoskeleton target molecules as well as with p53 are Ca^{2+}-dependent, thus linking the cellular functions of these proteins with changes in intracellular Ca^{2+} concentrations and consequently with the energetic status of the cells [124].

4.2. S100A4 in disease

4.2.1. S100A4 and cancer

In the last years, the number of cancer cases has increased worldwide, making it the second leading cause of death behind cardiovascular disease [128]. Environmental factors such as increased pollution, together with unhealthy lifestyles including tobacco smoking, alcohol consumption, changing diet patterns and lack of exercise, as well as increased life expectancy associated with better medical services, have been considered responsible for this situation. There were 14.1 million new cancer cases and 8.2 million deaths attributable to cancer worldwide in 2012 [128]. Prevention and treatment measures to reduce cancer incidence have been introduced, but little progress is being made [129]. Consequently, most cancers continue to appear, grow, and metastasize due to the lack of effective management strategies [128].

S100A4, together with many other proteins, have been seen to be involved in the complex multi-step process of cancer metastasis at the molecular level [124,130]. It has been well established that S100A4, secreted from both tumour and non-malignant cells, plays a key role in the regulation of angiogenesis, cell migration and inflammation [131,132]. It was first shown to be associated with tumour metastasis in 1989 [133], and later, it was discovered that transfection of *S100A4* could intensify the tumorigenic potential and induce the metastatic phenotype *in vivo* [134].

It was not until the year 2000 that S100A4 overexpression was identified as a marker of poor prognosis and high metastatic poten-

tial. This was seen in a case of human breast cancer [135]. From this date, S100A4 levels have been found to be increased in many types of cancers and tumour microenvironments, including brain, breast, lung, gastric, liver, pancreatic, colorectal and prostate cancers amongst others, in addition to osteosarcoma, leukaemia and malignant melanoma, always associated to poor prognosis [136–139]. Thus, S100A4 is now a strong likely biomarker for cancer diagnosis and metastasis prediction.

Intracellular S100A4 expressed by cancer cells, as well as by fibroblasts and immune cells, interacts covalently with target molecules such as actin, non-muscle myosin IIA and tropomyosin [140], all of them associated with cell migration, metastasis and tumour cell spread [104,123]. Intracellulas S100A4 has also been seen to interact with p53, methionine aminopeptidase 2, and liprin-β1, although not all of them have been confirmed *in vivo* [141].

As an extracellular protein, S100A4 released from tumour and/or stromal cells can alter the tumour microenvironment by stimulating angiogenesis and attracting immune cells to the developing tumour lesions [142], as well as by inducing release of several cytokines and growth factors. Importantly, studies using breast adenocarcinoma and cervical carcinoma cell lines [143] have shown that extracellular S100A4 can signal through RAGE to induce nuclear translocation of intracellular S100A4, which when in the nucleus may function as a transcription factor for various genes including those encoding adherence junction proteins, and thereby regulating cell motility. Nuclear expression of S100A4 in tumour cells is therefore a substantial, independent indicator of poor prognosis. This also connects extracellular S100 proteins with intracellular responses [144].

S100A4 has been seen to induce and drive metastasis in many cancers, but experiments with transgenic mice have revealed that it is not a tumour-initiating oncogene, as well as having suggested that *S100A4* needs to couple with an oncogene in order to induce cancer [145]. The proposed mechanism by which S100A4 promotes metastasis in many cancer types is *via* epithelial-to-mesenchymal transition (EMT), a complex molecular process involving a change in cell morphology and function in which cells acquire fibroblastic phenotype and stem cell features [146]. Transforming growth factor β (TGF-β), a key triggering factor of the EMT process, induces upregulation of *S100A4* through the activation of the SMAD pathway, decreasing expression of epithelial cell markers and increasing expression of mesenchymal cell markers [147].

S100A4 was initially described to promote EMT through downregulation of the cell-adhesion molecule E-cadherin [148]. Since then, other mechanisms of S100A4-induced activation of EMT have been described in different types of cancer. In colorectal cancer, S100A4-induced EMT is mediated by TGF-β-induced activation of the phosphatidyl inositol 3 kinase (PI3K)/protein kinase B (PKB)/mammalian target of rapamycin (mTOR)/ribosomal protein S6 kinase beta 1 (p70S6K) signalling pathway [149]. In pancreatic cancer, it is mediated by the sonic hedgehog-gli1 (SHH-GLI1) signalling pathway [150]. In gallbladder cancer, overexpression of c-Myc and MMP14 induces loss of E-cadherin expression and subsequent increase in S100A4 expression [151]. In prostate cancer, NF-κB-dependent transcriptional activation of MMP9 induces S100A4-mediated cell invasion and malignant phenotypes [152]. In osteosarcoma, S100A4-induced tumour invasion and metastasis is also mediated through the dysregulation of MMPs and the expression of tissue inhibitors of metalloproteinases (TIMPs) [153], whereas in leukaemia, preferentially expressed antigen of melanoma (PRAME) suppresses heat shock protein HSP27 and S100A4 expression, inducing cell apoptosis and inhibiting cell proliferation and tumorigenicity [154].

