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REVIEW ARTICLE

The SPARC protein: an overview of its role in lung cancer and pulmonary fibrosis and its potential role in chronic airways disease

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The SPARC (secreted protein acidic and rich in cysteine) protein is matricellular molecule regulating interactions between cells and their surrounding extracellular matrix (ECM). This protein thus governs fundamental cellular functions such as cell adhesion, proliferation and differentiation. SPARC also regulates the expression and activity of numerous growth factors and matrix metalloproteinases essential for ECM degradation and turnover. Studies in SPARC-null mice have revealed a critical role for SPARC in tissue development, injury and repair and in the regulation of the immune response. In the lung, SPARC drives pathological responses in non-small cell lung cancer and idiopathic pulmonary fibrosis by promoting microvascular remodelling and excessive deposition of ECM proteins. Remarkably, although chronic airway conditions such as asthma and chronic obstructive pulmonary disease (COPD) involve significant remodelling in both the airway and vascular compartments, the role of SPARC in these conditions has thus far been overlooked. In this review, we discuss the role of SPARC in lung cancer and pulmonary fibrosis, as well as potential mechanisms by which it may contribute to the disease process in asthma and COPD.

Abbreviations

COPD, chronic obstructive pulmonary disease; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; IPF, idiopathic pulmonary fibrosis; NSCLC, non-small cell lung cancer; PAI-1, plasminogen activator inhibitor-1; SPARC, secreted protein acidic and rich in cysteine

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These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b]Alexander *et al.*, 2015a,b).

Introduction

The SPARC (secreted protein acidic and rich in cysteine) family of proteins modulate interactions between cells and the extracellular environment. They regulate extracellular matrix (ECM) assembly and deposition and growth factor signalling. SPARC family proteins have in common three domains: an acidic N-terminal domain, a cysteine-rich follistatin-like (FS) domain and an α-helical extracellular (EC) calcium-binding domain with an EF-hand motif. They are classified into four groups based on sequence homology of the EC domain (Table 1). The FS and EC domains are conserved, conferring activities common to the SPARC family, while the N-terminal domain varies between the family members (Yan and Sage, 1999; Brekken and Sage, 2001; Bradshaw, 2012). Given these structural and functional similarities, there may be a level of redundancy with respect to their physiological actions, but this is not yet clearly established.

One of the best studied members of this protein family is SPARC. SPARC is a highly conserved matricellular protein and, although it is most often encountered as a secreted glycoprotein, it is also expressed on the cell surface and within the intracellular compartment. Interestingly, while extracellular SPARC functions as a matricellular protein, intracellular and membrane-associated SPARC regulate cellular apoptotic pathways (Tang and Tai, 2007; Fenouille *et al.*, 2010) (Table 2). SPARC expression is elevated during embryonic development and is diminished in normal adult tissues. Significantly, however, its expression is increased in epithelial cells exhibiting a high turnover rate such as those in the gut, skin and glandular tissue, during tissue injury and inflammation, and under conditions of abnormal tissue growth associated with neoplasia, suggesting its importance in tissue regeneration and repair (Yan and Sage, 1999; Brekken and Sage, 2001; Chiodoni *et al.*, 2010).

SPARC-null mice have yielded significant insight into its biological functions. These mice exhibit several aberrant features, related mainly to dysregulation of ECM structure and composition. For instance, they have less and smaller fibrillar collagen within connective tissues of the heart, in adipose tissue and in the skin (Bradshaw *et al.*, 2003a,b; Bradshaw *et al.*, 2009; Bradshaw *et al.*, 2010). SPARC-null mice also exhibit early onset cataracts due to altered morphology of collagen IV (the major structural protein of the lens basement membrane) and compromised structural integrity of the lens capsule (Gilmour *et al.*, 1998; Yan *et al.*, 2002). Other aberrant manifestations include osteopenia, accelerated wound healing and greater deposition of subcutaneous fat (Delany *et al.*, 2000; Bradshaw and Sage, 2001; Bradshaw *et al.*, 2003a). Notably, the reported biological effects of SPARC at the tissue and cellular level are quite variable, but given it acts as a 'communicator' at the cell-ECM interface, this is thought to be due to differences in the cellular and tissue microenvironment. Hence, this calls for the need to scrutinize the role of SPARC in a tissue- and cell-specific manner and in specific pathophysiological contexts.

Importantly, there is now a large body of evidence implicating SPARC in several chronic diseases including cancer,

Table 1

Classification of SPARC family proteins

Group	SPARC family proteins
1	SPARC (osteonectin, BM-40) Hevin (SPARC-like 1)
2	Secreted modular calcium binding protein (SMOC) 1 and 2
3	Testican 1, 2 and 3 (SPOCK, SPARC/osteonectin, CWCV and Kazal-like domains proteoglycans)
4	Follistatin-like protein 1 (FSTL1, TSC-36/Flik, follistatin-related protein, TGF-β inducible protein)

