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REVIEW

S100 proteins as therapeutic targets

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Abstract

The human genome codes for 21 S100 protein family members, which exhibit cell- and tissue-specific expression patterns. Despite sharing a high degree of sequence and structural similarity, the S100 proteins bind a diverse range of protein targets and contribute to a broad array of intracellular and extracellular functions. Consequently, the S100 proteins regulate multiple cellular processes such as proliferation, migration and/or invasion, and differentiation, and play important roles in a variety of cancers, autoimmune diseases, and chronic inflammatory disorders. This review focuses on the development of S100 neutralizing antibodies and small molecule inhibitors and their potential therapeutic use in controlling disease progression and severity.

Keywords S100 protein · Calcium binding · Small molecule inhibitor · Neutralizing antibody

In humans, there are 21 S100 protein family members (Zimmer et al. 2012). The nomenclature for this family of small calcium-binding proteins derives from the observation that the two founding family members, S100A1 and S100B, are soluble in 100% saturated ammonium sulfate (Moore 1965). The majority of S100 genes cluster on the long arm of human chromosome 1 (*S100A1–S100A14*, *S100A7s*, *and S100A16*), with the remaining family members distributed on chromosomes 4 (*S100P*), 5 (*S100Z*), 21 (*S100B*), and the X chromosome (*S100G*) (Henry et al. 2012; Ravasi et al. 2004). Although the genomic loci encoding the S100 proteins are highly conserved in mammals, there are species differences (e.g., between humans and mice) that complicate the biological evaluation of several family members and their contribution to human disease. For example, the human *S100A7* locus encodes three proteins (S100A7, S100A7A, and S100A7L2), whereas the mouse locus encodes a single protein (S100A7A) (Zimmer et al. 2012). Additionally, S100A12 and S100P are not expressed in mice.

S100 family members share a high degree of sequence and structural similarity, and typically form homodimers, with the exception of the S100A8/S100A9 heterodimer (Donato et al. 2013; Zimmer et al. 2012). Each S100 subunit is composed of four α-helices and contains two EF-hands (helix-loop-helix motifs that are Ca^{2+}-binding domains): a C-terminal canonical EF-hand composed of 12 amino acids and an N-terminal S100 EF-hand composed of 14 amino acids that is unique to the S100 family (Kawasaki et al. 1998). The two EF-hands are connected by a loop or hinge region consisting of 12–14 amino acids, which exhibits the most sequence divergence within the family and is critical for interactions with target proteins (Marenholz et al. 2004). In the absence of a protein target, S100 proteins exhibit modest Ca^{2+}-binding affinities that are well below intracellular calcium concentrations. However, Ca^{2+}-binding affinities increase by 5–300-fold in the presence of peptide and protein targets (Malashkevich et al. 2008; Markowitz et al. 2005; Wright et al. 2009). This increase in affinity can be understood in terms of structural rearrangements, as Ca^{2+} binding induces a significant conformational reorganization that reorients helix 3 to expose a hydrophobic cleft required for target recognition (Fig. 1). Several studies suggest that in the absence of a protein target, Ca^{2+}-bound S100 proteins sample a number of conformational states with predominantly weak Ca^{2+}-binding affinities; target binding reduces dynamics throughout the protein and shifts the ensemble towards conformations with high Ca^{2+}-binding affinities (Liriano et al. 2012; Palfy et al. 2016). As a consequence of this coupling, target binding is typically Ca^{2+}-dependent. Despite the fact that Ca^{2+} binding induces a similar conformational reorganization in all S100 family members examined to date, structural studies of S100-target complexes have shown that S100 family members utilize distinct mechanisms for

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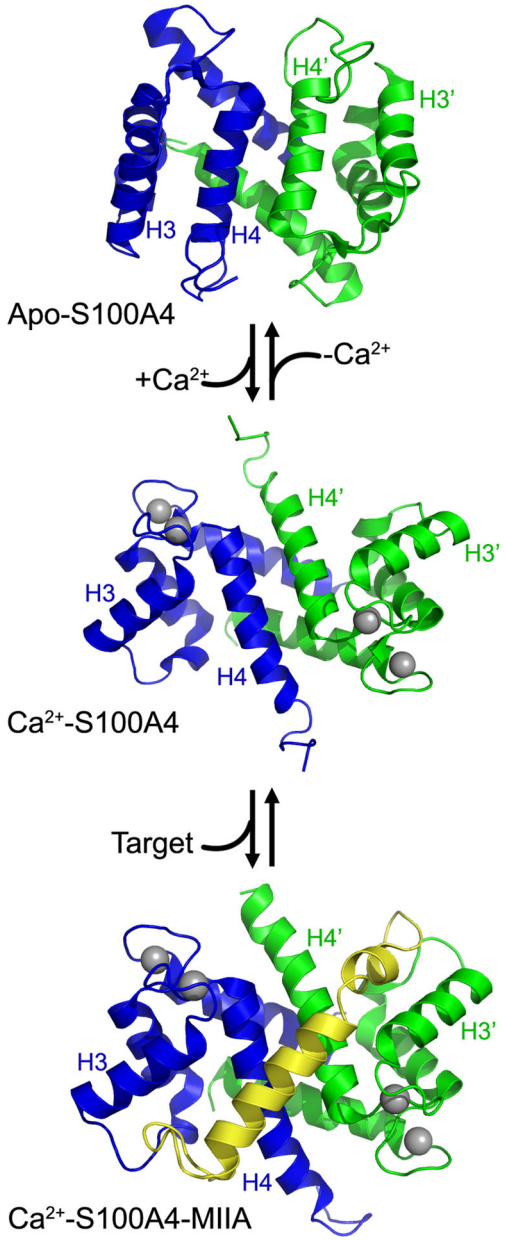

