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Matricellular proteins and inflammatory cells: A task force to promote or defeat cancer?

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ABSTRACT

In the last years it became clear that the tumor microenvironment plays a major role in neoplastic growth. Proteins secreted either by the malignant cells or by the tumor-associated stromal cells act as extracellular signal transductors, orchestrating tumor progression. Sentinel cells of the innate immune system patrol the different organs and have proven either to promote tumor growth or induce tumor suppression. In recent years, members of the matricellular family of extracellular proteins were shown to be involved in different aspects of the inflammatory response during tumor development, although in contradictory ways. In this review we discuss the evidence available up to date that relates matricellular proteins with the regulation of the inflammatory response and tumor progression.

Advances in the understanding of tumor biology in the last years evidenced that cancer represents a unique ecosystem within an organism. The importance of the cellular environment in cancer establishment and progression has been demonstrated in different types of human cancer. Nests of malignant cells are intermingled with tumor-associated stromal cells, all assembled on a complex mesh of extracellular matrix that provides the support and might promote tumor progression. In a tumor, the interaction between malignant cells, tumor-associated fibroblasts, endothelial cells and cells from the innate and adaptive immune response ultimately defines the progression of the disease [1].

1. Cancer and the adaptive immune response

The different and complex aspects of the immune response against tumors had represented a huge challenge in the traditional view of immunity as a perfectly tuned defense system against pathogenic insults. Several reviews summarized what is already known regarding tumor ability to evade immune surveillance [2,3].

Cells of the innate immune system such as natural killer cells, monocytes/macrophages, dendritic cells, neutrophils, basophils, eosinophils and mast cells constitute the first line of defense of the organism to any external or internal insult. After this acute inflammatory response is activated, a more complex process occurs that activates an efficient adaptive immune response, involving B lymphocytes, and $CD4^+$ and $CD8^+$ T cells. However, tumors facing immune surveillance seem to be like moles in a secret service agency: as virtual "insiders", they are able to elude the usual vigilance measures that the system establishes. In a recently proposed cancer immunoediting hypothesis, Schreiber and co-workers integrated in a single view the defensive abilities of the immune system with the capacity of tumors of evading this defense [4]. Accordingly, immune surveillance, recognized as the capacity of the adaptive immune response of recognizing and destroying developing tumors, may act as an evolutive force for selection of tumor variants with reduced immunogenicity that can evade the immune response. Surviving tumor cell clones are developing alternative immunosuppressive tools aimed to counteract the adaptive immune response, which otherwise should be able to eliminate malignant cells. These immunosuppressive strategies cover essentially every step of the T cell-mediated response to antigens, from defects in TCR signaling and impaired antigen processing and presentation, to activation of negative costimulatory signals (e.g. CTL4/B7) and expression of immunosuppressive cells that eventually help the tumor fight the antitumor immune response, such as regulatory T cells (Tregs) [5], NKT cells [6] and plasmacitoid dendritic cells (DC) [7]. Moreover, tumor-induced antigen-specific T cell tolerance was thoroughly demonstrated for $CD4^+$ T cells; interestingly, the intrinsic antigen-presenting capabilities of the tumor cells themselves were proved not as relevant for tolerance induction

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as that induced by tumor antigen-presenting bone marrow-derived cells, specifically dendritic cells [8]. Lately, evidence has arisen to support the idea that $CD8^+$ T cell tolerance to tumor antigens also exists, although the molecular and functional mechanisms of this effect still remain to be established [9,10]. Overall, growing tumors need to overcome the activation of the adaptive immune response and do it efficiently by forcing the host immune system to tolerate them as if it were a normal self tissue.

2. Cancer and the innate immune response

The relationship between cancer and the innate immune response is more controversial than that described for the cancer/adaptive immune response interaction. When homeostasis is perturbed due to a pathogenic aggression, sentinel cells of the innate immune system, such as neutrophils, macrophages and mast cells, immediately release a multifactorial network of signals that mobilize and recruit additional leukocytes, thus delivering a host response designed to neutralize the pathogenic insult and subsequently heal the injured tissue. Once activated, macrophages release growth factors and cytokines, including VEGF, TNF, IL-6 and TGFβ which affect endothelial, epithelial and mesenchymal cells in the local environment [11]. The stimulation of inflammatory pathways was shown efficient enough to break tumor-induced T cell tolerance, leading to an effective T cell activation against tumors [12]. However, increasing evidence demonstrated that immune cells and inflammatory mediators within the tumor microenvironment can be either beneficial or detrimental for tumor progression [11,13,14]. The clue to distinguish which the most likely outcome would be appears to be whether inflammation is acute or chronic [15]. Most of the evidence regarding the involvement of chronic inflammation in tumor initiation came from epidemiological studies reporting that long-term usage of anti-inflammatory drugs significantly reduced colon, lung, esophagus and stomach cancer risk [16]. Moreover, anti-inflammatory drugs exhibited antitumorigenic effect in colon cancer, mostly due to their inhibition of COX activity, suggesting that inflammation-associated genes might also participate in advanced steps of cancer development [17]. A non-pharmacological finding that supports the idea that tumors may arise in chronically inflamed tissue is that individuals with long-lasting (more than 10 years old) ulcerative colitis have a higher likelihood of developing colorectal cancer [18]. In addition, the presence of mild emphysema confers a substantial risk of developing lung cancer, a fact that may be explained by the low level of inflammation that is seen in emphysema, as inhaled corticosteroids reduced the incidence of cancer [19].