4.2.2. S100A4 and non-cancer pathologies

Even though S100A4 is best known in a disease context for its participation in cancer progression and metastasis, an increase in *S100A4* expression has also been associated with several non-tumour pathophysiological processes including tissue fibrosis, inflammation, neuroprotection and cardiovascular events [155]. Numerous studies indicate that the S100A4-mediated EMT plays a crucial role in the appearance and development of both tumour and non-tumour pathophysiologies. The EMT process can be classified into three subtypes [156]: Type I EMT (non-pathological tissue development) takes place during regular organogenesis; type II EMT (pathological conditions) is related to wound healing, tissue regeneration, and organ fibrosis; finally, type III EMT is associated with neoplastic cells, which can migrate into surrounding tissues and infiltrate at metastasis sites [157–159].

S100A4 controls tissue fibrosis associated with type II EMT through several mechanisms. Epithelial cells that have undergone EMT express *S100A4,* inducing the production of extracellular matrix components and thereby initiating tissue fibrosis [160]. Moreover, TGF-β-induced *S100A4* expression induces secretion of fibronectin from fibroblasts, contributing to the establishment of a pro-inflammatory niche [161]. Given its specific expression patterns, S100A4 expression is regularly used to follow the development of tissue fibrosis [146]. Simultaneously, extracellular S100A4 secreted in response to inflammatory cytokines signals through RAGE, promoting the recruitment and chemotaxis of macrophages, neutrophils, and leukocytes *via* the activation of the MAPK and NF-κB pathways [108], thereby activating a positive feedback-regulated pro-inflammatory cycle through the upregulation of various pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, and thus regulating inflammation and immune functions [162]. S100A4 is also involved in angiogenesis, thus inducing its metastasis-promoting mechanisms *via* interaction with annexin 2 and stimulation of MMP production [105,163]. Interestingly, it has also been seen that silencing S100A4 inhibits retinal neovascularization in a mouse model of oxygen-induced ischaemic retinopathy, an inflammatory disease [164].

It has been described that certain members of the S100 protein family display obesity-facilitating properties. For instance, S100B promotes obesity by reducing insulin sensitivity [165], while overexpression of S100A16 can promote adipogenesis in 3T3-L1 preadipocytes [166]. S100A4 expression has also been described to have a role in the pathogenesis of a number of autoimmune diseases and other inflammatory conditions including rheumatoid arthritis, systemic sclerosis, psoriasis [31], diabetes retinopathy [167] and inflammatory myopathies [106]. Given that S100A4 white adipose tissue (WAT) expression has been reported to associate positively with expression of genes involved in inflammation and immune cell activation, as well as with those involved in ECM formation, organization and migration [168], S100A4 may also have obesity-facilitating properties, given that obesity has been described to be a state of low-grade chronic inflammation [169].

Adipokine secretion from WAT has been associated with WAT dysfunction and metabolic complications of obesity. The size of fat cells might constitute a determinant factor for metabolic disease linked to pathological WAT [170]. WAT can be made of a large number of small fat cells (hyperplasia) or a small number of large fat cells (hypertrophy). Hypertrophic WAT is closely related to insulin resistance (IR), risk of type 2 diabetes (T2D) and other metabolic abnormalities [171]. The correlation between S100A4 expression and fat cell size suggests that S100A4 could constitute an indicator of WAT hypertrophy, which could consequently explain its association with IR [168]. S100A4 could therefore be classified as a novel adipokine linked to a pathological adipose phenotype, including adipocyte hypertrophy and increased expression and secretion of proinflammatory factors [168].

The known association between S100A4 and cancer suggests that perhaps it has a role in linking obesity/IR with cancer. It is known that in cancer cells, WNT/β-catenin signalling increases *S100A4* gene transcription, leading to an increase in tumour progression and invasiveness [172]. Conversely, the inhibition of this pathway reduces S100A4 mRNA levels, and hence cell migration and invasion [173]. Other fac-

tors known to be involved in regulating S100A4 expression in different cancer cell types are C/EBPβ [174], c-Myb [175] and SHH [150].

While the mechanism of transcriptional regulation of S100A4 in different AT cells are yet to be fully elucidated, given the commonality between obesity/IR and WAT dysfunction to both T2D and certain types of cancer, it is tempting to speculate involvement of S100A4 in both. Indeed, the auto-inflammatory component of T2D is, in part, associated with the excessive AT proliferation that causes hypoxia in AT [176]. Rapid AT expansion causes a reduction in oxygen availability, exposing cells to hypoxia. This will result in activation of hypoxia inducible factor 1α (HIF-1α), a transcription factor that activates transcription of several apoptosis-related genes, as well as other factors including S100A4. Given that HIF-1α can also participate in the ROS response that results from hyperglycaemia in diabetes, this may therefore represent a unifying molecular mechanism in diabetes (Fig. 3).