Fig. 1 S100 protein organization. Ribbon diagrams of apo-S100A4 (PDB 1M31), Ca^{2+}-S100A4 (PDB 2Q91), and the Ca^{2+}S100A4-myosin-IIA (MIIA) peptide complex (PDB 3ZHW). The individual S100A4 subunits are shown in blue and green, the Ca^{2+} ions are shown as gray spheres, and the myosin-IIA peptide is in yellow. Ca^{2+} binding induces a significant conformational reorganization that reorients helix 3 to expose a hydrophobic cleft that is required for target binding

target recognition (Bhattacharya et al. 2003; Dempsey et al. 2012; Kiss et al. 2012; Lee et al. 2008; Oh et al. 2013; Ozorowski et al. 2013; Rety et al. 2000; Rety et al. 1999; Rustandi et al. 2000; Wright et al. 2009). The distribution of hydrophobic and charged residues, as well as differences in surface geometries, all contribute to the range of target binding modes observed amongst S100 family members (Ozorowski et al. 2013; Ramagopal et al. 2013; Wafer et al. 2013). The growing number of S100-target structures has provided important insights into the chemical and physical determinants controlling target selectivity, which can be exploited for the development of selective S100 therapeutics. This review focuses on the development of S100 protein small molecule inhibitors, as well as more recent efforts on biologics that specifically target S100 proteins in the extracellular milieu.

Intracellular and extracellular functions

The diversity of the S100 proteins enables cells to selectively respond to changes in intracellular Ca^{2+} levels. The S100 proteins are expressed in a cell- and tissue-specific manner in vertebrates (Donato 2003) and have non-redundant roles in a wide range of biological processes such as proliferation, migration and/or invasion, and differentiation. S100 proteins regulate the activity of numerous intracellular protein targets, and some targets are regulated by multiple S100 family members (Donato et al. 2013; Hermann et al. 2012; Liu et al. 2015). The Ca^{2+}-dependent regulation of these interactions enables S100 proteins to function as calcium sensors that transduce changes in intracellular calcium concentrations into biochemical and biological responses. There are a number of well-characterized S100-target protein interactions, including S100B and p53 (Bresnick et al. 2015), S100A4 and nonmuscle myosin-IIA (Dulyaninova and Bresnick 2013), and S100A10 and annexin A2 (Liu et al. 2015). However, the complete repertoire of intracellular protein targets and corresponding cellular functions are not well described for the majority of S100 proteins.

S100s proteins lack signal sequences and are typically considered cytoplasmic proteins. Nonetheless, several family members are secreted via nonclassical pathways and/or are released by cells to function as extracellular factors (Donato et al. 2013; Marenholz et al. 2004; Ryckman et al. 2003; Yan et al. 2008). Extracellular S100 proteins have been reported to bind several cell surface receptors, including the advanced glycosylation end product-specific receptor (also known as RAGE) (Koch et al. 2010; Park et al. 2010; Penumutchu et al. 2014; Xie et al. 2007; Yatime et al. 2016), TLR4 (Ehrchen et al. 2009), CD36 (Tondera et al. 2017), FGFR1 (Riuzzi et al. 2011), CD166 antigen (also known as ALCAM) (von Bauer et al. 2013), the interleukin-10 receptor (Dmytriyeva et al. 2012), EMMPRIN (also known as cell surface glycoprotein extracellular matrix metalloproteinase inducer) (Hibino et al. 2013), neuroplastin-β (Sakaguchi et al. 2016), CD68 (Okada et al. 2016) and ErbB4 (Pankratova et al. 2018). Some S100 proteins, such as S100B and S100A12, are reported to bind multiple cell surface receptors (Koch et al. 2010; Riuzzi et al. 2011; Tondera et al. 2017; von Bauer et al. 2013; Xie et al. 2007). Despite the identification of potential cell surface receptors for several family members, for most

S100 proteins, the biochemical mechanisms mediating these S100-receptor interactions and the downstream consequences of S100 signaling are not known.