On the other side, the idea that innate immunity can suppress tumor growth came from William Coley's vaccination protocols in the late 19th century [20] that is still used in the form of the BCG vaccine for bladder cancer treatment. This simple vaccine triggers an innate immune response through the induction of different factors. But, only in the last years, experimental models are beginning to elucidate the molecular mechanisms by which innate immune cells can regulate tumor progression ([11], and references therein). Infiltrating dendritic cells can bias an immune response to a type 2 immunosuppressive phenotype, while type 1 cells might augment the antitumor response. An example of the duality of this delicate balance is evidenced in *Helicobacter*-induced mucosa-associated lymphoid tissue (MALT) lymphoma; proliferation of malignant B cells is driven by Th2-polarized, immunocompetent T cells [21]. However, vaccination against *Helicobacter* using a whole-cell sonicated vaccine was effective in generating a Th1-response that prevented lymphoma formation [22]. Similarly, type 1 macrophages are associated with a type 1 antitumor response while type 2 macrophages might reduce antitumor immune responses. Granulocytes infiltrate can either promote or suppress tumor growth depending on the metastatic capacity of the malignant cells [23]. Interestingly, it has been suggested that the innate antitumor immune activity can be re-activated through the release of endogeous factors following tumor cell death [24]. More recent evidence demonstrated that tumor-infiltrating neutrophils and macrophages might elicit angiogenesis through the secretion of matrix metalloproteases that can release VEGF from angiogenic islets, allowing its interaction with its cognate receptor [25]. Thus, different processes that are essential for tumor development, such as enhanced cell survival, angiogenesis, tissue remodeling and suppression of adaptive immune response, are regulated by leukocyte infiltrates in the tumor microenvironment.

3. Matricellular proteins: at the cross road of tumor progression and inflammatory response

The orchestrated anti- or pro-tumorigenic immune response is influenced by a non-structurally related family of proteins named "matricellular proteins" that are not intrinsic components of the extracellular matrix (ECM) scaffold, are released by different types of cells in the tumor environment, and show only temporal interaction with ECM proteins. Matricellular proteins are commonly secreted by normal and malignant cells and along with scaffolding proteins such as collagens and fibronectin, matricellular proteins are the major constituents of the ECM [26]. The principal members of these group of proteins that include the thrombospondin family (TSP 1–5), SPARC, osteopontin, testicans 1–3, tenascins (C and X), hevin, SMOC 1 and 2, the CCN family [1–6] and the recently added family of galectins [27], are involved in the modulation of the adhesive state of cells.

Matricellular proteins are normally induced during tissue injury and participate in different aspects of wound healing. The wound healing response comprises a series of overlapping processes that include inflammation, proliferation, migration, neovascularization and matrix remodeling. These aspects are also of relevance in tumor establishment and progression. In normal wound healing the participation of neutrophils and activated macrophages is transient and gives way to the proliferative and remodeling phases. However, during non-resolvable healing processes such as the foreign body response, a chronic inflammatory response may persist for years. In this context of tissue repairing, there is experimental evidence that matricellular proteins affect the inflammatory response in different ways (see below).

Tumors are characterized by the overproduction of matricellular proteins that are believed to play a key role in tumor progression [28,29]. Since tumors resemble wounds that do not heal, and wound healing induces the expression of matricellular proteins that act in tissue remodeling, we can hypothesize that matricellular proteins may be among the first proteins produced abnormally by tumor cells, helping them to disengage from neighbor normal cells, proliferate and invade surrounding normal tissue, while at more advanced steps they are involved in tumor-induced angiogenesis and recruitment of inflammatory cells (Fig. 1).

A paradigmatic member of the matricellular family of proteins is SPARC (Secreted Protein Acidic and Rich in Cysteines). SPARC, also named osteonectin, is a 32 kDa-protein, whose Mr might increase up to 45 kDa due to glycosilation [30]. It is secreted by fibroblasts and endothelial cells during normal development and in wound healing, and also by different types of malignant cells ([29] and references therein). Evidence is emerging that SPARC, as other matricellular proteins, is involved in regulating different