Table 2

Role of SPARC in different cellular compartments

Extracellular SPARC	References
Cell adhesion, proliferation, migration. Mediates interactions between cells and their surrounding ECM	(Sage *et al.,* 1989a,b; Everitt and Sage, 1992)
Regulates angiogenic activity	(Lane *et al.,* 1994; Kupprion *et al.,* 1998; Sage *et al.,* 2003; Zhang *et al.,* 2012; Gorantla *et al.,* 2013)
Binds to ECM proteins such as collagen I and IV	(Mayer *et al.,* 1991)
Regulates expression and activity of MMPs involved in ECM proteolysis and turnover	(Tremble *et al.,* 1993)
Regulates ECM-associated growth factors and signalling, for example VEGF, basic FGF and TGF-β	(Kupprion *et al.,* 1998; Motamed *et al.,* 2003; Schiemann *et al.,* 2003; Francki *et al.,* 2004; Nozaki *et al.,* 2006; Chandrasekaran *et al.,* 2007)
Membrane SPARC	
Augments apoptotic signalling via interaction with pro-caspase 8	(Tang and Tai, 2007)
Intracellular SPARC	
Enhances cell viability and renders resistance against apoptosis via activation of Fyn/ERK kinase signalling	(Fenouille *et al.,* 2010)

fibrosis, glaucoma and diabetes. In the lung, SPARC is heavily implicated in both cancer development and pulmonary fibrosis. Surprisingly, however, little is known about its role in other lung diseases featuring inflammation and tissue remodelling, most notably asthma and chronic obstructive pulmonary disease (COPD). The ECM micro-environment is essential for maintaining lung homeostasis, and perturbation of the ECM usually causes or accompanies chronic lung diseases. Because SPARC dictates crosstalk between cells and the ECM, a comprehensive understanding of its role in the lung and its contribution to pathological inflammation and remodelling are crucial. This review consolidates current understanding of the role of SPARC in lung cancer and idiopathic pulmonary fibrosis (IPF), highlights areas for future research in chronic airway diseases such as asthma and COPD and discusses potential strategies for exploiting and targeting SPARC for therapeutic purposes.

SPARC and lung cancer

SPARC expression in NSCLC tissues is associated with disease prognosis

Lung cancer is the leading cause of cancer deaths worldwide, and the 5 year survival rate remains poor at 16% (Dela Cruz *et al.,* 2011; Ferlay *et al.,* 2013). Lung cancer can be classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), depending on the type of cells affected. NSCLC is more common, accounting for approximately 85% of all lung cancer cases (Dela Cruz *et al.,* 2011). Although extensive evidence implicates SPARC in NSCLC, there have been no studies that have examined its role in SCLC.

SPARC is expressed heterogeneously in NSCLC tissues. It is predominantly found in the tumour-associated stroma, specifically in the cytoplasm and ECM of stromal fibroblasts. Within the tumour itself, SPARC expression is rare, but when present, it is localized to sites of necrosis (Koukourakis *et al.,* 2003; Siddiq *et al.,* 2004; Huang *et al.,* 2012). The tumour-associated stroma, comprising fibroblasts, immune cells, vasculature and ECM, is crucial for supporting and facilitating the tumour. Indeed, the interaction of the tumour with its surrounding stroma is essential for tumour growth, differentiation, progression and metastasis and thus determines the aggressiveness of the cancer (Tlsty and Coussens, 2006). The predominant stromal versus tumoral expression of SPARC in NSCLC suggests SPARC is important in supporting the survival and progression of lung tumours, most likely by assisting crosstalk at the tumour–stroma interface.

Interestingly, the localization of SPARC in NSCLC tissues is linked to disease prognosis. High levels of SPARC gene expression within NSCLC tumours, albeit rare, are associated with longer survival, while its absence is a negative prognostic factor (Schneider *et al.,* 2004; Huang *et al.,* 2012). On the other hand, patients bearing SPARC-positive stroma have significantly poorer overall post-operative survival. Indeed, the expression of SPARC within the stroma is often associated with extensive tumour necrosis, acidity, hypoxia and oxidative stress, all of which are key features of an aggressive tumour (Koukourakis *et al.,* 2003). These findings support the idea that stromal SPARC supports tumour growth and tumour–stroma interactions, contributing to a more aggressive malignancy. When expressed within the tumour, SPARC could be protective and possibly buffer the aggressiveness of the tumour itself, highlighting the tissue-specific functions of SPARC.

The expression of SPARC within NSCLC tumours appears to be heavily influenced by epigenetic factors. Shao and colleagues showed that treatment of patient-derived tumour xenografts with the demethylating agent, 5-aza-2′-deoxycytidine (decitabine), leads to increased SPARC expression, suggesting that low or absent expression of

SPARC in these tumour xenografts is due to methylation of its gene promoter region (Shao *et al.,* 2011). Interestingly, SPARC has been identified as a downstream target of the tumour suppressor gene ras-association domain family 1 isoform A (RASSF1A), which is also known to be hypermethylated at its promoter region and down-regulated in lung cancer. Notably, in tumours where RASSF1A is 'switched-off', SPARC mRNA expression is also decreased (Ito *et al.,* 2005). Thus, epigenetic factors that enhance DNA methylation status ultimately affect SPARC expression in the tumour. Given that tumor, rather than stromal, localization of SPARC within NSCLC tissues is associated with disease prognosis, further studies are needed to establish the factors that regulate differential SPARC expression in NSCLC, and whether SPARC serves different functions in the tumour and in the stroma.