Specificity and regulation of S100-receptor interactions

Multiple S100 proteins bind TLR4 (Cerezo et al. 2014; Foell et al. 2013; Vogl et al. 2007) and RAGE (Leclerc et al. 2009). The ectodomain of RAGE is composed of three immunoglobulin domains (V, C1, and C2), and several S100 proteins have been reported to bind each domain, suggesting that these S100 proteins may have overlapping binding sites (Leclerc and Heizmann 2011). For example, S100B, S100A1, S100A2, S100A5, and S100A6 all bind the V domain (Leclerc et al. 2009; Ostendorp et al. 2007; Yatime et al. 2016). Given that multiple extracellular S100 proteins are typically associated with specific pathologies (e.g., elevated S100A8/S100A9, S100A4, and S100B in the serum of rheumatoid arthritis patients) (Austermann et al. 2018; Bresnick et al. 2015), this raises the question as to whether distinct S100 proteins can elicit differential signaling responses via interactions with the same cell surface receptors.

Recent studies with S100A8/S100A9 suggest that oligomerization can locally restrict S100 protein activity. Biochemical and cellular studies indicate that extracellular S100A8/S1009 elicits many of its effects via interactions with TLR4 (Cheng et al. 2008; Vogl et al. 2007) and RAGE (Bjork et al. 2009; Ghavami et al. 2008; Turovskaya et al. 2008). While the S100A8/S100A9 heterodimer can bind TLR4, the higher calcium ion concentrations found in the extracellular milieu (in the range of 2–3 mM (Brini et al. 2013; Goldstein 1990)) induces the formation of S100A8/S100A9 tetramers. This masks the TLR4 binding interface on the S100A8/S100A9 heterodimer, providing a mechanism for modulating S100 biological activity (Vogl et al. 2018). In contrast, S100A8 or S100A9 homodimers, which also bind TLR4, do not form tetramers (Vogl et al. 2006). Thus, this autoinhibitory mechanism allows for selective regulation of S100A8/S100A9 heterodimer activity. Oligomerization may also contribute to the regulation of other S100 protein-receptor interactions. For example, in the presence of calcium, S100B forms stable tetramers that bind RAGE with higher affinity than the S100B dimer (Ostendorp et al. 2007). Similarly, calcium and zinc induce the formation of S100A12 hexamers, which are required for RAGE and TLR4 binding (Kessel et al. 2018; Moroz et al. 2009). In addition, S100 oligomers are reported to bind different multimeric states of RAGE (e.g., S100A12 hexamers bind RAGE tetramers and S100B dimers bind RAGE dimers) (Xie et al. 2007; Xue et al. 2016). Together, these data suggest that S100 protein oligomerization is an important mechanism for regulating the functional diversity of this family of proteins.

In addition to oligomerization, covalent modification may also regulate the extracellular functions of S100 proteins. An intramolecular disulfide bond modulates the antimicrobial activity of S100A7 (Cunden et al. 2017) and transglutaminase 2-mediated crosslinking of S100A11 dimers is required for signaling via the p38 MAPK pathway in chondrocytes (Cecil and Terkeltaub 2008). Other types of post-translation modifications may also regulate oligomerization and/or activity. For example, citrullination promotes the formation of a S100A3 homotetramer (Kizawa et al. 2008), and a number of S100 proteins are *S*-nitrosylated, including S100B (Bajor et al. 2016), S100A1 (Lenarcic Zivkovic et al. 2012) and S100A8/A9 (Lim et al. 2011). Other types of oxidative modification such as *S*-glutathionylation, cysteinylation and the formation of intra- and intersulfinamide bonds have also been observed in S100 proteins (Lim et al. 2011; Orre et al. 2007). Additionally, sumoylation and phosphorylation of S100 proteins have been reported (Miranda et al. 2010; Sakaguchi et al. 2004; Schenten et al. 2018). Whether S100 proteins with post-translational modifications are released into the extracellular environment and how these modifications modulate S100 structure or function has largely not been determined.

S100 neutralizing antibodies

During both local and systemic inflammation, tissue and serum levels of several S100 proteins correlate with disease severity (Donato et al. 2013; Kessel et al. 2013; Nefla et al. 2016). In addition, extracellular S100 proteins can function as damage-associated molecular pattern (DAMP) proteins, thereby triggering proinflammatory responses via binding to pattern recognition receptors expressed on epithelial cells and innate and adaptive immune cells. This can induce autoimmune conditions and inflammatory disorders (Donato et al. 2013; Foell et al. 2007; Nefla et al. 2016; Xia et al. 2017; Zackular et al. 2015). Function-blocking antibodies targeting cell surface receptors and ligands are major classes of protein therapeutics for the treatment of cancers and immune disorders (Brufsky 2010; Mansh 2011; Saif 2013; Scott et al. 2012). Given the substantial literature showing that extracellular S100 proteins mediate inflammatory responses in cancer and autoimmune and chronic inflammatory diseases (Austermann et al. 2018; Bresnick et al. 2015; Grigorian et al. 2008), S100 neutralizing antibodies may provide a novel therapeutic strategy. To date, antibodies targeting S100A8/A9, S100A4, S100A7 (Padilla et al. 2017), and S100P (Dakhel et al. 2014) have demonstrated efficacy for a number of pathological conditions. Since antibodies targeting S100A8/A9 and S100A4 have been examined in the most detail, our

discussion will focus on studies examining the biological activity of these antibodies.