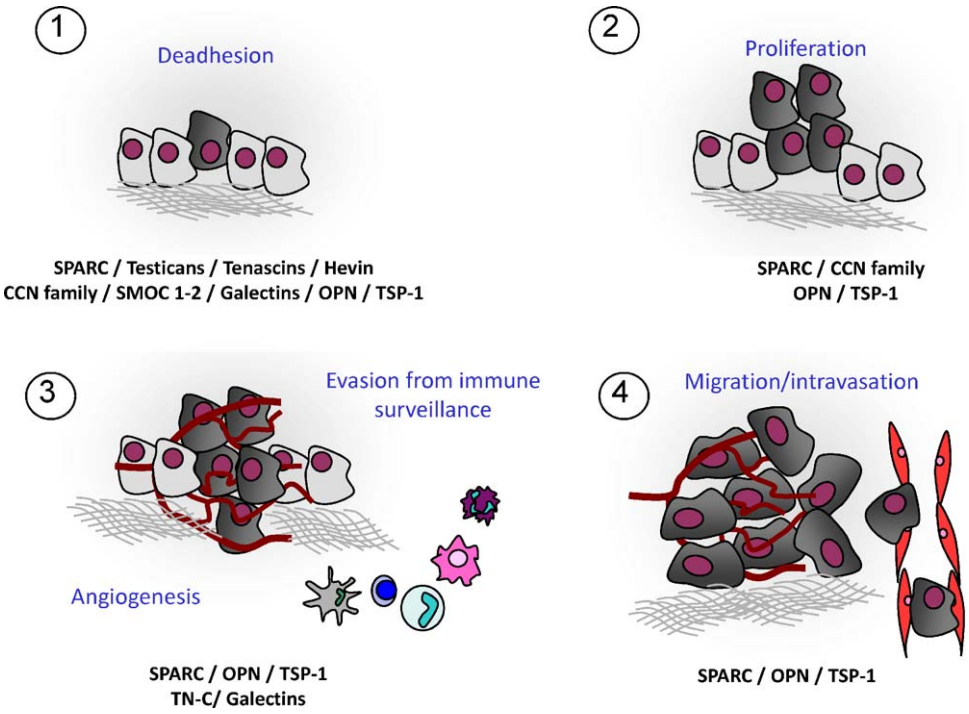

Fig. 1. Matricelullar proteins involved in early stages of cancer progression. Matricellular proteins play key roles in the different steps of malignant growth, from tumor cell disengagement from matrices to evasion from immune surveillance, recruitment of vessels and intravasation into the circulation for dissemination.

aspects of the inflammatory response in cancer. Seminal studies from our group have shown that enforced downregulation of SPARC expression in human melanoma cells ($SPARC_{low}$) by using antisense RNA or shRNA, obliterated their *in vivo* growth capacity in nude mice [31–34]. This effect was accompanied by diminished activity of MMP-2 and MMP-9 and invasive capacity and reduced recruitment of inflammatory cells into the tumor mass [31]. More recent data demonstrated that SPARC produced by melanoma cells inhibited directly the antitumor cytotoxic capacity of polymorphonuclear leukocytes (PMN) recruited to the tumor environment [32]. Moreover, *in vivo* depletion of PMN completely reverted the lack of *in vivo* growth of $SPARC_{low}$ melanoma cells [33], strongly indicating that SPARC may act as a biological shield that protects tumors from the acute antitumor inflammatory response. In support of this, $SPARC_{low}$ cells also stimulated the *in vitro* migration of human and murine PMN, while had no effect on the *in vitro* migration of human or murine monocytes [34]. Both the *in vitro* and *in vivo* recruitment of PMNs were mediated by the overexpression of specific chemokines such as GRO, IL8 and leukotrienes and involved both soluble and cell membrane bound FasL [34]. Indirect evidence suggests that SPARC-effect on PMN might be mediated by integrin-dependent signaling. Indeed, recent work highlighted that SPARC exerts some of its functions, including fibronectin matrix production and assembly, through interaction with integrin-linked kinase [35–38]. Interestingly, GRO and IL-8 were shown to be induced by fibronectin-mediated integrin activation [39,40]. Thus, it can be hypothesized that PMN recruitment in the melanoma model may be mediated by the modulation of integrin engagement that occurs in the absence of SPARC.

4. Matricellular proteins, cytokines and chemokines: collaborative efforts against cancer?

TGFβ, a well-known cytokine with controversial activities in cancer growth demonstrated paradoxical roles in inflammation with both proinflammatory and anti-inflammatory responses [41]. Different studies have shown that SPARC can induce TGFβ expression [42–46] while TGFβ can increase SPARC levels in several cell types, suggesting the existence of a bi-directional loop between these two proteins [47–51]. TGFβ role in cancer, similar to the one previously described for SPARC, is not only autocrine but also paracrine, affecting neighboring cells that might or might not express TGFβ. TGFβ signaling influences tumor cell autonomous signaling that can suppress or promote tumor progression and metastasis dissemination depending on the context of stimulation (reviewed in [52]. TGFβ was shown to inhibit T cell cytotoxicity [53] and macrophage effector functions [54]. Moreover, TGFβ also inhibited the activation of neutrophils, that in the absence of inhibitory factors would normally kill FasL-expressing cells [55]. Interestingly, FasL was detected at the cell surface of $SPARC_{low}$ melanoma cells and treatment of $SPARC_{low}$ cells with anti-FasL neutralizing antibody reduced dramatically PMN recruitment to the tumor area suggesting a proinflammatory role for FasL [32]. In addition, the *in vivo* recruitment of secondary waves of PMNs also required enhanced production of IL-1 suggesting that FasL expression and IL-1 production induced by enforced down-regulation of SPARC expression are absolute requirements for the continuous recruitment of PMN and hence tumor elimination [56]. These data suggest that SPARC-expressing cancer cells may be blocking PMN activation in part through a TGFβ-mediated pathway, and that a decrease in SPARC expression with a concomitant decrease of TGFβ levels may enable PMN activation through the expression of FasL by malignant cells (Fig. 2). A very recent study highlighted a novel mechanism that might explain, at least in part, the contradictory effects of infiltrating neutrophils on tumor growth [57]. Growing tumors appeared to recruit pro-tumorigenic neutrophils (named TAN2 for tumor-associated neutrophil 2); however, blockade of TGFβ activity polarized the recruitment and activation of antitumorigenic TAN1 [57]. Although depletion of $CD8^+$ T cells completely obliterated TAN1 antitumorigenic effect *in vivo*, TAN1 exhibited a direct cytotoxic effect on tumor cells [57]. Based on this study and previous available data regarding SPARC, it is likely that both TGFβ and

