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Tenascins in stem cell niches

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ABSTRACT

Tenascins are extracellular matrix proteins with distinct spatial and temporal expression during development, tissue homeostasis and disease. Based on their expression patterns and knockout phenotypes an important role of tenascins in tissue formation, cell adhesion modulation, regulation of proliferation and differentiation has been demonstrated. All of these features are of importance in stem cell niches where a precise regulation of growth versus differentiation has to be guaranteed. In this review we summarize the expression and possible functions of tenascins in neural, epithelial and osteogenic stem cell niches during normal development and organ turnover, in the hematopoietic and pro-inflammatory niche as well as in the metastatic niche during cancer progression.

1. Introduction

The four tenascins (-C, -R, -X, and -W) comprise a family of large oligomeric extracellular matrix (ECM) glycoproteins in vertebrates. All tenascin subunits are composed of an N-terminal domain assembling to homotrimers or -hexamers ("hexabrachions"), a variable number of tandem epidermal growth factor (EGF) and fibronectin type III (FNIII) repeats, and a fibrinogen homology domain (FBG) at the C-terminus (Chiquet-Ehrismann and Chiquet, 2003; Chiquet-Ehrismann and Tucker, 2011). Each of the four tenascins exhibits a unique time- and tissue-specific expression pattern in the embryo and in the adult. Tenascin-C is found in many developing organs but is often restricted to specific sites, e.g. around budding or invaginating epithelia (hence its name: "holding nascent structures"; Chiquet-Ehrismann et al., 1986; Fig. 1). After birth, tenascin-C distribution is reduced to a few tissues bearing high tensile stress (tendons, ligaments, smooth muscle) and in addition to certain locations of high cell turnover (e.g. lymphoid organs, hair buds in skin; see below). Moreover, prominent de novo expression of tenascin-C in the adult is a hallmark of injury, regeneration, and cancer (Chiquet-Ehrismann and Chiquet, 2003; Chiquet-Ehrismann and Tucker, 2011). Of the other family members, tenascin-R is found exclusively in the developing and adult nervous system (Rathjen et al., 1991). Tenascin-X is present primarily in skin and muscle ECM, and mutations in this protein cause Ehlers Danlos syndrome associated with mild myopathy both in mice (Voermans et al., 2011) and man (Voermans et al., 2009). Finally, tenascin-W is expressed in kidney, smooth muscle, and most prominently in pre-osteogenic areas in the embryo and periosteum in the adult (Scherberich et al., 2004).

Many in vitro experiments have been performed to gain insight into the interactions and cellular functions of tenascins, but results turned out to be context-dependent and sometimes conflicting. Tenascins are neither obligatory structural components of ECM, nor are they unequivocal cell adhesion proteins like, for example, fibronectin (Chiquet-Ehrismann and Chiquet, 2003; Chiquet-Ehrismann and Tucker, 2011). Rather, a general consensus developed from these experiments that tenascins primarily change the interactions of cells with other ECM components and with growth factors, and thereby modulate cell adhesion, spreading, migration, and proliferation in a cell-type- and context-

Abbreviations: APC, antigen-presenting cell; CAR, CXCL-12–abundant reticular; DC, dendritic cell; EGF, epidermal growth factor; ECM, extracellular matrix; DKK, dickkopf; FNIII, fibronectin type III; FBG, fibrinogen-like; 5-FU, fluorouracil; HSC, hematopoietic stem cell; HUVEC, human umbilical vascular endothelial cell; LPS, lipopolysaccharide; miR, microRNA; NK, natural killer cell; TLR4, toll-like receptor 4; TNC, tenascin-C; SVZ, subventricular zone.

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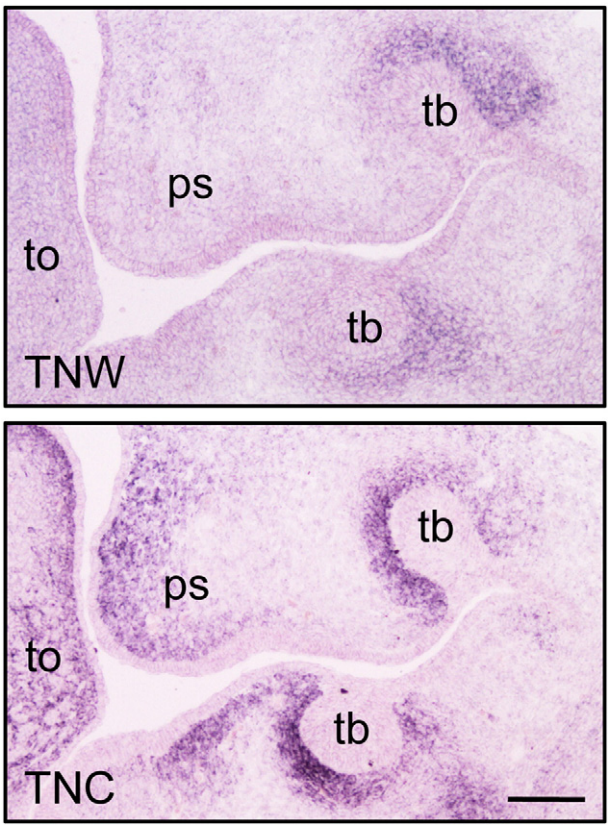

Fig. 1. *Expression of tenascins around embryonic tooth buds.* In situ hybridization of frontal serial sections through the head of a E13.5 mouse embryo, probed for tenascin-W (TNW) and tenascin-C (TNC) mRNA, respectively. Sections were counterstained with neutral fast red (pink); the specific signal appears purple. At the bud stage, the two tenascins are expressed in the mesenchyme surrounding the invaginating dental epithelium. At later stages, these cells will differentiate into odontoblasts, pulp and periontontal ligament cells. Note that tenascin-W is preferentially expressed at the buccal, and tenascin-C at the lingual aspect of the molar tooth buds (S. Blumer and M. Chiquet, unpublished. For methods and RNA probes see d'Amaro et al., 2012). to, tongue; ps, palatal shelf; tb, tooth bud. Bar, 100 μm.