S100A8/A9

The S100A8/A9 heterodimers are the best characterized S100 family members with respect to extracellular functions. Extracellular S100A8/S100A9 is strongly associated with inflammatory and autoimmune diseases, including rheumatoid arthritis, spondyloarthritis, systemic sclerosis, and systemic lupus erythematosus (Austermann et al. 2018). Function-blocking S100A9 antibodies inhibit dextran sulfate sodium (DSS)-induced acute colitis and attenuate azoxymethane/DSS-induced colitis-associated cancer (Zhang et al. 2017b), reduce neutrophilic inflammation and airway reactivity in a murine asthma model (Lee et al. 2017), and diminish immune cell infiltration and preserve bone/collagen in a model of rheumatoid arthritis (Cesaro et al. 2012).

In solid cancers, elevated S100A8/A9 expression within the tumor microenvironment or in plasma correlates with aggressive disease (Cheng et al. 2008; Hauschild et al. 1999; Laouedj et al. 2017; Miller et al. 2017; Tidehag et al. 2014). In particular, extracellular S100A8/A9 plays an important role in the recruitment of myeloid cells and myeloid-derived suppressor cells (MDSCs), which promote tumor growth and the establishment of the pre-metastatic niche (Acharyya et al. 2012; Cheng et al. 2008; Hiratsuka et al. 2006; Ichikawa et al. 2011). Tumor-derived TGFβ and VEGFA upregulate the expression and secretion of S100A8/A9 in lung-associated myeloid and endothelial cells (Hiratsuka et al. 2006). S100A8/A9 induces the expression of serum amyloid 3, which in turn recruits $CD11b^{+}$ myeloid cells to pre-metastatic sites (Hiratsuka et al. 2008). This process produces a proinflammatory environment that recruits circulating tumor cells (CTCs) to the lung; S100A8 and S100A9 neutralizing antibodies block the recruitment of both myeloid cells and CTCs (Hiratsuka et al. 2006; Hiratsuka et al. 2008). In acute myeloid leukemia (AML), S100A8 antibodies, but not S100A9 antibodies, induce AML cell differentiation, reduce leukemic burden and increase survival (Laouedj et al. 2017). In addition, peptibodies, peptide-Fc fusion proteins that target S100A8 and S100A9, reduce tumor burden in multiple cancer models (Qin et al. 2014). Lastly, in murine models of breast cancer, S100A9 antibodies have been used in conjunction with single-photon emission computed tomography (SPECT) for the in vivo detection of S100A8/A9 as a marker for the establishment of the pre-metastatic niche (Becker et al. 2015; Eisenblaetter et al. 2017). Together, these studies highlight the potential use of S100A8 and S100A9 antibodies as both therapeutic and diagnostic reagents.

S100A4

S100A4 has a direct and causative role in tumor metastasis (Bresnick et al. 2015). In animal models of breast and other cancers, S100A4 overexpression in tumor cells promotes an aggressive metastatic phenotype, while inhibition of S100A4 expression significantly reduces metastatic burden (Ambartsumian et al. 1996; Davies et al. 1993; Davies et al. 1996; Grigorian et al. 1996; Maelandsmo et al. 1996; Takenaga et al. 1997; Xue et al. 2003). S100A4 is also expressed in normal cells and tissues, including fibroblasts, lymphocytes, macrophages, osteoclasts, and other bone marrow-derived cells (Bruhn et al. 2014; Erlandsson et al. 2013; Hashimoto et al. 2013; Li et al. 2010; Takenaga et al. 1994). Stromal S100A4, and in particular extracellular S100A4, is thought to promote tumor metastasis by stimulating an inflammatory, pro-tumorigenic environment (Bettum et al. 2014; Grum-Schwensen et al. 2005; Hansen et al. 2015; O'Connell et al., 2011). Consistent with a role in mediating inflammatory responses, extracellular S100A4 is associated with the pathogenesis of several autoimmune and chronic inflammatory diseases such as osteoarthritis (Amin and Islam 2014; Yammani et al. 2009), rheumatoid arthritis (Klingelhofer et al. 2007; Oslejskova et al. 2009), psoriasis (Zibert et al. 2010), Crohn's disease (Cunningham et al. 2010), bacterial colitis (Zhang et al. 2017a), and fibrosis (Chen et al. 2015). S100A4 blocking monoclonal antibodies have been shown to limit tumor metastasis and T cell recruitment in syngeneic mouse models of breast cancer (Grum-Schwensen et al. 2015; Klingelhofer et al. 2012), to inhibit the growth of pancreatic tumors in immunocompromised mice (Hernandez et al. 2013), to decrease azoxymethane/DSS-induced colon inflammation and tumorigenesis (Zhang et al. 2018), and to reduce epidermal thickness in a mouse model of human psoriasis (Zibert et al. 2010). While these studies support a role for extracellular S100A4 in promoting an inflammatory phenotype, the receptors responsible for S100A4-mediated inflammatory responses are not well characterized.