4.3. S100A4 therapeutics

S100A4 has proven to be a valuable biomarker and therapeutic target for many types of cancer. As a biomarker, the identification of S100A4 levels in tumour tissues or in body fluids could predict prognosis and metastasis of cancer patients in the early stages, whereas as a target, the inhibition of *S100A4* expression can reduce metastasis *in vivo*. Several molecular targeting strategies for S100A4 have been developed [177]. The use of these new techniques has made it possible to discover, for instance, the exact atomic structure of the interaction between intracellular S100A4 and NMIIA [101]. However, there is a currently unmet clinical need to develop new therapeutic agents that function to modulate S100A4 expression and activity.

S100A4 expression is intimately associated with the proliferation, aggressive phenotype and metastatic behaviour of numerous types of human cancers, and as such is linked to poor outcome of cancer patients. Therefore, therapeutic strategies aimed at reducing *S100A4* expression or biological activity might help reduce metastatic cancer, improve prognosis and increase survival rates of patients with cancer, as well as to combat non-tumour pathophysiology processes such as tissue fibrosis, inflammation, immune reaction, neuroprotection and cardiovascular disease.

Strategies to decrease the S100A4-mediated metastatic action include inhibition of *S100A4* expression using miRNA-, siRNA- or shRNA-based knockdown of S100A4 with the use of neutralizing antibodies, or with the use of specific small molecule inhibitors. It was reported in 1996 that ribozyme-based knockdown of *S100A4* successfully reduced the S100A4-mediated osteosarcoma metastatic phenotype [178], and more recently that this effect is mediated by the repression of MM9 [179]. It has also recently been seen that shRNA-mediated *S100A4* knockdown reduces metastasis formation in colorectal cancer *in vivo* [180], while siRNA-mediated *S100A4* knockdown induces apoptosis and inhibits metastasis of anaplastic thyroid cancer cells *in vitro* [181]. Moreover, miR-3189-3p mimics have been seen to intensify the effects of *S100A4* siRNA on the inhibition of proliferation and migration of gastric cancer cells [182].

S100A4 neutralizing antibodies have been demonstrated to decrease tumour metastasis and T-cell recruitment in murine models of breast cancer [183] and pre-metastatic lungs [184], as well as to block the growth of pancreatic tumours in immunocompromised mice [185].

Transcription of *S100A4* is controlled by the β-catenin/TCF complex [172], therefore strategies that promote β-catenin degradation and/or block the establishment of the β-catenin/TCF complex such as the use of calcimycin, niclosamide or sulindac will be able to inhibit *S100A4* transcription [186–188]. In fact, it was reported that *in vitro* treatment of colorectal cancer cells with niclosamide reduces *S100A4* expression, subsequently inhibiting tumour cell migration, invasion, proliferation and colony formation [187].

5. Conclusions

Molecular characterisation of primary tumour lesions has been used to identify and evaluate the risk in the development of tumour metastasis and to predict prognosis and therapy responses in various types of cancer. As a result, several S100 members, mainly S100A4 and S100A8/9, have been identified as key players in the pathogenesis of many types of cancer, as well as of several other disease conditions in-