dependent manner. For this reason, they have been classified within the heterogeneous group of "matricellular" proteins (Roberts, 2011). For example, tenascin-C inhibits the spreading of fibroblasts by blocking the interaction of fibronectin with cellular syndecan-4 (Huang et al., 2001), a mechanism that indirectly inhibits full activation of integrin α5β1 and the RhoA/ROCK pathway (Midwood and Schwarzbauer, 2002). Presumably as a consequence of this "anti-adhesive" (or rather anti-spreading) activity, tenascin-C negatively affects the growth of normal fibroblasts (Orend et al., 2003), but stimulates proliferation and migration of cancer cells (Ruiz et al., 2004; Orend, 2005). On the other hand, tenascin-C appears to be a bona fide cell adhesion protein for lymphoid and certain other cell types, mediating direct interactions with cellular integrin α9β1 (Schreiber et al., 2009; Ellis et al., 2013). Such a Janus-like activity can have paradoxical effects. As a substrate for embryonic sensory ganglion explants, for example, tenascin-C promotes neurite growth but at the same time inhibits glial cell migration (Wehrle-Haller and Chiquet, 1993). Similar bimodal activities have been ascribed to tenascin-R and tenascin-W (Chiquet-Ehrismann and Tucker, 2011).

Prompted by its intriguing expression pattern in embryonic development, the tenascin-C gene was among the very first to be deleted by homologous recombination in mice. Much to the surprise of involved researchers at the time, the knockout mice were born apparently normal (Saga et al., 1992), leading to the suggestion that tenascin-C was a "superfluous" protein (Erickson, 1993). After frustrating experiences in the following decade, during which many other "important" genes were knocked out in mice causing either no or an unexpected phenotype, the importance of redundancy and compensatory mechanisms was recognized in vertebrate development (Humbert et al., 2004). Work on tenascin-C function was slowly resumed, and recent data indicate that although dispensable for normal development, this ECM component is a stress protein whose importance becomes apparent when organ homeostasis is challenged by physical or chemical injury, mechanical overload, infection, or cancer (Midwood et al., 2011). A similar general statement can be made for the other family members (tenascin-X in addition appears to have a structural function; see above). As already mentioned, tenascins are prominently expressed at sites of tissue renewal, injury, and regeneration (Chiquet-Ehrismann and Chiquet, 2003). Not surprisingly, therefore, new data indicate that these ECM proteins are important functional components of various stem cell niches (both physiological and pathological) and are involved in stem cell maintenance and renewal. Current evidence is reviewed in the following chapters.

2. Tenascins in development and organ turnover

The most conspicuous phenotypes reported for mice lacking tenascin-C were (1) their abnormal nervous system development and organization which was accompanied by accelerated maturation of oligodendrocyte precursors and reduced proliferation of oligodendrocyte precursors (Garcion et al., 2001, 2004), and (2) their abnormal responses to injury and stress after snake venom induced glomerulonephritis (Nakao et al., 1998), reduced recruitment of myofibroblasts after myocardial injury (Tamaoki et al., 2005) or reduced fibrosis during hepatitis (El-Karef et al., 2007). A recent summary of the phenotypes reported for tenascin-C deficient mice can be found in Chiquet-Ehrismann and Tucker (2011). Together with the restricted expression of tenascin-C at sites of organogenesis these phenotypes suggested a function of tenascin-C in certain stem cell niches affecting proliferation and differentiation of stem or progenitor cells involved in either creating an organ during development or providing a niche for progenitors for normal organ turnover or regeneration after injury.

2.1. Neural stem cell niches

Indeed, the functions of tenascin-C in the neural stem cell niche are well documented. Tenascin-C is abundant in the subventricular zone (SVZ) of the central nervous system, both during development and in the adult. The subsequent identification of neural stem cells in the SVZ led to this ECM-enriched niche being described as "brain marrow" (Thomas et al., 1996). Tenascin-C in the neural stem cell niche regulates cell proliferation. This was first demonstrated by Garcion et al. (2001), who showed decreased BrdU incorporation in the SVZ of the lateral ventricles of postnatal tenascin-C knockout mice. A second role for the tenascin-C found in neural stem cell niches was proposed by Garwood et al. (2004), who cultured oligodendrocyte precursor cells from tenascin-C enriched parts of the brain on ECM made by either wild type astrocytes or astrocytes from tenascin-C knockout mice. They observed more rapid differentiation of the oligodendrocyte precursors in the absence of tenascin-C. Tenascin-C may regulate proliferation and differentiation through the RNA binding protein Sam68. Using a gene trap-based screen, Moritz et al. (2008) found that Sam68 is downregulated by tenascin-C in cultured neural stem cells. Increased expression of Sam68 leads to a decrease in the proliferation of glial precursors in vitro (Moritz et al., 2008) and results in a delay in the appearance of oligodendroglia (Czopka et al., 2010). Interestingly, another BrdU incorporation study revealed increased proliferation in the ventral-most part of the SVZ of the spinal cord of tenascin-C knockout mice during the embryonic period corresponding to the onset of gliogenesis (Karus et al., 2011). The BrdU-positive cells were positive for FGF3 expression, a marker of immature astrocytes. Thus, tenascin-C may play different roles in the proliferation and appearance of different types of glia.

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Karus et al. (2011) also noted that the increase in immature astrocytes in the spinal cords of the knockout mice did not result in an increase in astrocytes in the white matter, suggesting that migration was negatively impacted by the lack of tenascin-C. These studies demonstrate that tenascin-C in neural stem cell niches is necessary for the normal proliferation, differentiation and migration of different glial types. It is interesting to compare these observations with those studying the effects of tenascin-R on neural stem cells. Tenascin-R deficiency promotes neuronal differentiation and inhibits proliferation of neural stem cells in the adult dentate gyrus (Xu et al., 2013). Prenatally, tenascin-R, secreted by niche cells, binds to β1-integrin receptors on neural stem cells to facilitate self-renewal and the absence of tenascin-R in *Tnr* −/− mice leads to increased numbers of GABAergic interneurons (Xu et al., 2013). Recombinant fragments corresponding to the EGF repeats of tenascin-R increase the differentiation of neurons from cultured neurospheres. Conversely, fragments of FNIII domains 6–8 decrease neural stem cell proliferation while increasing the appearance of astrocytes (Liao et al., 2008). Also in contrast to tenascin-C, which generally promotes cell migration, both the FNIII domains 6–8 and the EGF repeats of tenascin-R can inhibit the migration of cells from neural stem cell-derived neurospheres in vitro (Huang et al., 2009).