In vitro, biochemical studies support the interaction of S100A4 with RAGE and TLR4 (Bjork et al. 2013; Leclerc et al. 2009). While extracellular S100A4 is reported to stimulate downstream signaling events in a number of systems, the role of RAGE in mediating cellular responses to S100A4 is controversial (Grotterod et al. 2010). Most notably, a number of studies on extracellular S100A4 and associated downstream signaling events have reported that the bioactive form of S100A4 is an oligomer of a higher order than the canonical dimer (Cerezo et al. 2014; Forst et al. 2010; Novitskaya et al. 2000). However, these studies used a His-tagged S100A4, which forms large multimers (~200 kDa) (Novitskaya et al. 2000). It is well established that histidine tags can affect the oligomeric states and functions of proteins (Amor-Mahjoub

et al. 2006; Majorek et al. 2014; Sprules et al. 1998). Indeed, biophysical studies with untagged S100A4 in the presence of calcium have reported the formation of only S100A4 dimers and tetramers, but not higher order oligomers (House et al. 2011; Malashkevich et al. 2008; Streicher et al. 2010). The high molecular weight S100A4 species detected in the plasma of cancer patients or synovial fluid from osteoarthritis and rheumatoid arthritis patients may represent higher order S100A4 oligomers, but could also represent S100A4 dimers or tetramers bound to target proteins present in the extracellular milieu (Ambartsumian et al. 1996; Klingelhofer et al. 2007). These observations underscore the need to rigorously validate biochemical reagents and highlight the need to re-evaluate the biological functions of extracellular S100A4 using untagged S100A4.

Small molecule inhibition of S100 proteins

Given the roles of S100 proteins in proinflammatory processes in human disease, strategies for the pharmacological modulation of S100 protein function have received considerable attention. One approach is the inhibition of S100 gene transcription (Gao et al. 2018; Sack et al. 2011; Stein et al. 2011). Transcription of *S100A4* is directly mediated by the β-catenin/TCF complex (Stein et al. 2006), and compounds that induce β-catenin degradation and/or block the formation of the β-catenin/TCF complex (e.g., calcimycin—a calcium ionophore; niclosamide—an antihelminth drug; and sulindac—a nonsteroidal anti-inflammatory drug) inhibit *S100A4* transcription (Dahlmann et al. 2016; Sack et al. 2011; Stein et al. 2011). In addition, duloxetine, a serotonin-norepinephrine reuptake inhibitor, was identified recently as a S100B transcriptional inhibitor (Gao et al. 2018). However, the effectiveness of this general strategy may be limited by the long half-life of S100 proteins, as a study in NIH3T3 cells showed that several S100 proteins have half-lives on the order of 90–140 h (Schwanhausser et al. 2011). Such long half-lives can make it difficult to sufficiently reduce protein levels to achieve a therapeutic response. In addition, these transcriptional inhibitors are known to affect the expression of multiple gene targets, which could cause significant toxicities (Dahlmann et al. 2016). Despite these potential limitations, both S100A4 and S100B transcriptional regulators have exhibited efficacy in a number of cancer models (Dahlmann et al. 2016; Gao et al. 2018; Stewart et al. 2016). Moreover, niclosamide, an FDA-approved drug, is currently under evaluation for safety and efficacy in a phase II clinical trial for patients with metastatic colorectal cancer whose disease has progressed under previous therapy (Burock et al. 2018).

Most protein-protein interactions are typified by large interfaces composed of relatively "flat" featureless surfaces that are difficult to disrupt with small molecules. However, the target binding clefts of S100 proteins, which are exposed upon Ca^{2+} binding, can readily bind small molecules. As a consequence, there has been significant success in the identification of small molecules that block S100-target protein interactions. Several anti-allergy drugs such as cromolyn, amlexanox, tranilast, and olopatadine are reported to bind multiple S100 proteins (Fig. 2) (Mack and Marshall 2010; Okada et al. 2002; Rani et al. 2010; Shishibori et al. 1999). Cromolyn, which blocks the coimmunoprecipitation of S100P with RAGE, also attenuates the growth of pancreatic tumors and sensitizes tumors cells to gemcitabine, a chemotherapeutic agent (Arumugam et al. 2013; Kim et al. 2012). Amlexanox is a S100A13 antagonist that blocks interactions with fibroblast growth factor 1 (FGF1), and inhibits the release of the S100A13-FGF1 complex in vivo (Mouta Carreira et al. 1998). In addition, amlexanox sensitizes *MLL/AF4*-positive acute lymphoblastic leukemia to TNFα treatment via the downregulation of S100A6 expression through an unknown mechanism (Tamai et al. 2017). While these anti-allergic compounds exhibit promising effects on S100-mediated pathologies they are not selective S100 inhibitors. For example, amlexanox also inhibits IκB kinase ε and TANK-binding kinase 1, proteins that promote a proinflammatory response associated with the development of obesity (Beyett et al. 2018; Reilly et al. 2013). These observations suggest that the anti-inflammatory responses observed with amlexanox and other anti-allergics are likely due to the modulation of multiple cellular pathways.