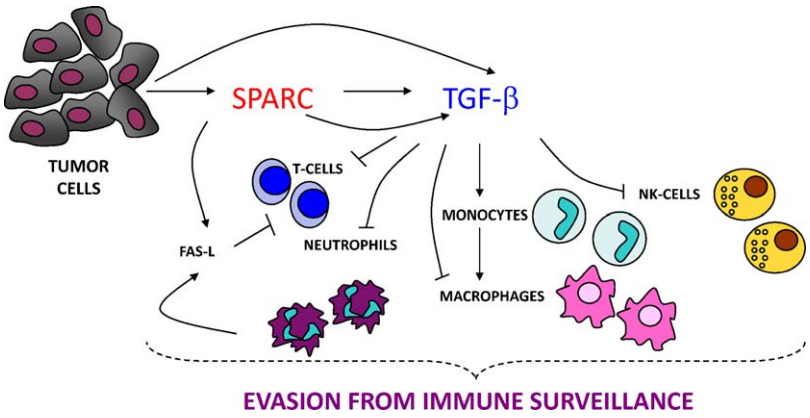

Fig. 2. The axis SPARC-TGFβ as a key mediator of antitumor immune surveillance. A model of the role of the duet SPARC-TGFβ on inhibition of inflammatory cell activity. Tumor cells may secrete both SPARC and TGFβ independently; alternatively, SPARC may induce the expression of TGFβ.

SPARC can coordinately act on the recruitment and activation of neutrophils with pro- or antitumorigenic activity. While this is an appealing hypothesis, no evidence was observed of TGFβ involvement associated with the antitumor attack of PMN following enforced downregulation of SPARC expression, despite the fact that melanoma cells expressed TGFβ in a constitutive, non-inducible fashion [58]. However, it must be emphasized that SPARC data were obtained with human tumor cells xenografted in nude mice where the $CD8^+$ T cells response is absent. Although it is still early to extrapolate these studies to humans, in particular the existence of TAN1 and TAN2 cells [59], the study by Fridlender et al. might pave the way to clearly understand the link between a central cytokine such as TGFβ, the matricellular protein SPARC and tumor-associated neutrophils.

The existence of a potential mechanism of neutrophils recruitment to the tumor microenvironment that involves in addition to TGFbeta and SPARC, also IL-8, GRO, leukotrienes, FasL, IL-1 and additional cytokines and chemokines [59] through paracrine and autocrine effects is very appealing, but warrants further investigation in terms of the precise role of each compound and the contribution of the different cell components of the tumor mass.

5. The matricellular protein SPARC and the apparent controversial roles in inflammation and cancer

SPARC role in human cancer seems controversial, as it may act as pro- or antitumorigenic apparently depending on the tumor type and the biological context in which the experimental evidence was obtained ([29] and references therein). While in the human melanoma models in nude mice SPARC produced by malignant cells can modulate the recruitment and antitumor activity of PMN through the production of both chemotactic and apoptotic factors, in mammary tumor growth the overall scenario appears different. Indeed, SPARC-producing mammary carcinoma cells obtained from c-erbB-transgenic mice showed reduced tumor growth in SPARC-null mice compared to wild-type mice [60]. This was accompanied by a potent inflammatory response, that was able to deeply infiltrate the tumor parenchyma inhibiting tumor growth [60]. More recently, it was shown that SPARC produced and secreted into the tumor microenvironment by infiltrating macrophages augmented tumor cell migration and metastases dissemination of murine 4T1 mammary tumor cells [61]. According to this view, SPARC secreted into the tumor microenvironment, irrespective of the cell source, will affect metastatic dissemination through modulation of cell-matrix interaction. While this is very appealing, studies in melanoma demonstrated that only the modulation of SPARC levels produced by the melanoma cells themselves – but not by surrounding fibroblasts – was responsible for the inflammatory infiltrate and tumor rejection [33]. Moreover, the fact that the administration of melanoma cells containing only one tenth of $SPARC_{low}$ cells also induced tumor rejection strongly suggests that SPARC secreted into the tumor microenvironment by wild-type melanoma cells was unable to block PMN attack suggesting that SPARC is acting through additional mediators [32]. Indeed, the more plausible explanation is that expression of FasL in $SPARC_{low}$ cells promoted PMN attack and the further recruitment of new waves of PMN. Similar results were observed when malignant cells were enforced to express FasL [56]. Also in this scenario, administration of only one tenth of FasL expressing malignant cells was sufficient to induce a PMN-mediated tumor rejection [56].