2.2. Epithelial stem cell niches and pluripotent stem cells

Tenascin-C is also present in human corneal development and is expressed in preterm cornea. Levels are reduced in neonates and expression is restricted to the limbus in the child and adult (Maseruka et al., 2000). The limbal stem cells are responsible for the maintenance of the cornea. In a screen for limbal-specific transcripts, Wnt and TGF-β/BMP signaling components as well as tenascin-C were identified (Nakatsu et al., 2013). In a similar screen using the vervet monkey, tenascin-C was also found to be one of the limbal-specific transcripts (Ding et al., 2008). At the basal side of the limbal epithelial stem cells, limbal fibroblasts and melanocytes are located forming the corneal epithelial stem cell niche (Secker and Daniels, 2008). This is the area where tenascin-C is located. tenascin-C is also found in the niche of the limbus in the mouse, as is tenascin-W (Scherberich et al., 2004).

Skin and hair represent another tissue with a high turnover requiring pools of stem cells, not only to replenish the epithelium and the keratinized hair, but also as a source of melanocytes that give color to these tissues. There are two main stem cell compartments in whiskers: the keratin-15-positive epithelial stem cells of the bulb region and an undifferentiated pluripotent nestin and CD34-positive, keratin-15-negative stem cell population in the trabecular region (Amoh et al., 2010). When CD34-positive, keratin-15-negative cells are cultured, they can differentiate into neurons, glia, keratinocytes, smooth muscle cells, adipocytes and melanocytes (Amoh et al., 2005; Wong et al., 2006). Tenascin-C was identified in the bulge region of human hair follicles adjacent to keratin-15 positive epithelial stem cells (Kloepper et al., 2008; Fig. 2A). Interestingly, we found tenascin-C and tenascin-W in the stem cell niche of mouse whiskers adjacent to the bulge region harboring the epithelial stem cells (Tucker et al., 2013). This adjacent trabecular region contains pluripotent CD34-positive stem cells that may be derived from neural crest, which are surrounded by a tenascin-rich matrix (Fig. 2B). It has been proposed that the CD34-positive stem cells migrate from their niche along the glassy membrane to the whisker bulb to participate in the formation of the whisker shaft (Amoh et al., 2010), and when these cells are cultured on tenascin-C or tenascin-W they acquire a motile phenotype (Tucker et al., 2013). Tenascin-C, but not tenascin-W, also promotes the proliferation of these cells in vitro (Tucker et al., 2013). In addition to the niches described in more detail above, the dental pulp stem cell niche was also found to contain tenascin-C (Liu et al., 2007; Miyagi et al., 2012), and in cultures tenascin-C was associated with the cells that showed odontoblast-like differentiation and mineralization (Liu et al., 2007).

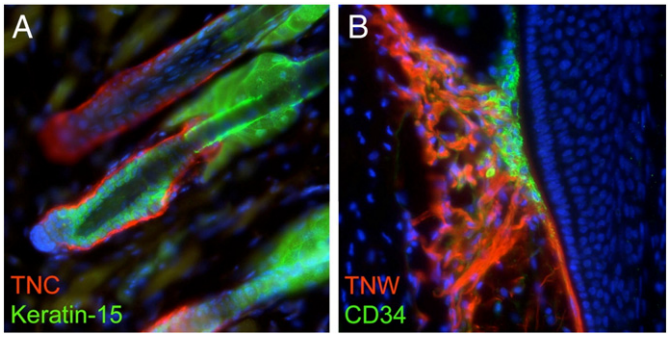

Fig. 2. *Tenascin-C and tenascin-W in stem cell niches of hair and whisker follicles.* (A) Tenascin-C is found in the matrix surrounding the keratin-15-positive bulge of facial hair follicles. (B) CD34-positive stem cells are embedded in a tenascin-W-rich extracellular matrix in the trabecular region immediately adjacent to the bulge of whisker follicles. For more details, see Tucker et al. (2013).

2.3. Osteogenic stem cell niche

Another stem cell compartment exists in the periosteum, which is crucial for the turnover of bone. It consists of an outer fibrous layer containing fibroblasts and a cambium layer harboring the progenitor cells that develop into osteoblasts. Using transgenic mice with tamoxifen-inducible Cre recombinase and GFP under the control of a 2.4 kb *Prx1* promoter, GFP-expressing periosteal cells could be isolated that expressed Prx-1 and other periosteal markers, including tenascin-W (Kawanami et al., 2009). These GFP-expressing periosteal cells showed chondrogenic and osteogenic potential in vitro and in vivo (Kawanami et al., 2009). Both during development as well as in adult bone these layers are rich in tenascins. While tenascin-C is more abundant in the fibrous layer, tenascin-W is particulary abundant in the stem cell niche of the cambium where the osteoblast progenitors are located (Scherberich et al., 2004). Similarly, tenascin-W was detected in osteoblasts at the edge of developing bone prior to mineralization and in culture tenascin-W was induced during mineralization of an osteoblast cell line (Mikura et al., 2009). Functionally, addition of tenascin-C and tenascin-W increased the emergence of mineralized foci in primary cultures of chicken osteoblasts, and addition of tenascin-W to embryonic frontal bone explants accelerated new bone formation (Meloty-Kapella et al., 2008). Using a different model it was found that addition of recombinant tenascin-W suppressed canonical Wnt signaling, thereby inhibiting proliferation and differentiation of the pre-osteoblast cell line MC3T3-E1. Thus, tenascin-W seems to be active at later stages of osteogenesis during maturation and mineralization (Kimura et al., 2007). The periosteal stem cells are also important in the adult and expression of both tenascin-C and -W increases during fracture healing (Kimura et al., 2007; Kilian et al., 2008).

3. Tenascin-C and inflammation

Our immune response is designed to protect us from danger posed by pathogen invasion and tissue injury. Innate immunity, our first line of defense, provides non-specific protection against these insults whereas adaptive immunity is antigen-specific and provides lifelong immunological memory. Tenascin-C contributes to the immune response in two distinct ways. Although possessing a restricted postnatal distribution, tenascin-C is constitutively expressed in the adult bone marrow, thymus, spleen and lymph nodes where it helps to create a specific niche that supports immune cell proliferation, differentiation and function. In addition, tenascin-C is specifically up-regulated at sites of tissue injury and infection, where it also controls immune cell behavior.