Phenothiazines, a class of anti-psychotic compounds, also interact with multiple S100 family members (Garrett et al. 2008; Marshak et al. 1985; Pingerelli et al. 1990; Wilder et al. 2010) as well as other EF-hand-containing proteins such as troponin C and calmodulin (Fig. 2) (Cook et al. 1994; Feldkamp et al. 2015; Vandonselaar et al. 1994; Vertessy et al. 1998). Structural studies of the S100A4-trifluoperazine (TFP) complex demonstrate that two TFP molecules reside in the target binding cleft of each S100A4 subunit, and that TFP binding induces the assembly of Ca^{2+}-S100A4-TFP dimers into a five-fold symmetric pentameric ring (Malashkevich et al. 2010). Prochlorperazine (PCP) also induces the formation of a pentameric ring of Ca^{2+}-S100A4 dimers. Phenothiazine-mediated oligomerization may be unique to S100A4, as chlorpromazine does not induce the formation of higher order S100B oligomers (Wilder et al. 2010). Notably, the architectures of the TFP-binding pockets, the number of bound TFP molecules, and the orientation of the TFP molecules are quite different between S100A4, troponin C, and calmodulin (Cook et al. 1994; Feldkamp et al. 2015; Malashkevich et al. 2010; Vandonselaar et al. 1994; Vertessy et al. 1998). Given the differences in TFP-binding modes and the large number of phenothiazine derivatives that are

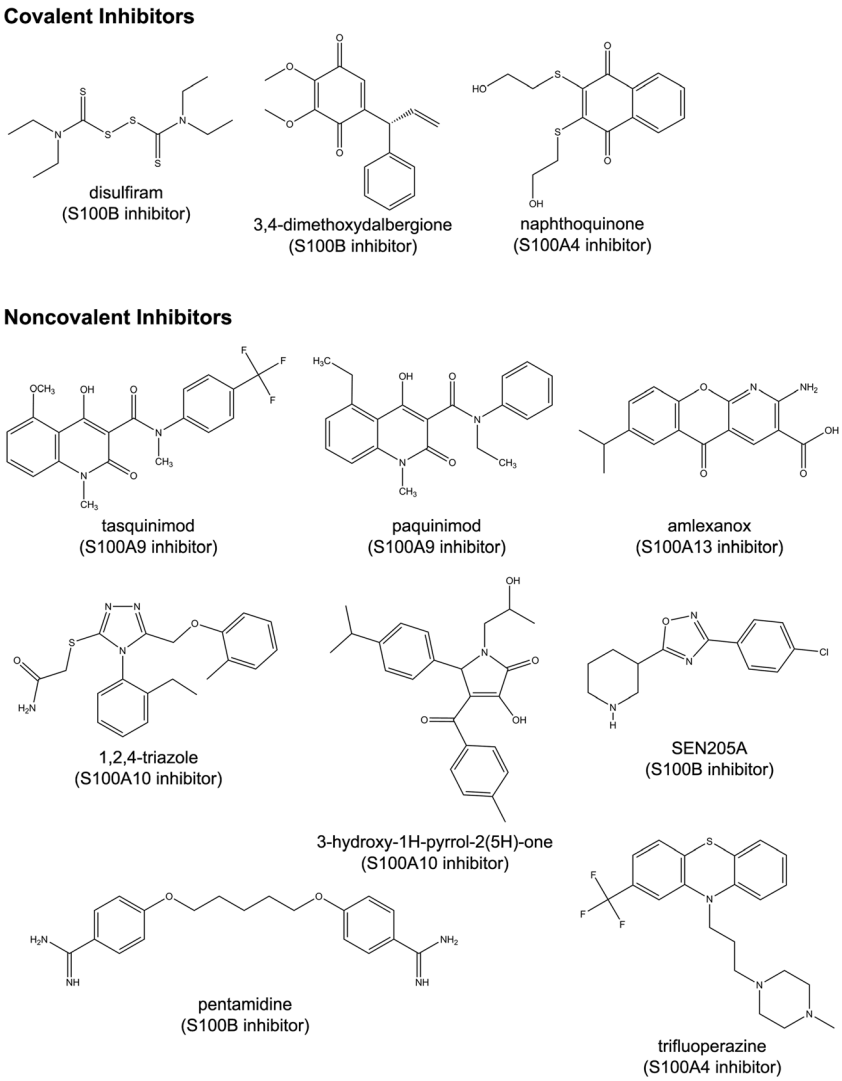

Fig. 2 Chemical structures of S100 inhibitors

available, it may be possible to selectively target these proteins with appropriate phenothiazine analogs (Brem et al. 2017; Montoya et al. 2018; Pluta et al. 2017).