In clear contrast, overexpression of SPARC in ovary cancer cells decreased their tumorigenic capacity in nude mice and increased cancer cell apoptosis [62] Moreover, enforced SPARC overexpression attenuated the response of ovarian cancer cells to the pro-tumorigenic effect induced by infiltrating macrophages suggesting that SPARC is acting as an oncogenic protein in ovarian cancer [63]. It was shown that SPARC overexpression decreased macrophage chemoattractant protein (MCP)-1 production by cancer cells reducing macrophage recruitment [63]. In addition, SPARC overexpression downregulated the expression of several proinflammatory cytokines and proteases [64]. Thus, enforced expression of SPARC in ovary cancer microenvironment appears to restrict tumor growth through a mechanism that involves the inhibition of macrophage infiltrate which otherwise would have promoted tumor growth. Interestingly, the phenotype of infiltrating macrophages was not assessed in any of the models to establish whether type 1 or 2 macrophages were infiltrating the tumor mass and if SPARC produced by malignant cells could skew their phenotype or select specific clones. More recent studies suggest that data on SPARC role in inflammation obtained with the use of SPARC-null mice should be taken with caution. Indeed, it was shown that SPARC plays a role in maturation of immune cells and SPARC-null mice exhibit an altered development of the immune system [65].

6. SPARC and inflammation in models other than cancer

It is of interest that studies performed in non-cancer models also evidenced a contradictory role of SPARC in the recruitment and activation of inflammatory cells. As mentioned above, SPARC-null mice exhibited alterations in their capacity to mount an immune response despite the fact that they exhibited only slightly lower counts of white blood cells and neutrophils in peripheral blood, and a decreased proportion of CD19(+) B cells with an increased proportion of CD3(+) T cells, compared to wild-type mice

[65]. In this regard, SPARC-null mice had a greatly attenuated response to bacterial LPS in the footpad swelling model, suggesting that in the absence of SPARC, mice were unable to mount an innate immune response [65]. On the other hand, SPARC−/− mice exhibited increased neutrophil and leukocyte infiltration in bleomycin-induced lung injury and thioglycolate-induced peritonitis [66], that was accompanied by a greater fibrotic response. However, more recent studies demonstrated that enforced down-regulation of SPARC expression in a thioacetamide-liver fibrosis model significantly reduced liver fibrosis that was accompanied by decreased recruitment of inflammatory cells [67]. At what degree the data obtained in the different studies could be affected by the model used is difficult to ascertain. One potential explanation of these differences in leukocytes recruitment is that the extracellular matrix in SPARC-null mice is considerably laxer than in wild-type counterparts due mainly to anomalies in collagen deposition [68–71]. Thus, inflammatory cells may encounter less matrix resistance to reach their targets in SPARC-null mice. In agreement with this hypothesis, SPARC-deficient mice never formed granulomas in response to attenuated Salmonella infection through the skin, allowing immune cells to find the infection site and then reach lymph nodes, where they were able to mount a defensive response that would let mice survive a later challenge with a virulent strain of Salmonella [72]. On the contrary, wild-type mice formed SPARC-expressing granulomas that, although efficient in mounting an acute inflammatory reaction, contained infection so well that prevented dendritic cells to alert T cells in lymph nodes, avoiding a successful adaptive response [72]. Consistent with a key role of SPARC in the proper arrangement of the ECM scaffold, recent studies in a model of contact hypersensitivity (CHS), demonstrated an exaggerated CHS response in SPARC null mice along with a greater number of epidermal Langerhans cells migrating to draining nodes [73], suggesting that in SPARC absence, immune cells migrate more freely and access lymph nodes more effectively. On the other hand, a significant decrease in the amount of recruited macrophages in response to angiotensin II was found in the tubulointestinal space of SPARC null mice respect to wild type mice, despite the absence of differences in MCP-1 levels between both mouse strains [74]. Thus, defining the precise role of a matricellular protein like SPARC could be confounded by the limitations of the animal model used.

It seems therefore that SPARC may affect immune cells' recruitment through the modulation of chemokines production or its effect on extracellular matrix architecture (i.e. collagen and fibronectin deposition). However, the final outcome of the inflammatory response, at least during tumor development, may vary depending on the balance of SPARC produced by different sources within the tumor environment. For instance, SPARC produced by malignant melanoma cells abolished PMN-mediated neutralization of tumor growth regardless of the changes in collagen deposition, angiogenesis and fibroblast recruitment that SPARC modulation induced in the surrounding tumor-associated stroma, while SPARC expressed by neighboring fibroblasts had no effect on melanoma cell growth or the inflammatory response [33].

7. Other matricellular proteins in the inflammatory response during cancer and wound healing

There is clear evidence that matricellular proteins other than SPARC play also key roles in the inflammatory response, with consequences both in cancer as in normal wound healing. Kyriakides and Bornstein summarized the state of the art in relationship to the role of matricellular proteins during wound healing and the foreign body response [75]. Normal wound healing is characterized by being self limiting, contrary to the foreign body response which involves a chronic inflammatory response, with the deposition of a fibrous capsule largely devoid of blood vessels. Data obtained with *thrombospondin 1* (TSP1) [76,77] indicated that it impaired the inflammatory response during wound healing. TSP1 is, a potent chemotactic agent for neutrophils [78]. Early in 1989 it was demonstrated that thrombospondin-1 (TSP-1) expressed both by human squamous epithelial cells and monocytes plays a role in monocyte-mediated killing of transformed cells [79]. More recently, overexpression of TSP1 in melanoma cells enhanced macrophage recruitment into xenograft tumors grown in immunodeficient mice, and polarized macrophages to the M1 antitumorigenic phenotype [80]. Consistent with the enhancement of macrophage recruitment observed in cancer models, TSP1-null mice exhibited a reduced inflammatory response with a decrease in macrophage recruitment [81]. TSP1 was also reported as a major activator of TGFβ1 which is also necessary for the normal progression of wound healing and may mediate, at least in part, TSP1 effects [82]. Interestingly, SPARC has been shown to inhibit production of TSP1 in endothelial cells [38]. However, its effects on the expression of TSP1 in tumors are not reported.