SPARC promotes metastasis in NSCLC by promoting cell invasion and development of the tumoral vasculature network

Metastasis is thought to occur during the early phase of NSCLC. It is the key factor driving the aggressiveness of NSCLC and the primary cause of mortality. The recurrence rate of NSCLC following surgery is remarkably high at 40%, suggesting the presence of underlying micro-metastases which are not readily detected at the time of surgery (Varlotto *et al.*, 2009). Metastasis is a multi-step process, involving the initial local invasion of tumour cells into the stroma, followed by dissemination of tumour cells into the vasculature and then colonization at distant organs (Quail and Joyce, 2013).

SPARC has been identified as a key mediator of cell invasion in NSCLC and thus may play an important role in NSCLC metastasis. Indeed, it has been shown that Snail, a zinc finger transcription factor that is up-regulated in NSCLC tissues, promotes cell invasion in A549 lung epithelial cells in a SPARC-dependent manner (Yanagawa *et al.,* 2009; Grant *et al.,* 2014). It is proposed that Snail enhances cell invasion by up-regulating TGF-β1 and SPARC expression via the activation of MAP kinase, MEK/ERK signalling pathways (Grant *et al.,* 2014). Consistent with this finding, cell invasion is inhibited when SPARC expression is suppressed by the zinc finger transcription factor Kruppel-like factor 4 (KLF4). This is corroborated by evidence showing that KLF4-transfected A549 cells recover their invasive ability when SPARC expression is restored (Zhou *et al.,* 2010).

Further to its role in cell invasion, SPARC is also implicated in the development of the tumor vascular network. The vasculature is essential for tumour growth and metastasis it provides oxygen and nutrients essential for tumour survival and facilitates the migration of detached tumour cells to distant organs (Quail and Joyce, 2013). Interestingly, within the tumour site, SPARC is highly expressed in small immature, but not large, blood vessels, suggesting it is important in blood vessel maturation and, perhaps, that it is no longer required once the vasculature develops. Notably, and consistent with evidence that localization of SPARC to the stroma is associated with poorer prognosis, stromal SPARC expression is associated with a higher density of mature intra-tumor vessels. Interestingly however, it is not associated with overall vascular density or the expression of angiogenic factors such as VEGF and basic FGF, suggesting SPARC has a minimal role in the formation of new vessels (Koukourakis *et al.,* 2003). Thus, SPARC appears to primarily enhance tumour growth and progression by promoting vessel maturation under unfavourable hypoxic and acidic conditions within the tumour micro-environment.

SPARC and pulmonary fibrosis

SPARC confers resistance to apoptosis in lung fibroblasts and is a downstream effector of TGF-β-induced fibrosis in IPF

Pulmonary fibrosis is the end stage of parenchymal lung diseases that result in respiratory insufficiency. The most common form of pulmonary fibrosis, IPF, typically presents with alternating regions of normal lung parenchyma, interstitial inflammation, fibrosis and honeycombing (distorted architecture) and is characterized by excessive deposition of ECM protein and irreversible destruction of lung architecture (Wuyts *et al.,* 2013). Notably, SPARC is expressed in lung tissue obtained from IPF patients but is absent in healthy subjects. In IPF lung tissue, SPARC is mainly localized to the cytoplasm of migrating and synthetically active fibroblasts within fibroblastic foci, suggesting SPARC is involved in the initial phase of fibrosis (Kuhn and Mason, 1995). Consistent with this finding, lung fibroblasts isolated from IPF patients constitutively express more SPARC than those derived from subjects without IPF (Chang *et al.,* 2010). Together, these findings provide strong support for the involvement of SPARC in IPF pathogenesis.

Resistance to apoptosis in lung fibroblasts is a fundamental feature of IPF. In this disease, repeated injury of alveolar type II (ATII) epithelial cells leads to sustained recruitment of repair mediators. In addition, resident fibroblasts proliferate and differentiate into myofibroblasts which deposit ECM proteins. Critically, these myofibroblasts are resistant to apoptosis and thus sustain a non-degradative ECM, leading to the development of fibrotic scars and loss of alveolar function (Wuyts *et al.,* 2013; Xu *et al.,* 2016). Particularly, SPARC expression in IPF lung fibroblasts leads to downstream activation of β-catenin and increased expression of plasminogen activator inhibitor-1 (PAI-1), which confers resistance to plasminogen-induced apoptosis. Thus, overexpression of SPARC in IPF potentially drives tissue fibrosis via the induction of PAI-1 expression, leading to a pool of myofibroblasts that are resistant to apoptosis and, consequently, a dysregulated ECM milieu (Chang *et al.,* 2010).