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3.1. The hematopoietic niche

The bone marrow is the major postnatal site of hematopoiesis. All blood cells derive from a common hematopoietic stem cell (HSC), which resides in a specific compartment of the bone marrow, the hematopoietic niche (Schofield, 1978). Traditionally, megakaryocytes, erythrocytes, mast cells, basophils, neutrophils, eosinophils, monocytes and macrophages were thought to arise from common myeloid progenitor cells derived from HSCs, with natural killer cells, and T and B lymphocytes deriving from common lymphoid progenitor cells. However, some degree of plasticity between the two lineages has been observed (Dzierzak and Speck, 2008). HSCs do not exist in isolation in the bone marrow; the stroma of the hematopoietic niche also contains a range of cell types including fibroblasts, adipocytes, osteoblasts, osteoclasts and endothelial cells. Interaction of HSCs with stromal cells is crucial for HSC maintenance, proliferation and differentiation (Ehninger and Trumpp, 2011) and stromal cells synthesize ECM molecules and soluble factors that modulate HSC behavior (Mercier et al., 2012).

Tenascin-C is expressed specifically in the periosteal region and artery walls in healthy bone marrow. Expression increases in abnormal marrow, for example in myeloid leukemia and myelofibrosis (Soini et al., 1993). Thin fibers containing tenascin-C fill the intersinusoidal spaces between bone marrow cells in human and murine marrow, and bone marrow cell cultures also deposit tenascin-C positive fibers between cells. Adherent stromal cells were identified as the source of tenascin-C in bone marrow cell populations, rather than the non-adherent HSCs and progenitor cells (Ekblom et al., 1993; Klein et al., 1993). Stromally expressed tenascin-C acts to anchor HSCs; adhesion of freshly isolated bone marrow cells to preformed stromal cell layers was inhibited by anti-tenascin-C antibodies and hematopoietic cell lines adhered to purified tenascin-C (Klein et al., 1993). Moreover, interaction of HSCs with tenascin-C markedly enhanced cell proliferation (Seiffert et al., 1998).

These adhesive and mitogenic capabilities of tenascin-C appear to be important in driving HSC differentiation. The bone marrow, as well as the resting hematocrit, white blood cell count and bone marrow mononuclear cell count were not different in mice lacking tenascin-C (*Tnc* −/−) compared to wild type (*Tnc*+/+) mice (Ohta et al., 1998). However, long term bone marrow cultures from *Tnc*−/− mice produced markedly lower numbers of non-adherent hematopoietic cells than *Tnc*+/+ mice. Cells also survived for less time in culture. Moreover, the capacity of bone marrow cells to form multi-lineage colonies was also reduced in *Tnc*−/− mice. Addition of exogenous tenascin-C to the *Tnc*−/− cultures rescued these defects, but only when added to heterogeneous cultures containing stromal cells. It had no effect when added to the HSC or progenitor cell population in the absence of the stromal cells (Ohta et al., 1998). Consistent with these data, tenascin-C expression by bone marrow stromal cell lines isolated from SV40-T antigen transgenic mice specifically confers the ability of stromal cells to support erythroid colony formation by liver derived cells in co-culture (Seki et al., 2006). Together these data imply that stromal tenascin-C expression drives hematopoiesis, not by directly acting on progenitor cells, but by enhancing stromal cell-mediated HSC adhesion and proliferation.

Most recently, Nakamura-Ishizu et al. (2012) confirmed that steady-state hematopoietic parameters of *Tnc* −/− mice (peripheral blood counts, bone marrow cellularity, HSC frequency, bone marrow lineage composition, and HSC proliferation) were similar to *Tnc* +/+ mice. However, tenascin-C expression was transiently upregulated in *Tnc* +/+ mice following myeloablation with injection of fluorouracil (5-FU) or sublethal irradiation, returning to baseline levels concomitant with hematopoietic recovery. After these treatments, *Tnc*−/− mice showed higher lethality, with delayed white blood cell, hemoglobin and platelet recovery, and reduced proliferating bone marrow HSCs. Transplantation of *Tnc*+/+ bone marrow cells into irradiated *Tnc*−/− mice did not rescue these defects, indicating that tenascin-C expression in the bone marrow niche, rather than in HSCs, is important for hematopoietic recovery. Upon myeloablation, tenascin-C was predominantly expressed by CXCL-12–abundant reticular (CAR) cells, a subpopulation of stromal cells that drive the proliferation and maintenance of HSCs. Tenascin-C was located in close contact with HSCs, which themselves expressed little tenascin-C but did express high levels of α9β1 integrins, receptors that bind to the FNIII3 domain within tenascin-C (Nakamura-Ishizu et al., 2012). Indeed, neutralizing antibodies to α9-integrin inhibited HSC proliferation and adhesion to primary cultured osteoblasts (Schreiber et al., 2009). In addition, purified HSCs adherent to a mixture of fibronectin and tenascin-C exhibited enhanced proliferation in an α9-integrin dependent manner compared to cells on fibronectin alone (Nakamura-Ishizu et al., 2012). However, studies using recombinant tenascin-C fragments identified that the FBG domain and FNIII repeats 1–5 and 6–8 can support the adhesion of bone marrow cell isolates. Adhesion to all 3 sites was β1-integrin independent, but binding to FBG and FNIII6-8 was inhibited by heparin. Moreover, the FBG and the alternatively spliced FNIII domains were shown to stimulate proliferation, while FNIII3 containing domains variously had no effect, or inhibited, cell proliferation (Seiffert et al., 1998). As ever, experimental context and cell type seem to be key to defining the response to tenascin-C in vitro.

3.2. The lymphoid progenitor cell niche

In addition to the bone marrow, maturation, activation and proliferation of lymphocytes also occurs in the lymphoid tissues. A small number of HSCs enter the thymus from the blood where they differentiate and expand to generate a large population of immature T cells each expressing a distinct T-cell receptor. Cells that possess autoreactive receptors are eliminated and those with functional receptors survive. Thus the thymus acts as a primary lymphoid tissue that supports HSC differentiation, but which also drives central tolerance. Secondary or peripheral lymphoid organs, such as the lymph nodes and spleen, maintain these immature T cells, and it is here that they encounter activated APCs, whereupon they expand and mature before circulating in search of their specific antigen.