Osteopontin (OPN), a secreted phosphorylated glycoprotein, was first shown to be important in immune activity and bacterial resistance [83]. Later, it was reported that OPN expression is strongly associated with tumorigenesis, as high plasma levels or increased expression levels of OPN in cancer tissue are associated with poor prognosis in breast [84–87] multiple myeloma [88] and prostate cancer [89]. Most of OPN effects in biology have been related to integrin-mediated pathways, as osteopontin interacts with α4β1 and other integrins [90–92]. In prostate cancer, for example, proliferation induced by OPN is accompanied by a sustained activation of the EGF receptor (EGFR); colocalization of the OPN ligand integrin β1, and EGFR on the cell surface, suggests that the association of these cell surface receptors may be the principal mechanism involved in the long-term activation of EGFR [90]. However, other mechanisms that justify OPN effects on tumor biology cannot be overruled. In this sense, early work showed that tumor-secreted OPN inhibited macrophage cytotoxicity against tumors, promoting metastatic dissemination [93,94]. However, OPN is also secreted by other components of tumor-associated stroma, such as endothelial cells and macrophages, indicating that, similar to SPARC, OPN dynamic production between all the cells that compose the tumor mass might be central to understand its role in tumorigenesis. For instance, OPN produced by endothelial cells was shown to favor angiogenesis and therefore tumor growth [95], however, OPN secreted by macrophages inhibited tumor growth [96,97]. OPN is also highly expressed in chronic inflammatory diseases [98], possessing chemotactic activity for macrophages and neutrophils [99,100]. More recently, it was also shown that an antisense-mediated local inhibition of OPN expression at wound tissue results in accelerated healing and reduced granulation tissue [101].

Tenascin C (TN-C) is an extracellular matrix glycoprotein whose expression is increased in cancer and non-cancerous inflammatory diseases. Studies on tumor biopsies showed that TN-C expression correlates with angiogenesis and tumor proliferation in glioblastoma [102], and with increased malignacy of primary melanoma [103]. A spatial correlation between higher densities of macrophagic/microglial infiltration and TN-C expression in perinecrotic areas in glioblastomas was also shown, suggesting that TN-C may play a crucial role in regulating trafficking of cells of the monocyte lineage in human gliomas [104]. Moreover, increased expression of TN-C correlates with recurrence of NSCLC, where it inhibits effector functions of tumor-infiltrating lymphocytes [105]. In TN-C null mice, however, no effect was evident on the temporal occurrence of mammary tumors and their metastatic dissemination in lungs, although the TN-C-null stromal compartment contained

Table 1
Summary of published evidence that relates matricellular proteins, innate and adaptive immune response and tumor progression.

Type of immune response		
Protein	Innate	Adaptive
Osteopontin	• Inhibits macrophage cytotoxicty favoring metastatic phenotype [93] • Inhibits antitumor macrophage activation [94] • Downregulation of its receptor in tumor cell protects them from activated macrophages [97] • Recruits proangiogenic monocyte [95] • Macrophage-derived OSP inhibits tumor growth [96]	
Thrombospondin-1	• Recruits and enhances macrophage antitumor activity [80] • Inhibits monocyte cytotoxicity [79]	
Tenascin-C	• Regulates traffic of cells of monocyte lineage [104] • Modulates monocyte/macrophage recruitment [106]	• Inhibits TIL proliferation [105]
Galectin-1		• Inhibition of galectin-1 in tumor cells promotes T cell-mediated tumor rejection [116]
Galectin-3	• Downregulation of galectin-3 sensitizes colon cancer apoptosis [119]	• Its expression by tumor cells correlates with cells to TAM promoting apoptosis of TILs [118] • Inhibits tumor- reactive T cells and promotes tumor Growth [117]
Galectin-9		• Increases antitumor immunity mediated by dendritic cells [120]
SPARC	• Inhibits recruitment of pro-tumorigenic macrophages and downregulates associated inflammation in ovary cancer [64] • Inhibits polymorphonuclear leukocyte recruitment and tumor rejection in melanoma [32,33] • SPARC produced by host leukocytes, determines the assembly and function of tumor-associated stroma through the organization of collagen type IV [60] • Macrophage-derived SPARC induces cancer cell migration in a model of spontaneous metastasis [61]	

significantly more monocytes/macrophages than tumor stroma from TN-C wild-type mice [106]. Thus, all the evidence indicates that in a similar way to SPARC in the melanoma model, TN-C might promote tumor growth while at the same time blocking the inflammatory infiltrate. Consistent with these observations in cancer, seric tenascin also correlates with hepatic fibrogenesis and inflammation in chronic hepatitis B [107]. Moreover, TN-C knock out mice have a diminished allergic reaction, including a decreased production of several cytokines, to asthma-inducing stimuli [108].