Moreover, TGF-β induces SPARC expression in human lung fibroblasts (Shibata and Ishiyama, 2013). TGF-β is a key pro-fibrotic mediator secreted by ATII epithelial cells, macrophages and myofibroblasts following injury. It promotes lung fibrosis in IPF by mediating the recruitment of fibroblasts and their differentiation into myofibroblasts, by stimulating the production of ECM proteins such as collagen and fibronectin, and suppressing the activity of MMPs, plasminogen activators and elastases involved in ECM turnover (Bocchino *et al.,* 2010; Chang *et al.,* 2010; Ferlay *et al.*, 2013; Wuyts

et al., 2013). This suggests SPARC could be a downstream effector of TGF-β-induced fibrotic responses. Of note, TGF-β and SPARC are both capable of inducing PAI-1 expression, but whether TGF-β induces PAI-1 in a SPARC-dependent manner is yet to be determined (Chang *et al.,* 2010; Ueno *et al.,* 2011). In addition, TGF-β also plays a key role in driving the production of ROS and consequently oxidant-induced epithelial injury in IPF (Camelo *et al.,* 2014). Lung fibroblasts derived from IPF patients have an intrinsic capacity to generate greater levels of ROS, compared with those from healthy subjects, and SPARC mediates TGF-β-induced hydrogen peroxide production in these cells (Shibata and Ishiyama, 2013). Thus, future studies should examine whether TGF-β/SPARC signalling is an important axis that underlies pro-fibrotic and pro-oxidant responses in IPF pathogenesis.

Mouse models of bleomycin-induced IPF reveal a distinct role for SPARC in inflammatory versus fibrotic components of the disease

Consistent with data from human studies, bleomycin-induced pulmonary fibrosis in mice is associated with higher levels of SPARC expression in the lung and, as observed in human IPF tissues, SPARC is predominantly expressed in the cytoplasm of fibroblasts localized to areas of lung injury. As might be expected, SPARC-null mice develop less fibrosis and express lower levels of collagen following bleomycin exposure (Strandjord *et al.,* 1999; Sangaletti *et al.,* 2011). Interestingly, however, Savani and colleagues reported increased collagen deposition and fibrosis and increased destruction of the alveolar architecture in bleomycin-treated SPARC null mice (Savani *et al.,* 2000). The reason for the difference in findings is not immediately clear, although Savani and Strandjord employed the same strain of SPARC-null mice, excluding this as a factor.

In addition to examining the role of SPARC in the fibrotic response, Sangaletti also examined its role in the underlying interstitial inflammation. Intriguingly, they found that while SPARC-null mice were protected against bleomycin-induced fibrosis, they had more intense inflammation, indicating that SPARC acts to depress the inflammatory response. Moreover, using chimeric mice, they showed that fibroblast-derived SPARC induces fibrosis by promoting the assembly of mature, functional collagen fibers, while leukocyte-derived SPARC attenuates fibrosis by reducing the extent of underlying inflammation (Sangaletti *et al.,* 2011). Interestingly, in the study mentioned above, Savani reported increased fibrosis together with increased inflammation. While this is inconsistent with the findings of Sangeletti, it is possible that the extensive fibrosis observed in this study may have been driven by the inflammatory response, although this was not examined (Savani *et al.,* 2000). Nevertheless, the net effect of SPARC in pulmonary fibrosis is likely to be due to its temporal expression by distinct cell types at distinct disease stages. Indeed, it is possible that fibroblast-derived SPARC mediates the onset of the fibrotic process following lung injury while leukocyte-derived SPARC acts at later stages to resolve inflammation. Therefore, the cell-specific and temporal actions of SPARC and how they differentially affect the disease process certainly require further investigation.

SPARC and chronic airways disease

SPARC activity overlaps with TGF-β, a key mediator in asthma and COPD

Asthma and COPD are heterogeneous inflammatory disorders of the respiratory tract characterized by airflow limitation, which is typically variable and reversible in asthma, but progressive and irreversible in COPD. Chronic airway inflammation is a hallmark of both conditions and is thought to drive the structural abnormalities of the airways, collectively termed airway remodelling. There are overlapping features in asthma and COPD, but the pattern of inflammation and remodelling is distinct in each condition. Importantly, however, TGF-β is a well-established mediator of asthma and COPD and is regarded as the 'master switch' that orchestrates remodelling processes in both conditions, albeit via distinct mechanisms (Postma *et al.,* 2014).

While the expression and function of SPARC in asthma and COPD have not been studied to date, TGF-β induces SPARC expression in many cell types, and it is well established that SPARC is a downstream effector of TGF-β signalling (Sarkozi *et al.,* 2011; Shibata and Ishiyama, 2013; Grant *et al.,* 2014). Moreover, SPARC has also been shown to regulate TGF-β expression and activity, indicating the presence of a reciprocal regulatory relationship. SPARC induces phosphorylation of Smad2, a principal mediator of TGF-β signalling in lung epithelial cells (Schiemann *et al.,* 2003). Furthermore, the combined stimulation of mesangial cells with SPARC and TGF-β induces a synergistic increase in Smad2 phosphorylation. Consistent with this, mesangial cells isolated from SPARC-null mice exhibit reduced levels of phosphorylated Smad2, which can be restored with the addition of exogenous SPARC (Francki *et al.,* 2004). Interestingly, TGF-β neutralizing antibodies inhibit SPARC-induced Smad2/3 nuclear translocation in lung epithelial cells, indicating that regulatory effects of SPARC on Smad signalling may be due to its ability to induce TGF-β expression (Schiemann *et al.,* 2003). Furthermore, there is evidence to suggest that SPARC regulates TGF-β/Smad signalling by directly interacting with TGF-β receptors. Specifically, it has been shown that the SPARC binds to the TGF-β-receptor type II (TGFBR2) in a TGF-β1-dependent manner (Francki *et al.,* 2004). It is possible that SPARC binds to a structural conformation that encompasses TGF-β1 and TGFBR2 or that SPARC interacts with TGFBR2 following a conformational change induced by TGF-β1.