Other examples of small molecule S100 inhibitors include covalent inhibitors that modify cysteine residues in helix 4 of S100B and S100A4. Despite the proximity of these cysteines to the C-terminal EF-hand, their modification does not affect Ca^{2+} binding, but does disrupt Zn^{2+}-mediated conformational rearrangements in S100B, and target binding to both S100A4 and S100B (Cavalier et al. 2014; Dulyaninova et al. 2011). While these compounds exhibit efficacy in disrupting S100-target interactions in vitro, selectivity is an issue. The covalent S100A4 and S100B inhibitor, 2,3-bis[2-hydroxyethylsulfanyl]-1,4-naphthoquinone, also inhibits the activities of multiple protein tyrosine phosphatases through the modification of an active site cysteine (Brisson et al. 2005; Vogt et al. 2008). Similarly, other covalent S100B inhibitors are reported to have a number of targets, including transglutaminase 2 (Palanski and Khosla 2018), alcohol dehydrogenase (Koppaka et al. 2012), and protein kinase C (Herbert et al. 1990). Nonetheless, these compounds represent new chemical scaffolds for the development of S100 inhibitors with improved affinity and specificity.

In addition to covalent S100 inhibitors, non-covalent inhibitors include paquinimod (ABR-215757) and tasquinimod (ABR-215050), quinoline-3-carboxamide derivatives that disrupt the interaction of S100A8/S100A9 with TLR4 and RAGE (Bjork et al. 2009; Kallberg et al. 2012); 4-aroyl-3-hydroxy-5-phenyl-1H-pyrrol-2(5H)-one analogs and substituted 1,2,4-triazoles that inhibit the interaction between S100A10 and annexin A2 (Reddy et al. 2012; Reddy et al. 2011); pentamidine, which blocks the interaction of S100B with p53 (Charpentier et al. 2008; Markowitz et al. 2004), and SEN205A and distamycin A, which target the S100B-p53 interaction site (Agamennone et al. 2010; Cerofolini et al. 2015) (Fig. 2). While these compounds have been evaluated for their ability to disrupt specific S100 protein-target

interactions, it is unknown if they can inhibit the binding of all ligands for a particular S100 protein.

Although current efforts are focused on improving the affinity, selectivity, and biological half-life of these S100 inhibitors, a number of these compounds have been evaluated in murine models of disease and some have advanced to human clinical trials. Paquinimod reduces inflammation and disease progression and/or severity in a number of inflammatory models (Fransen Pettersson et al. 2018; Tahvili et al. 2018; Wache et al. 2015). Tasquinimod inhibits tumor growth and metastasis in several models of prostate cancer, possibly by limiting the recruitment of MDSCs and tumor-associated macrophages to the tumor microenvironment (Raymond et al. 2014). However, tasquinimod has also been reported to be a potent negative allosteric regulator of HDAC4; inhibition of HDAC4-mediated deacetylation of HIF-1α and other factors compromises cancer cell survival and tumor angiogenesis (Isaacs et al. 2013). Regardless of whether tasquinimod acts through S100A9, HDAC4, or both, tasquinimod improves progression-free survival in patients with metastatic castration-resistant prostate cancer (Fizazi et al. 2017; Pili et al. 2011), but does not exhibit clinical efficacy in heavily pre-treated patients with advanced hepatocellular, ovarian, renal cell, and gastric cancers (Escudier et al. 2017). S100B is overexpressed in cultured melanoma cells and is a strong biomarker for melanoma (Gaynor et al. 1980; Hauschild et al. 1999). Pentamidine, an FDA-approved anti-parasitic that targets S100B and disrupts its interaction with p53 (Markowitz et al. 2004), exhibits efficacy against ex vivo melanoma samples (Smith et al. 2010). Pentamidine is under evaluation in patients with relapsed or refractory melanoma and in patients with solid tumors, including pancreatic, colon, and hepatocellular cancers (www.clinicaltrials.gov, NCT00810953, NCT00809796, NCT02210182).

Within the S100 family, S100B has been most thoroughly studied with respect to small molecule inhibitors. An examination of S100B-inhibitor complexes has revealed three discrete pockets that accommodate small molecules (Fig. 3) (Cavalier et al. 2014; Hartman et al. 2013). Site 1 is the target binding site (e.g., TRTK peptide or p53 C-terminal peptide) and involves interactions with residues from the hinge region and helices 3 and 4. SEN205A is an example of a site 1 inhibitor (Agamennone et al. 2010). Site 2 interactions involve residues from the hinge and helix 4, and site 3 interactions utilize residues from the C-terminal loop and helix 1. Examples of inhibitors that occupy these sites include compounds that covalently modify Cys84 of S100B (site 2) (Cavalier et al. 2014), and amlexanox and chlorpromazine, which bind site 3 in S100A13 and S100B, respectively (Rani et al. 2010; Wilder et al. 2010). For the S100B-pentamidine and S100A4-TFP complexes, in which two inhibitor molecules are bound per S100 subunit, both sites 2 and 3 are occupied (Charpentier et al. 2008; Malashkevich et al. 2010). Despite minimal overlap with the S100B target–