Tenascin-C is expressed during rodent thymus development, persisting after birth (Saga et al., 1991; Hemesath and Stefansson, 1994). It localizes to the thin network of delicate fibers that surround thymic fibroblast-like reticular cells, and is similarly distributed in the reticular networks of postnatal murine lymph nodes and spleen (Ocklind et al., 1993). In the human thymus and spleen tenascin-C is also laid down in the reticular meshwork, starting from gestation week 18 and remaining in the adult (Hemesath and Stefansson, 1994; Freitas et al., 1995). Electron microscopy revealed cytoplasmic tenascin-C in fetal reticular cells (Liakka et al., 1995) and indeed cultured human thymic reticular cells synthesize tenascin-C, expression which is inducible in the absence of serum by TGF-β (Hemesath and Stefansson, 1994). In reactive lymph nodes, tenascin-C is predominantly found in the reticular network of T-cell dependent zones and this network appears thicker in chronically stimulated tissues, for example, sarcoid lymph node, myasthenic hyperplastic thymus, Hodgkin's disease, malignant follicular lymphoma and hairy cell leukemia (Soini et al., 1992; Chilosi et al., 1993).

Tenascin-C rich reticular fibers contain fibronectin, laminin and collagen fibrils, to which tenascin-C binds (Tanaka et al., 1996). Ultrastructural analyses of human, monkey and rodent lymph nodes confirmed reticular expression of tenascin-C in T-cell rich areas, specifically within basement membrane-like sheaths covering reticular fibers and within the fibers (Kaldjian et al., 2001; Sobocinski et al., 2010). Their appearance corresponds with the beginning of lymphatic colonization, raising the possibility that they aid this process by forming a framework to which cells can attach and migrate upon (Liakka and Autio-Harmainen, 1992). Indeed, tenascin can support lymphocyte tethering and rolling under flow conditions in vitro via its FBG domain (Clark et al., 1997), as well as enhancing lymphocyte infiltration into the

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liver during chronic hepatitis in mice (El-Karef et al., 2007). Moreover, the FNIII1-5 domains of tenascin-C prevent T-cell β1-integrin–dependent adhesion to fibronectin (Hauzenberger et al., 1999). These studies indicate that tenascin-C may form a 'T-cell highway' in the reticular network of lymphoid tissues, creating pathways free from fibrillar ECM, breaking strong adhesive bonds, and providing molecular "footholds" to aid movement. However, tenascin-C can also inhibit transmigration of activated T cells and Jurkat cells by reducing their pro-migratory morphology and delaying ERK activation (Huang et al., 2010), suggesting it may also act as a stop signal for T-cells that have arrived at their destination. Most recently, Ellis et al. (2013) revealed that tenascin-C is a key orchestrator of peripheral T-cell migration in vivo. While *Tnc* −/− mice have similar numbers of HSCs in the bone marrow compared to *Tnc* +/+ mice, they exhibit specific defects in CD3+ T-cells. Lower numbers of T-cell progenitors were also observed in the thymus; this was not due to changes in cell proliferation but instead progenitor cell redistribution to the spleen and lymph nodes, where they are not usually detected. This altered lymphoid progenitor cell homing to the thymus was dependent on α9β1 integrin expression (Ellis et al., 2013). Together these data provide evidence of the importance of tenascin-C in facilitating the recruitment of T-cells to the lymphoid tissues.

Accumulating evidence also highlights a role for tenascin-C in directly affecting T-cell behavior, although these reports are not yet easy to reconcile. Exogenously added tenascin-C inhibits proliferation of human peripheral blood CD4+ T-cells activated by anti-CD3, alone or in combination with other stimuli such as anti-CD28, fibronectin and IL-2 (Hemesath et al., 1994; Hibino et al., 1998; Puente Navazo et al., 2001; Parekh et al., 2005). It also inhibits CD4+ T-cell proliferation induced by mitogens, alloantigens or tetanus toxin antigen (Gundersen et al., 1997; Puente Navazo et al., 2001; Parekh et al., 2005) but has no effect on proliferation induced by phorbol ester (Hemesath et al., 1994; Hibino et al., 1998). However, tenascin-C has also been shown to play a role in promoting T-cell activation and polarization. It induces IL-5, IL-13 and IFNγ expression in murine spleen lymphocytes, and *Tnc* −/− mice are protected from bronchial asthma due to a dampened Th2 response (Nakahara et al., 2006). Tenascin-C also drives Th17 cell polarization in vitro (Kanayama et al., 2009; Kanayama et al., 2011; Ruhmann et al., 2012) and *Tnc* −/− mice fail to mount IL-17 mediated inflammation in models of rheumatoid arthritis (Midwood et al., 2009; Ruhmann et al., 2012).

3.3. The site of inflammation — a pro-inflammatory niche?

This idea that the ECM creates specialized niches to locally modulate cell behavior is not at all new, although it is rarely applied to the distinct ECM that is induced at sites of tissue injury. This transient ECM comprises a number of injury specific matrix molecules including tenascin-C, which is rapidly induced upon damage where it acts as a rather unique pro-inflammatory stimulus. This aspect of tenascin-C biology has been recently reviewed in Midwood and Orend (2009) and Udalova et al. (2011) and is summarized below. Unlike most inflammatory mediators, such as cytokines or growth factors, which comprise small, soluble molecules of a limited half-life, tenascin-C accumulates as part of a dense matrix specifically assembled at the site of injury. This physical presence can provide a scaffold for immune cell adhesion (Ruegg et al., 1989) and migration (Talts et al., 1999; Loike et al., 2001; Sumioka et al., 2011, 2013). It also directly interacts with cells to stimulate inflammatory behavior, although the mechanisms by which these functions are mediated are proving complex. For example, tenascin-C can induce cytokine, chemokine and protease expression using distinct mechanisms; activation of toll-like receptor 4 (TLR4) in primary human macrophages, synovial fibroblasts, chondrocytes and murine neutrophils (Midwood et al., 2009; Kuriyama et al., 2011; Patel et al., 2011; Liu et al., 2012) and activation of α9-integrin in primary murine and human arthritic synovial fibroblasts, macrophages and dendritic cells (Kanayama et al., 2009, 2011; Asano et al., 2013). It achieves this via ligation of integrins using FNIII3 (Kanayama et al., 2009, 2011) and activation of TLR4 via FBG (Midwood et al., 2009). Whether or not there is a direct interaction of the FBG of tenascin-C with TLR4 remains to be elucidated. In addition to driving de novo synthesis of pro-inflammatory mediators, it can also bind directly to these mediators; it interacts with a range of growth factors including FGF, PDGF and TGFβ via its FNIII5 repeat (De Laporte et al., 2013). As such it may further potentiate inflammation by acting as a reservoir for soluble mediators enabling their presentation in an active form at high local concentrations to immune cells.