Potential role of SPARC in airway wall remodelling

In view of the considerable overlap between TGF-β and SPARC with respect to their biological activity, and evidence of their reciprocal regulation and direct interaction, the investigation of SPARC biology in airway wall remodelling in asthma and COPD is an important area of future research. Indeed, SPARC may contribute to changes in airway structure and function via a number of possible mechanisms. In the sections below, we will discuss the potential role of SPARC with regard to three key aspects: changes in the ECM milieu, angiogenesis and epithelial-mesenchymal transition (EMT). Figure 1 summarizes potential mechanisms by which SPARC

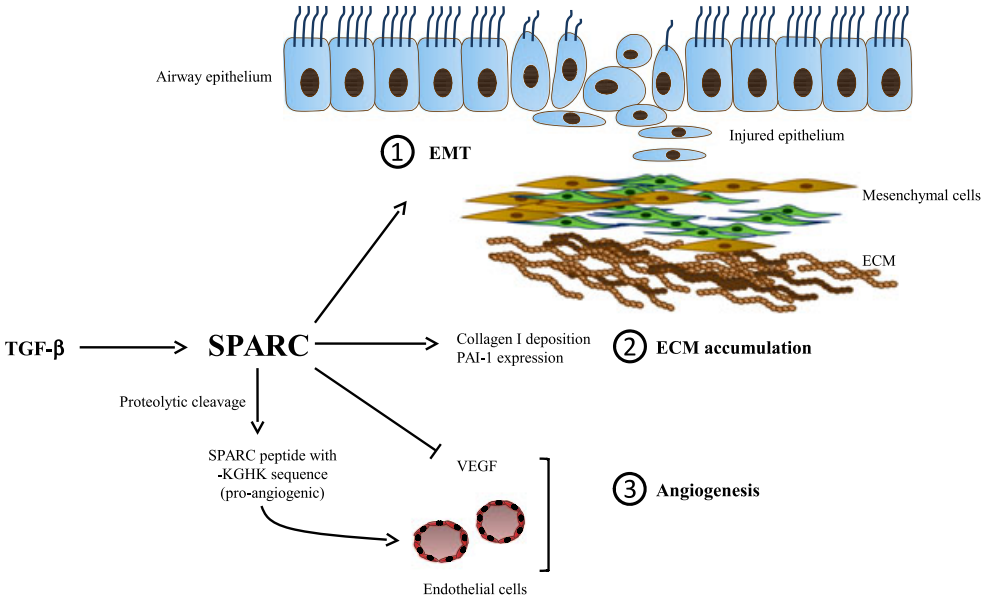

Figure 1

Proposed role of SPARC in airway and vascular remodelling in asthma and COPD: TGF-β induces SPARC mRNA and protein expression in various cell types, including lung cells. We propose that many of the pro-remodelling effects of TGF-β in asthma and COPD are mediated by SPARC. Acting downstream of the transcription factor Snail, SPARC may potentially drive TGF-β-induced EMT (A). Increased deposition of a non-degradative ECM within the airway wall may also be attributed to SPARC's ability to enhance collagen deposition and augment PAI-1 expression (B). SPARC inhibits the expression and secretion of the pro-angiogenic factor VEGF. However, cleavage of SPARC may potentially lead to the generation of SPARC peptide fragments with –KGHK sequence, which may confer pro-angiogenic activity. The balance of these processes may be an important determinant of angiogenic activity in airways disease (C).

might regulate airway and vascular remodelling in chronic disease of the airways.

As mentioned above, SPARC is an important regulator of the dynamic ECM milieu and has a role in maintaining the structural and functional integrity of the ECM. Altered deposition of ECM proteins is a key feature of airway wall remodelling in asthma and COPD, thus it is likely that any change in the expression and/or activity of SPARC will affect ECM changes in these conditions. In asthma, there is increased deposition of collagen I, III, V, fibronectin, tenascin, hyaluronan, versican, laminin α2/β2, lumican and biglycan while the deposition of collagen IV, decorin and elastin appears to be decreased (Bousquet *et al.*, 1992; Laitinen *et al.*, 1997; Huang *et al.*, 1999; Pini *et al.*, 2007). Similarly in COPD, there is evidence of increased deposition of collagen I, III and IV, fibronectin and laminin (Kranenburg *et al.*, 2006). As discussed above, there is altered deposition of collagen I and IV, as well as laminin, in SPARC-null mice, and it is well established that SPARC binds to collagen and is essential for the assembly and deposition of mature collagen fibres in the ECM (Bradshaw *et al.*, 2003b; Weaver *et al.*, 2006). Thus, the extent to which alterations in SPARC expression or activity influence collagen deposition in chronic airways disease is of particular interest for future research. Moreover, SPARC may regulate ECM synthesis via its interplay with the TGF-β/Smad 2/3 pathway which is known to regulate the synthesis of several ECM proteins including collagen, versican and biglycan (Postma and Timens, 2006). As mentioned, the ability of SPARC to induce PAI-1 expression could also be a downstream effect of TGF-β, resulting in the existence of apoptotic-resistant myofibroblasts that sustain a non-degradative ECM (Wuyts *et al.*, 2013). SPARC may also alter ECM synthesis and degradation via its ability to regulate the production and activity of numerous MMPs (Tremble *et al.*, 1993).