Galectins are the newest addition to the family of matricellular proteins [27], as they can display de-adhesive effects when added to strongly adherent cells. Galectins are beta-galactose-binding proteins expressed by immune cells and tissue-resident stromal cells that often serve as crosslinkers between specific glycoconjugates of the ECM and cell surface receptors [109]. Along with their effects on cell adhesion, migration, growth and apoptosis ([27] and references therein), a growing body of experimental evidence indicates that galectins may play critical roles in the modulation of chronic inflammatory disorders, autoimmunity and cancer through regulation of the balance between Th1 and Th2 cytokine responses [110]. In cancer, galectin-1 was shown to contribute to different steps of tumor progression including cell adhesion, migration and tumor-immune escape ([111,112] and references therein). Similar to cytokines that have an anti-inflammatory influence, galectin 1 has been shown to inhibit TNFα and IFNγ secretion from activated T cells *in vitro* [113] and *in vivo* [114,115]. Results from our group demonstrated that inhibition of galectin-1 expression in B16 murine melanoma cells by antisense expression, promoted T cell-mediated tumor rejection, while no direct involvement of inflammatory cells was observed [116]. Another member of the family, galectin-3, also promotes tumor growth by inhibition of tumor-reactive T cells [117], and its expression, as in the case of galectin-1, correlated with apoptosis of tumor-associated lymphocytes [118]. On the other hand, galectin 3 also affects innate immunity, as knock-down of galectin 3 in colon cancer cells sensitized tumor cell apoptosis induced by tumor-associated macrophages [119]. Recently, new evidence indicates that also galectin-9, another type of galectin, impacts the antitumor immune response by potentiating CD8(+) T cell-mediated antitumor immunity via Galectin-9-Tim-3 interactions between dendritic cells and CD8(+) T cells [120]. Table 1 summarizes the main evidence of the effect of matricellular proteins in inflammation and tumor biology.

Recently, another extracellular component, *versican*, has emerged as a key player in the link between inflammation and metastasis. Although versican is considered as a structural and not a matricellular protein, its important role as a regulator of a prometastatic inflammatory immune response makes it relevant for the purpose of this review. Versican is a chondroitin-sulphate proteoglycan upregulated in tumors [121] and secreted by metastasic tumor cells such as Lewis lung carcinoma (LLC) [122]. Kim et al. demonstrated that through the activation of toll-like receptor (TLR) 2 and its co-receptors TLR6 and CD14, versican expressed by LLC cells exerts an activator role for macrophages [122]. Tumor-associated macrophages, when activated, secrete TNF-α which is an important positive modulator of LLC metastatic behaviour. Further work is eagerly awaited to extend these observations to other cancer models, as this finding might open interesting therapeutic perspectives [123].

8. Cleavage of matricellular proteins and the appearance of cryptic activities

In the last few years, attention has been drawn to the role of proteolytic fragments of ECM proteins as unique effectors of biological functions. Given that SPARC and other matricellular proteins regulate protease expression ([31,124,125] and our unpublished observations), it is tempting to suggest that the release of pro- or anti-inflammatory peptides might be also an indirect effect of matricellular protein expression. In addition, matricellular proteins are themselves sensitive to protease cleavage and some of their fragments may have activity on their own. SPARC is cleaved by several proteases, like cathepsins, some metalloproteinases, elastases and serine proteases [126] and experimental evidence has suggested that SPARC-derived peptides participate in specific functions in cell growth and angiogenesis

[127,128]. We may speculate that fragments of SPARC, as well as from other matricellular proteins, may also have specific pro- or anti-inflammatory actions, but further experimental evidence is needed to test this possibility. In that respect, it was observed that whereas TSP-1 is critical for activation of TFGβ1 during bleomycin-induced fibrosis, a TSP-1 functional fragment appeared to compete with full TSP-1 for its receptor CD36 and inhibited activation of latent TGFβ1 in this inflammation model [129].

On the other hand, OPN is sensitive to cleavage by several proteases, most importantly, thrombin. Thrombin-mediated OPN cleavage generates two fragments, an RGD-containing N-terminal part that binds to integrins with a higher affinity than the full protein, and a C-terminal part which can interact with CD44 [130]. Engagement of CD44 proved to modulate lymphocyte activation, recirculation and homing, and also to participate in tumor biology, where it reduced Fas expression and Fas-mediated apoptosis [131] demonstrating an additional example of the relevance of matricellular protein cleavage and its effects on the immune response and cancer.

Given that the extracellular niche is rich in proteases, it is not surprising that cell surface proteins may also expose cryptic domains by shedding or clipping that can dynamically interact with the ECM and play a role in inflammation-associated with cancer progression. In many cases these newly exposed domains actually have functions distinct from their parental molecules and are called "matrikines". The term "matrikine" has been coined to name peptides obtained as a result of proteolytic cleavage of extracellular matrix proteins such as collagens, elastins and laminins [132] Matrikines involvement in wound healing and tumor progression have been reviewed elsewhere [133]. These matrikines display cryptic, cytokine-like activities such as potent induction of cell migration that are usually not expressed by their whole length precursors [132]. Although matricellular proteins are at present not included as precursors of the matrikine family, different studies have shown that matricellular proteins interact with matrikine precursors. For instance, SPARC has been shown to interact with fibril collagen types I, II and V and the basement membrane collagen type IV [134]. Moreover, SPARC cleavage increased its affinity to collagen type I [135]. Since ECM-peptides derived from collagen types I and IV, among others ECM proteins, have been reported to be active as chemotactic factors [136] it is tempting to hypothesize that matricellular protein's interactions with matrikines can greatly influence the inflammatory response.