Evidence is also emerging that tenascin-C plays a role in pathogen defense. Tenascin-C binds to *Streptococcus* (Vollmer et al., 2010), suggesting it may promote pathogenicity by maintaining elevated infectious tissue titers. Two recent papers also show that tenascin-C can directly modulate inflammation mediated by bacterial lipopolysaccharide (LPS) and in response to HIV. During sepsis induced by LPS, tenascin-C is essential for a robust early inflammatory response; it sustains the translation of pro-inflammatory cytokines by enhancing expression of the microRNA (miR) mir155 (Piccinini and Midwood, 2012). Conversely, tenascin-C was recently identified as a breast milk derived factor that confers very effective protection from HIV by binding to the V3 loop of the virus, preventing ligation of the envelope protein with CD4 and ablating subsequent immune activation (Fouda et al., 2013). Table 1 summarizes the different roles of tenascin-C during inflammation mediated by its expression at distinct sites throughout the body.

4. Tenascin-C in the metastatic niche

Tumor cells can spread from the primary site and form a new tumor at a different site within the same or another organ, which is defined as metastasis. Distant metastases can occur in several organs. To establish metastases, tumor cells migrate away from the primary tumor, travel through tissue, breach into blood or lymph vessels and exit from there to home to the distant organ where the tumor cells can colonize the tissue and establish micrometastases (sometimes with many years of dormancy) and macrometastases which ultimately destroy the organ and kill the patient (Chambers et al., 2002).

4.1. Expression of tenascin-C in metastasis

Disseminated tumor cells must find a supportive microenvironment (allowing survival and promoting proliferation) to establish a metastatic colony. This concept has been formulated by Paget (1989) as "seed and soil" hypothesis and suggests that the metastatic niche is prepared by the arriving tumor cells (the seed) and the organ microenvironment (the soil). The metastatic niche represents a specialized microenvironment that supports maintenance and growth of metastasis-initiating cells (Psaila and Lyden, 2009). How much the metastasis-initiating phenotype resides within the tumor cell itself and/or is determined by the microenvironment is a matter of debate and presumably a combination of both possibilities. The metastatic niche can be considered as a specialized microenvironment composed of a specific ECM, soluble factors and stromal and cancer cells secreting these molecules. Due to its high expression linked to metastasis, tenascin-C appears to be an important component of metastatic niches.

High tenascin-C expression in the primary tumor correlates with metastasis to lymph nodes, liver and lung, and was shown to be a predictor for poor prognosis (Midwood et al., 2011). Also, a high expression of tenascin-C in lung tissue of breast cancer patients correlated with reduced survival time until manifestation of lung metastases (Oskarsson et al., 2011). Together these observations suggest a role of tenascin-C in the primary tumor and the site of metastasis. However, we have little knowledge about the molecular mechanisms that underlie the pro-metastatic role of tenascin-C. We know that tenascin-C expression by either tumor or stromal cells in the primary tumor can promote cancer

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Table 1
The impact of tenascin-C on immune cell differentiation and function.

Process	Function	Location	Reference
Pathogen invasion	Supports streptococcal adhesion	Site of infection	Vollmer et al. (2010)
	Stimulates sustained cytokine translation upon bacterial infection by promoting macrophage expression of miR-155	Site of infection; circulating	Piccinini and Midwood (2012)
	Protects from HIV via binding to V3 loop of virus	Breast Milk	Fouda et al. (2013)
Thrombosis	Supports platelet adhesion and promotes platelet activation	Circulating	Schaff et al. (2011)
Innate immunity	Stimulates hematopoiesis (myeloid cells, NK cells); supports HSC adhesion and proliferation	Hematopoietic niche of bone marrow (adult); liver (fetus)?	Klein et al. (1993), Nakamura-Ishizu et al. (2012), Ohta et al. (1998), Papadopoulos et al. (2004), Seiffert et al. (1998), Seki et al. (2006)
	Promotes monocyte adhesion	Site of inflammation	Ruegg et al. (1989)
	Inhibits myeloid cell migration	Site of inflammation; circulating?	Loike et al. (2001), Talts et al. (1999)
	Stimulates macrophage migration	Site of inflammation; circulating?	Sumioka et al. (2011, 2013)
	Stimulates TLR4-mediated cytokine synthesis	Site of inflammation	Kuriyama et al. (2011), Liu et al. (2012), Midwood et al. (2009), Patel et al. (2011)
	Stimulates integrin-mediated cytokine synthesis	Site of inflammation	Asano et al. (2013), Kanayama et al. (2009, 2011)
	Binds to a variety of growth factors	Site of inflammation?	De Laporte et al. (2013)
Adaptive immunity	Stimulates hematopoiesis; supports HSC adhesion and proliferation (lymphoid cells)	Hematopoeitic niche of bone marrow, thymus	Klein et al. (1993), Nakamura-Ishizu et al. (2012), Ohta et al. (1998), Seiffert et al. (1998), Seki et al. (2006)
	Creates reticular network and fibrous scaffold	Lymphoid tissues (thymus, lymph node, spleen)	Kaldjian et al. (2001), Sobocinski et al. (2010)
	Directs T cell homing	Thymus	Ellis et al. (2013)
	Promotes lymphocyte migration	Reticular network of lymphoid tissues?	Clark et al. (1997), El-Karef et al. (2007), Hauzenberger et al. (1999)
	Limits T cell actin polymerization and migration	Reticular network of lymphoid tissues?	Huang et al. (2010)
	Regulates proliferation of T lymphocytes	Lymphoid tissues?	Hemesath et al. (1994), Hibino et al. (1998), Parekh et al. (2005), Puente Navazo et al. (2001), Gundersen et al. (1997)
	Create small bi-membranous conduits for transport of small mediators from the blood	Lymphoid tissues	Drumea-Mirancea et al., 2006
	Drives Th17 cell polarization	Lymph node	Kanayama et al. (2011), Ruhmann et al. (2012)
	Stimulates Th2 and B cell activation	Lymph node?	Kuhn and Mason (1995), Nakahara et al. (2006)
	Inhibits T cell activation	Lymph node?	Kuznetsova and Roberts (2004)

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cell dissemination and survival in the circulation. A promoting role of tenascin-C on proliferation, migration, invasion and epithelial-to-mesenchymal transition, which represent crucial steps in metastasis, is also known and has been extensively reviewed (Orend and Chiquet-Ehrismann, 2006; Midwood and Orend, 2009; Midwood et al., 2011; Brellier and Chiquet-Ehrismann, 2012). Here we will focus on the role that tenascin-C plays in establishing a metastasis promoting microenvironment, the metastatic niche, and will describe recent experiments that reveal this role of tenascin-C.