Angiogenesis and microvascular remodelling contribute to dysregulation of the vascular network and airway remodelling in asthma and COPD. This is manifested as either an increase in the number (angiogenesis) and size of blood vessels (vasodilatation) and enhanced vascular permeability (Calabrese *et al.*, 2006; Zanini *et al.*, 2009; Harkness *et al.*, 2014). SPARC appears to primarily act as an angiosuppressive molecule as it inhibits the expression and secretion of the key pro-angiogenic mediator VEGF and also acts to inhibit VEGF-induced growth of endothelial cells (Kupprion *et al.*, 1998; Zhang *et al.*, 2012; Gorantla *et al.*, 2013). Indeed, dermal fibroblasts derived from SPARC-null mice demonstrate enhanced VEGF production relative to those derived from wild-type mice (Bradshaw *et al.*, 2001). Another important consideration is that SPARC has the capacity to directly bind VEGF-A (Kupprion *et al.*, 1998; Nozaki *et al.*, 2006; Chandrasekaran *et al.*, 2007). Although it is not clear how this influences its activity, it is known that VEGF-A interacts with distinct receptors that can either promote or inhibit angiogenic processes (Rivera *et al.*, 2011). Thus, it will be important to determine whether direct interactions between SPARC and VEGF favour the anti-angiogenic response of SPARC mentioned above or whether this is altered in disease to induce pro-angiogenic responses instead.

Interestingly, while full-length SPARC is angiosuppressive, structural studies indicate that certain SPARC-derived peptide

fragments have pro-angiogenic effects. For instance, MMP3-cleaved peptides containing a KGHK sequence induce angiogenesis *in vivo* and *in vitro* (Lane *et al.,* 1994; Sage *et al.,* 2003). On the other hand, however, the EGF-like part of the same follistatin-like domain has anti-angiogenic activity (Chlenski *et al.,* 2004; Chlenski *et al.,* 2010). Thus, it appears that the extent and pattern of SPARC proteolysis could determine its overall angiogenic activity. Further studies should investigate whether the inflammatory environment in asthma and COPD favour SPARC proteolysis and the nature of the proteolytic fragments generated, as this may be a factor underlying pro-angiogenic processes in asthma and COPD. Finally, it should also be determined whether SPARC acts downstream of TGF-β to modulate VEGF expression and activity.

Another key factor underlying airway remodelling in chronic airways disease is aberrant wound repair in response to epithelial injury and damage. The EMT is characterized by the loss of epithelial tight junctions and increased mesenchymal markers and is an important component of the tissue repair response, but when dysregulated, EMT leads to an accumulation of mesenchymal cells and tissue fibrosis (Davies, 2009). Overexpression of SPARC induced fibroblast-like morphology in melanocytes, with concomitant loss of E-cadherin and P-cadherin expression, along with increased expression of mesenchymal markers (Robert *et al.,* 2006). Moreover, SPARC is a downstream mediator of the transcription factor Snail, a key regulator of TGF-β1-induced EMT formation (Grant *et al.,* 2014). Indeed, since TGF-β is one of the major factors implicated in dysregulation of EMT in asthma and COPD, it is likely that TGF-β/SPARC signalling is involved in this response.

Evidence for SPARC in the immune and inflammatory response

The role of SPARC in the immune response is less well understood, but this is an area of increasing interest and investigation. SPARC is expressed by various immune cell types, including macrophages, follicular dendritic cells and $CD4^+$ T cells (Sangaletti *et al.,* 2008; Piconese *et al.,* 2011). Apart from studies which have examined its role in bleomycin-induced lung inflammation (Savani *et al.,* 2000; Sangaletti *et al.,* 2011), there have been no other investigations of its role in the inflammatory component of lung disease. There is, however, a growing body of literature which suggests it has numerous immunoregulatory properties, and thus, its potential role in the airway inflammatory response in asthma and COPD is worthy of investigation.