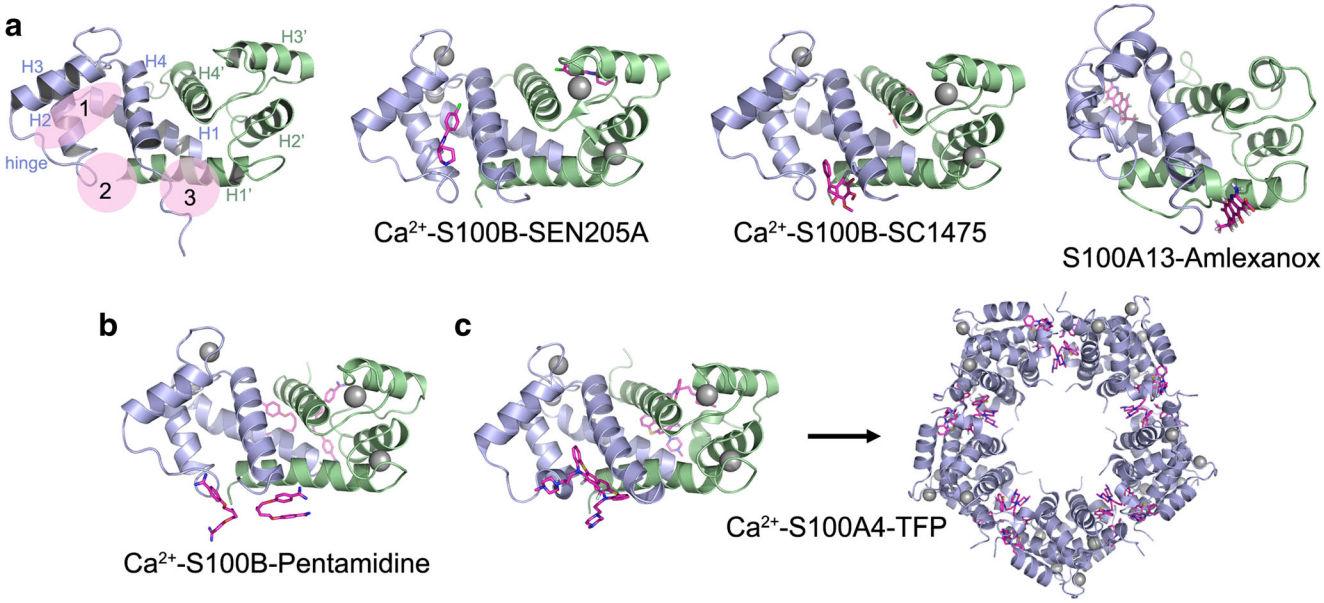

Fig. 3 S100 protein-inhibitor complexes. **a** Ribbon diagram of Ca^{2+}-S100B showing the general locations of the three binding sites that can accommodate small molecules and representative structures showing small molecules bound to each site. The individual S100 subunits are shown in light blue and green, the Ca^{2+} ions are shown as gray spheres and the inhibitors as pink sticks. Site 1: S100B-SEN205A (PDB 3HCM)—involves residues from the hinge and helices 2 and 3. Site 2: S100B-SC1475 (3,4-dimethoxydalbergione) (PDB 4PE4)—involves residues from the hinge and helix 4. Site 3: S100A13-amlexanox (PDB 2KOT)—involves residues from the C-terminal loop and helix 1. **b** Structures of Ca^{2+}–S100B-pentamidine (PDB 3CR4) and **c** Ca^{2+}–S100A4-trifluoperazine (TFP) (PDB 3KO0) showing two inhibitor molecules bound per S100 subunit and occupation of both sites 2 and 3. TFP binding induces the assembly of five Ca^{2+}–S100A4-TFP dimers into a pentameric ring

binding cleft, pentamidine disrupts p53 binding, suggesting that inhibition occurs via allosteric effects (Markowitz et al. 2004). Altogether, these data demonstrate that the binding of small molecules at different sites within a given S100 subunit allows for multiple mechanisms for inhibition, including small molecule–mediated S100 oligomerization (S100A4-TFP and S100A4-PCP), competitive inhibition with protein targets (S100A13-amlexanox; S100B-SEN205A) and allosteric regulation (S100B-pentamidine) (Charpentier et al. 2008; Malashkevich et al. 2010) (Agamennone et al. 2010; Rani et al. 2010). Moreover, the unique surface geometries and chemical features of each S100 family member should readily allow selective targeting of these proteins.

Conclusion

Significant advances have been made in understanding the intracellular and extracellular functions of S100 proteins and their roles in modulating proinflammatory and other responses that contribute to the development and progression of cancer and autoimmune and chronic inflammatory diseases. Despite this progress, a detailed understanding of the cell surface receptors that mediate extracellular S100 signaling is lacking. Furthermore, we do not fully understand the dynamics and regulation of S100 protein secretion, or the role of oligomerization and post-translational modifications in the regulation of intracellular/extracellular S100 activity. The continued development of antibodies and small molecule inhibitors will be important for attributing specific biological activities to particular S100 proteins and for defining the contribution of intracellular and extracellular S100 activities in biological processes. Furthermore, these reagents may have potential therapeutic applications for a number of cancers and immune disorders. S100 protein biology continues to provide a rich area of investigation and the evaluation of the cell biological and biochemical functions of these proteins will provide new insights into human disease.

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Compliance with ethical standards

Conflict of interest Anne R. Bresnick declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by the author.

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