4.2. Organization of tenascin-C in tumor matrix networks

Originally tenascin-C was reported to decorate ECM fibrils that possess a backbone of fibronectin or collagens (Chiquet and Fambrough, 1984), but whether tenascin-C can assemble into fibrillar networks on its own is unclear. Chen et al. (2009) showed that organization of tenascin-C into a fibrillar network correlated with metastasis in pancreatic cancer and this network formation was associated with MMP2 expression and activity. Fibroblasts co-cultured with pancreatic cancer cells secreted a fibrillar network containing tenascin-C, and this network formation was blocked with an MMP2 inhibitor. Support of a potential link of tenascin-C and MMP2 to metastasis is provided by a combined high expression of tenascin-C with MMP2 in breast cancer lung metastasis (Calvo et al., 2008).

Tenascin-C containing fibrillar networks have also been found in metastatic melanoma (Kaariainen et al., 2006). In melanoma, high tenascin-C mRNA expression correlates with invasiveness and metastasis. Moreover, the tenascin-C protein was found to assemble together with several other ECM molecules such as fibronectin, laminins and pro-collagen I into channel-forming matrix tracks. Melanoma cells were located within these matrix channels that are different from blood or lymphatic vessels since they lack endothelial cells (Kaariainen et al., 2006). While the origin of these matrix tracks is unclear (it is possible that they represent remnants of pruned blood or lymphatic vessels and/or originate from a genetic program that generates reticular fibers in the thymus and spleen), it is conceivable that tenascin-C positive matrix tracks contribute to metastasis by e.g. providing dissemination cues and/or local niches that promote survival of disseminated tumor cells, which has been extensively addressed (Midwood et al., 2011; Van Obberghen-Schilling et al., 2011).

Tenascin-C also forms matrix networks together with periostin (Kii et al., 2010). This observation is highly interesting since periostin also plays a role in promoting breast cancer lung metastasis as demonstrated in the MMTV-PyMT breast cancer model (Malanchi et al., 2012). Both ECM molecules may collaboratively promote metastasis through activation of Wnt signaling. Whereas periostin binds Wnt ligands and stimulates signaling that promotes colonization of metastasis-initiating cells presumably by presenting the Wnt ligand to its receptors (Malanchi et al., 2012), tenascin-C may generate a Wnt permissive microenvironment by downregulating the Wnt inhibitor DKK1, stabilizing β-catenin (Ruiz et al., 2004) and promoting expression of Wnt target genes (Oskarsson et al., 2011; Saupe et al., 2013). Although the hypothesis of a potential collaborative Wnt signaling activation by tenascin-C and periostin in driving breast cancer lung metastasis is intriguing, it lacks confirmation in the same model.

4.3. Role of tenascin-C in the tumor angiogenic niche

Tumor growth strongly depends on the supply of nutrients and oxygen. In the course of tumor development, the angiogenic switch is considered a crucial event in promoting malignancy (Hanahan and Weinberg, 2011). The angiogenic switch in development and cancer is characterized by vessel sprouting, new vessel formation, vessel maturation, and the recruitment of perivascular cells (Bergers and Benjamin, 2003). New blood vessels can be triggered by several factors including hypoxia, ECM molecules and pro-angiogenic growth factors. In tumors the newly formed vessels are frequently found to be highly chaotic (Shang et al., 2012). A recent study suggests that sites of new blood vessel formation, and in particular vessel sprouts represent a microenvironment that promotes metastasis. Whereas a stable microvasculature constitutes a dormant niche, sprouting neovasculature in metastatic tissue seems to promote micrometastatic outgrowth of dormant tumor cells. Thrombospondin-1 has been found to be associated with the stable microvasculature whereas periostin was associated with the sprouting vasculature (Ghajar et al., 2013). Given common networks of periostin with tenascin-C in tumor tissues, it is likely that in addition to periostin also tenascin-C plays a role in promoting sprouting angiogenesis associated with metastasis. This possibility is supported by cell culture experiments where tenascin-C (the FBG domain in particular) has been shown to promote bFGF-induced sprouting angiogenesis of bovine aortic endothelial cells (Schenk et al., 1999). Sprouting of human umbilical vein endothelial cells towards a source of tenascin-C was also seen in collagen gels (Martina et al., 2010; Fig. 3). Finally, also in the experimental PNET/Rip1Tag2 insulinoma model tenascin-C promoted tumor angiogenesis, which supports a role of tenascin-C in vessel sprouting in vivo (see next paragraph).

The role of tenascin-C in tumor angiogenesis was recently addressed in the PNET/Rip1Tag2 insulinoma model of multi stage tumorigenesis (Hanahan, 1985), which was used to generate the first stochastic tumor model with defined tenascin-C expression levels (Saupe et al., 2013). We generated Rip1Tag2 mice with either no or abundant tenascin-C expression, using *Tnc* −/− mice and mice with transgenic overexpression of human tenascin-C, respectively. In Rip1Tag2 mice with no or abundant tenascin-C expression, we found that the extent of angiogenesis correlated with the tenascin-C copy number. The number of endothelial cells/vessel density was highest in tumors with expression of transgenic tenascin-C and lowest in tumors lacking tenascin-C. We also observed that tenascin-C promoted the angiogenic switch suggesting an active role of tenascin-C in vessel sprouting, yet the underlying mechanism is not clear. Although tenascin-C promoted blood vessel formation, these vessels were highly abnormal (irregularly shaped, wider, discontinued, and bifurcated) and less functional in tumors overexpressing transgenic tenascin-C. Whether high expression of tenascin-C in the primary tumor had an impact on the lung vasculature potentially promoting lung metastasis was not analyzed, yet a correlated high tenascin-C expression in the primary tumor with increased lung micrometastasis is supportive of such a possibility (Saupe et al., 2013). A mechanistic link of tenascin-C to pro-angiogenic signaling has also been provided. It was shown that through its actin stress fiber disrupting activity tenascin-C downregulates DKK1 expression at the promoter level, which resulted in reduced expression of DKK1 and Wnt signaling activation in tumor and endothelial cells (Saupe et al., 2013). Since DKK1 binds LRP5/6 and thus inhibits LRP6-dependent CTGF, TGF-β and PDGF signaling (Ren et al., 2013), it is conceivable that through repression of DKK1 tenascin-C generates a microenvironment that is susceptible to pro-angiogenic and pro-metastatic signaling. Through binding of VEGFA, TGF-β and other soluble growth factors (De Laporte et al., 2013; Saupe et al., 2013) tenascin-C might regulate signaling induced by these factors.