Evidence from various disease models suggests that SPARC has pleiotropic roles in the immune and inflammatory response. For instance, thioglycollate-induced peritonitis in SPARC-null mice is associated with impaired leukocyte recruitment, indicating a role for SPARC in leukocyte trafficking (Kelly *et al.,* 2007). This is supported by evidence that leukocyte-derived SPARC binds vascular cell adhesion protein-1 and mediates leukocyte transmigration in endothelial monolayers *in vitro* (Kelly *et al.,* 2007). SPARC can also influence immune and inflammatory processes by regulating the availability of TGF-β. Using an experimental model of dextran sodium sulphate-induced colitis, Ng and colleagues showed that SPARC-null mice exhibit attenuated inflammatory responses and faster recovery, compared with their wild-type counterparts. In this case, the dampened inflammatory response was associated with increased expression of TGF-β, which has potent anti-inflammatory activities (Ng *et al.,* 2013). Similarly, loss of SPARC was associated with increased availability and activation of TGF-β in a model of pancreatic cancer. However, in this case, increased production of TGF-β was associated with a more aggressive malignancy, highlighting the distinct immunoregulatory effects of SPARC in different disease contexts (Arnold *et al.,* 2012).

In contrast to the studies mentioned above, SPARC exerts anti-inflammatory properties in some disease contexts, as discussed earlier in relation to bleomycin-induced lung injury (Savani *et al.,* 2000; Sangaletti *et al.,* 2011). Indeed, loss of SPARC has been associated with enhanced activation of immune and inflammatory responses in a number of experimental models (Savani *et al.,* 2000; Sangaletti *et al.,* 2005; Said *et al.,* 2007,2008; Sangaletti *et al.,* 2011; Thomas *et al.,* 2015). This may be attributed to lack of ECM structure and reduced ECM density and consequently a more permissive microenvironment that facilitates cellular trafficking and immune activation (Sangaletti *et al.,* 2005). Interestingly, it has been shown that SPARC limits bacterial spreading by inducing the formation of acute inflammatory reactions with granuloma-like features. However, at the same time, granuloma-associated SPARC inhibits dendritic cell migration to the draining lymph nodes and thus increases susceptibility to infection. Consistent with this, protective immunity against *Salmonella typhimurium* was restored in SPARC-null mice, thus providing further evidence that loss of SPARC may be associated with enhanced immune activation in certain contexts (Rotta *et al.,* 2008).

Of note, studies in SPARC-null mice have also identified an important role for SPARC in lymphopoiesis. SPARC-null mice display an impaired immune response that is associated with abnormal spleen architecture and altered B and T cell populations within the bone marrow (Rempel *et al.,* 2007). Indeed, loss of SPARC is associated with reduced numbers of B cell progenitors within the bone marrow and secondary lymphoid organs, suggesting that SPARC plays a role in the early stage of B cell lymphopoiesis (Luo *et al.,* 2014; Sangaletti *et al.,* 2014). In corroboration with this, loss of SPARC is associated with defective follicular dendritic cell networks in lymph nodes. This severely delays the arrangement of germinal centres where B cells proliferate and differentiate. Such defects result in the delayed development and differentiation of Th17 cells, indicating SPARC is essential for normal lymphopoietic function (Piconese *et al.,* 2011).

Although there is very limited understanding of the role of SPARC in the immune response, studies to date suggest a highly complex and pleitropic role. Whether SPARC is implicated in the aberrant and sustained activation of immune and inflammatory responses in chronic airways disease is a compelling question that warrants investigation. It is likely that SPARC will have direct immunomodulatory effects, as well as secondary effects consequent to alterations in ECM structure and TGF-β signalling. The cellular source of SPARC, in terms of immune cells rather than structural cells, is also likely to differentially influence immune and inflammatory responses in this setting (Sangaletti *et al.,* 2011).

Therapeutic implications

With mounting evidence implicating SPARC in respiratory disease, it is also essential to explore strategies by which this molecule may be targeted therapeutically. Pharmacological inhibition of SPARC is not currently possible as small molecule inhibitors and neutralizing antibodies have yet to be developed. However, the discovery of SPARC peptide fragments with distinct biological functions may open the way to new therapeutic opportunities. As mentioned above, full-length SPARC and its peptide fragment that contain an EGF-like module are angiosuppressive, while the SPARC peptide with the KGHK sequence is pro-angiogenic (Lane *et al.,* 1994; Sage *et al.,* 2003; Chlenski *et al.,* 2004; Chlenski *et al.,* 2010). Thus, specific peptide fragments containing the EGF-like module may potentially be developed to selectively inhibit angiogenesis in the absence of other effects attributed to the parent molecule. Rahman and colleagues have also shown that native SPARC enhances the efficacy of chemotherapy drugs via its ability to augment apoptosis in cancer cells. Moreover, they identified the N-terminus as the region responsible for this effect and further showed that a SPARC peptide fragment which spans the N-terminus domain has a greater chemosensitizing capacity than the parent molecule (Rahman *et al.,* 2011). While these findings are encouraging, further understanding of the biological actions of SPARC and that of its peptide fragments is necessary before their therapeutic potential can be fully realized.