9. Conclusion and future perspectives

The complex interaction that naturally occurs among the different players of the immune system calls for a delicate equilibrium to maintain immunological beneficial effects. Cancer, as a result of the malignant adaptation of cells to a deregulated environment, breaks this equilibrium. Recent evidence demonstrated that both inflammation-induced carcinogenesis and cancer immunoediting can occur in the same mouse tumor model [14]. Therefore, it is evident that immunity can both promote and eliminate developing tumors and give shape to tumor immunogenicity. Likewise, matricellular proteins seem to play different roles in cancer, depending on the cellular context in which they interact. Fig. 3 intends to depict a summary of the roles of matricelullar proteins in the context of tumor establishment and progression.

Several of the actions related to matricellular proteins are or may be mediated by TGFβ. In the tumor microenvironment, TGFβ is a ubiquitous protein expressed by different cell types, such as the malignant cells themselves, carcinoma-associated fibroblasts, T cells, PMN, monocytes, macrophages and NK cells. TGFβ has a role in early tumor suppression but later it can contribute to tumor progression ([52,137] and references therein). Most matricellular proteins that have a role in inflammation and tumor development seem to regulate TGFβ levels; however, not all activities of matricellular proteins are mediated by this cytokine. Several effects of matricellular proteins may instead be mediated by interactions with cell membrane integrins, either directly or through interactions with other integrin-binding proteins. More-

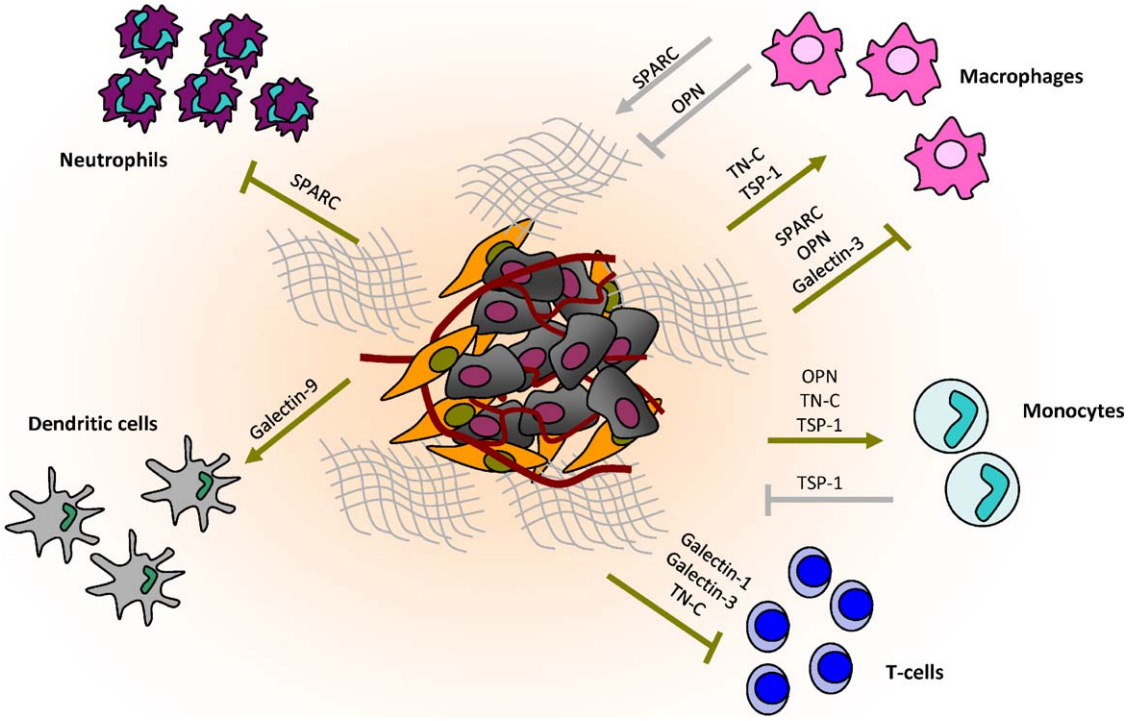

Fig. 3. Matricelullar proteins and their role in the inflammatory response during cancer. Malignant and tumor-associated stromal cells (fibroblast and endothelial cells) secrete different matricellular proteins that modulate the inflammatory response, either favoring or not tumor progression.

over, proteolytic processing of matricellular proteins may expose hidden interacting sites, providing in this way a further point of control of the final biological outcome. Thus, in order to be able to manipulate the tumor environment for the successful treatment or prevention of cancer, further studies on the contextual and timely role of matricellular proteins such as SPARC are needed to shed light on the molecular mechanisms these matricellular proteins are involved in, that ultimately lead to tumor progression.

Conflict of interest

None.

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