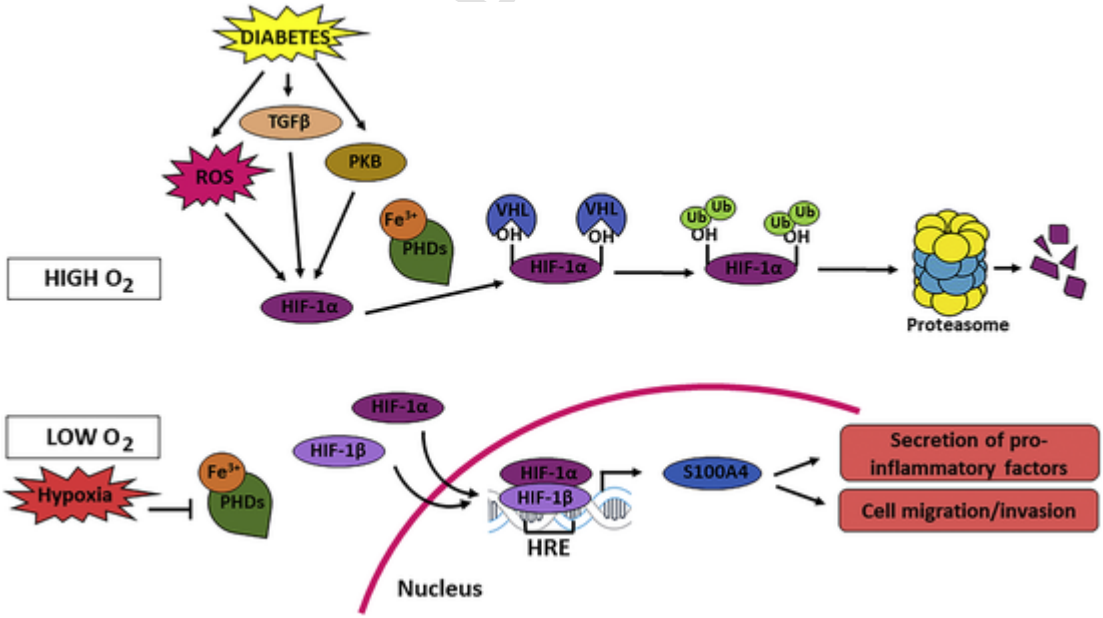

Fig. 3. Oxygen-dependent regulation of HIF-1α and induction of S100A4 transcription. In normoxic conditions, PHDs hydroxylate HIF-1α, priming it for poly-ubiquitination by VHL, which leads to its proteasomal degradation. In situations of hypoxia however, PHDs are inactivated, therefore HIF-1α is stabilized and translocates to the nucleus, where it binds to HIF-1β and other co-factors. Together, they bind to HRE in the promoter region of target genes including S100A4. Increased levels of S100A4 induce secretion of proinflammatory factors and cell migration and invasion. In addition to hypoxia, other factors found to be upregulated in diabetes such as TGF-β, PKB, and ROS, can also activate HIF-1α even in nonhypoxic conditions. Abbreviations: HIF-1α hypoxia inducible factor 1 alpha; HIF-1β hypoxia inducible factor 1 beta; HRE hypoxia responsive elements; PHDs prolyl hydroxylases; PKB protein kinase B; ROS reactive oxygen species; TGF-β transforming growth factor β; VHL von Hippel-Lindau ubiquitin-ligase.

cluding diabetes and other inflammatory diseases. Elucidating the mechanisms of action of S100 proteins in the pathophysiology of these diseases may therefore lead to the development and application of novel, more effective therapeutic approaches. Future research should therefore focus on the validation of the S100 proteins as biomarkers in early disease detection and prognosis, and in the development of novel strategies based around anti-S100 therapies.

Abbreviations

5-HT1B	5-hydroxytryptamine 1B serotonin receptor
AP1	Activator protein 1
AT	Adipose tissue
C/EBPβ	CCAAT enhancer binding protein beta
CCL	Chemokine ligands
CD36	Cluster of differentiation 36
DAMP	Damage associated molecular pattern
DSS	Dextran sulphate sodium
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
EMT	Epithelial-to-mesenchymal transition
FGFR	Fibroblast growth factor receptor
FSP-1	Fibroblast specific protein 1
GPCR	G-protein coupled receptor
HIF-1α	Hypoxia inducible factor 1 alpha
HSP	Heat shock protein
ICAM-1	Intracellular adhesion molecule 1
IFN-γ	Interferon gamma
IL	Interleukin
ILK	Integrin linked protein kinase
IR	Insulin resistance
JAK	Janus kinase
JNK	c-Jun N-terminal kinase
MAPK	Mitogen activated protein kinase
MIP-1α	Macrophage inflammatory protein 1 alpha
MMP	Matrix metalloproteinase
mTOR	Mammalian target of rapamycin
MTS-1	Metastasin 1
NF-κB	Nuclear factor kappa B
NMIIA	Non-muscle myosin 1A
OA	Osteoarthritis
p70S6K	Ribosomal protein S6 kinase beta 1
PHD	Prolyl hydroxylase
PI3K	Phosphatidyl inositol 3 phosphate
PKB	Protein kinase B
PRAME	Preferentially expressed antigen of melanoma
RA	Rheumatoid arthritis
RAGE	Receptor for advanced glycation end products
ROS	Reactive oxygen species
SHH-GLI1	Sonic hedgehog-gli 1
STAT	Signal transducer and activator of transcription
T2D	Type 2 diabetes
TG2	Transglutaminase 2
TGF-β	Transforming growth factor beta
TIMP	Tissue inhibitors of metalloproteinases
TLR	Toll-like receptor
TNF-α	Tumour necrosis factor alpha
VCAM-1	Vascular cell adhesion molecule 1
VEGF	Vascular endothelial growth factor
VHL	Von-Hippel-Lindau ubiquitin ligase
WAT	White adipose tissue

Author contributions

LLG: Data curation. Writing – original draft.
KG: Supervision. Writing – review and editing.
MDT: Conceptualization. Supervision. Writing – review and editing.

Uncited reference

[70]

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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