Therapeutic modulation of SPARC expression in specific disease contexts may also be possible via strategies that exploit its epigenetic regulation. As mentioned above, reduced intratumoral SPARC is associated with poor survival in NSCLC (Schneider *et al.,* 2004; Huang *et al.,* 2012). Thus, the use of demethylating agents that selectively target the tumour site to increase SPARC expression may improve prognosis in these patients. The ability of SPARC to bind albumin may also be potentially exploited for therapeutic purposes. In some cancers, high levels of intratumoral SPARC is associated with a more favourable treatment response which is thought to be due to better localization and retention of albumin-bound chemotherapy drugs at the tumour site (Sawyer and Kyriakides, 2016). Indeed, it has been shown that the efficacy of albumin-bound paclitaxel (nab-paclitaxel, *Abraxane*) in patients with head and neck tumours correlates with tumoral SPARC expression (Desai *et al.,* 2009). Consistent with this, tumour SPARC expression was also positively correlated with the inhibitory effects of *Cellax* on tumour growth in a breast cancer mouse model. Compared with native docetaxel, *Cellax*, which is a polymer-docetaxel conjugate, has a greater ability to absorb albumin, and better internalization of this drug is observed in tumours in which SPARC is highly expressed (Hoang *et al.,* 2015).

In NSCLC, the level of SPARC expression within the tumor region is not related to treatment response or the overall survival of patients receiving albumin-bound drugs. Thus, the 'albumin effect' is likely to be dependent on the type of tumour or other yet to be identified factors (Shao *et al.,* 2011; Neesse *et al.,* 2014; Schneeweiss *et al.,* 2014; Kim *et al.,* 2016). Further investigation of the mechanisms by which SPARC influences the retention of albumin-bound drugs may lead to improved therapies for lung cancer and other respiratory diseases. Collectively, the emerging evidence suggests that SPARC expression at pathological sites, whether high or low, may be exploited for therapeutic purposes via a number of strategies. Thus, SPARC may serve as a potential 'biomarker' for targeted therapies in certain patients and disease settings.

Conclusion and future directions

SPARC is an ECM-associated protein that does not contribute structurally to the ECM but mediates interactions at the cell-matrix interface. This link governs fundamental cellular functions including cell adhesion, proliferation and differentiation. Thus, perturbations in the cellular microenvironment and/or cellular function may be accompanied by altered expression and activity of SPARC, as is evident in respiratory diseases such as lung cancer and IPF.

Interestingly, a recent study demonstrated increased expression of the SPARC family member, follistatin-like protein 1 (FSTL1) in lung macrophages of patients with severe asthma, and further demonstrated that FSTL1 induces airway remodelling in mouse models of asthma (Miller *et al.,* 2015). Moreover, it has recently been shown that the enigmatic protein high mobility group box 1 (HMGB1) induces SPARC expression in airway epithelial cells (Chen *et al.,* 2016). This is of relevance, because HMGB1 is implicated in asthma and COPD (Sukkar *et al.,* 2012) and has also been identified as a mediator of EMT and ECM synthesis in airway epithelial cells, thus suggesting a potential link between HMGB1 and SPARC signalling in chronic airways disease (Ojo *et al.,* 2015; Chen *et al.,* 2016). Together with our discussion above, these studies provide further impetus for investigation of SPARC in asthma and COPD.

As a starting point, further studies should establish whether pathological abnormalities associated with aberrant airway function in asthma and COPD are related to changes in the expression and/or activity of SPARC. Added to this, it is important to determine to what extent SPARC contributes to TGF-β-dependent effects in asthma and COPD and whether SPARC/TGF-β interactions contribute to these. Indeed, while TGF-β is an attractive target for drug development in chronic airways disease, its global inhibition is associated with increased risk of cancer and autoimmune disease (Akhurst and Hata, 2012; Al-Alawi *et al.,* 2014). Thus, given the close relationship between TGF-β and SPARC, the latter may prove to be a better alternative for therapeutic targeting, although this requires improved understanding of the interplay between TGF-β and SPARC and the role of SPARC in disease pathogenesis.

There is a strong association between COPD and the development of lung cancer; long-term smokers with COPD have 4.5-fold increase in cancer risk (Adcock *et al.,* 2011). Of note, genome-wide association studies have identified overlapping candidate genes, *CHRNA3* and *CHRNA5* (neuronal acetylcholine receptor subunit α-3/5) for COPD and lung cancer, suggesting common inherent genetic predispositions for these conditions, although oxidative stress and EMT formation in COPD are also thought to be the precursors of malignant transformation (Houghton, 2013). Given that SPARC is implicated in NSCLC, the possibility that SPARC

provides the molecular link between COPD and lung cancer progression certainly warrants investigation.

In conclusion, SPARC is emerging as a key player in numerous respiratory diseases, and there is a strong basis for its further investigation in chronic inflammatory airways disease. SPARC exhibits heterogeneous expression in certain pathologies, and its actions are not only dependent on the cellular source, but also the cellular and tissue microenvironment. Thus, future studies should examine the expression and activity of SPARC in distinct structural cells implicated in airway remodelling, for example airway epithelial cells, fibroblasts and airway smooth muscle cells, as well as in immune and inflammatory cells involved in the airway inflammatory response. Elucidation of the cell and tissue-specific roles of SPARC in chronic airways disease may certainly open the door to new opportunities for the therapeutic management of these conditions.

Conflict of interest

The authors declare no conflicts of interest.

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