4.4. Function of tenascin-C in cancer cell survival and lung metastasis

Several cell culture and murine cancer models have been used to address the roles of tenascin-C in metastasis. In a transgenic MMTV-PyMT model that had been engineered to lack tenascin-C by knock out technology, the authors did not see less metastasis (Talts et al., 1999). These mice stochastically develop adenocarcinomas in the mammary gland that metastasize to the lung. Despite a lack of an effect on metastasis, in the absence of tenascin-C the tumor nests and the ECM was differently organized, and the tumors were more infiltrated by macrophages. These data suggest that other mechanisms may have promoted lung metastasis in the absence of tenascin-C. It remains to be seen what

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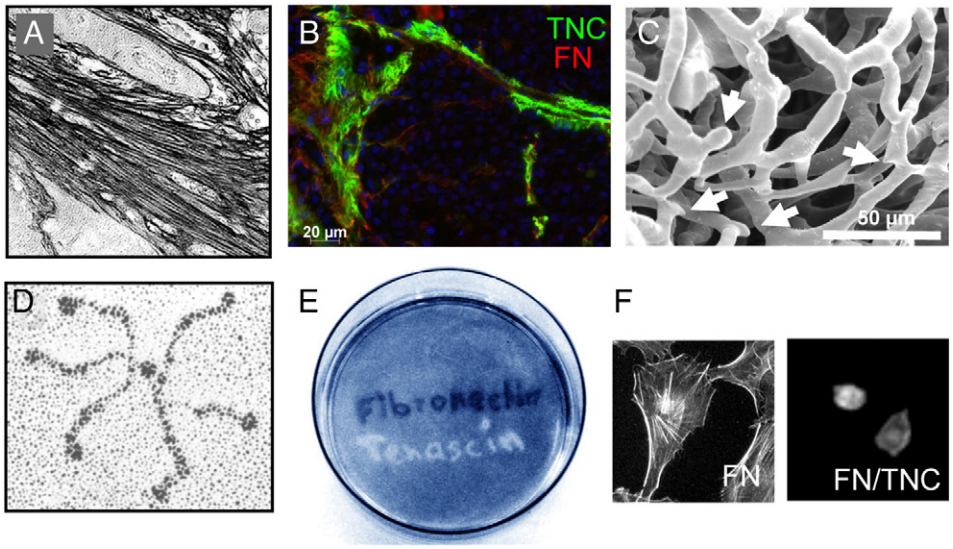

Fig. 3. *Tenascin-C containing niches in tumor tissue.* (A) Tenascin-C organization into matrix tracks revealed by immunostaining in sections of colon cancer tissue (picture taken from Midwood et al., 2011). (B) Tenascin-C forms fibrillar tracks together with fibronectin (FN) in RT2 insulinoma (picture taken from Van Obberghen-Schilling et al., 2011). (C) Scanning electron micrograph of the vasculature of a double transgenic RT2/TNC tumor with high transgenically expressed tenascin-C (taken from Saupe et al., 2013) showing a largely disturbed vasculature with vessel branching (arrows). (D) Electron micrograph of purified tenascin-C revealing its oligomerization into a hexamer (taken from Spring et al., 1989). (E) Demonstration of the opposite adhesive properties of a fibronectin and tenascin-C substratum for mouse L cells upon plating on a substratum generated with the respective purified molecule (taken from Chiquet-Ehrismann, 1991). Note that more cells adhere on the fibronectin substratum than on plain culture plastic whereas cells do not attach on the tenascin-C substratum. (F) While T98G glioblastoma cells form actin stress fibers upon spreading on fibronectin (FN), cells remain rounded with no actin stress fibers formed on a mixed fibronectin/tenascin-C substratum (FN/TNC; pictures taken from Orend, 2005).

these mechanisms are, and whether they are a direct consequence of the absence of tenascin-C. By using different murine immunodeficient xenograft models with human cancer cells, several studies tried to elucidate the role of tenascin-C in lung metastasis. Orthotopic grafting of breast cancer and melanoma cells by intravenous or orthotopic injection reduced the ability to form metastases in the lung (Tavazoie et al., 2008; Fukunaga-Kalabis et al., 2010; Oskarsson et al., 2011). Upon tail vein injection of breast cancer cells, a knock down of tenascin-C reduced lung colonization only at early time points, but not when cells had already reached the lung (Oskarsson et al., 2011). This observation suggests that tumor-derived tenascin-C is required while cells are in the circulation and presumably until the lung tissue has been instructed to provide tenascin-C by stromal cells. The major tenascin-C-providing stromal cells in the lung appear to be S100A4 (Mts1/FSP) positive cells, and depletion of S100A4+ cells reduced lung colonization of grafted 4 T1 cells. The authors tested whether tenascin-C is important for the colonization of tumor cells in the lung by grafting 4 T1 cells into tenascin-C knockout mice, and observed that indeed the number of metastases in the lungs was reduced (O'Connell et al., 2011). In this model tenascin-C decreased apoptosis of the cancer cells at the metastasis site, however it did not change their proliferation. To address the role of tenascin-C in tumor cell survival a breast cancer oncosphere model was applied, where a tenascin-C knock down reduced the survival of metastasis-initiating cells but did not affect their self-renewal capacity (Oskarsson et al., 2011). Similar observations had been made with neuroblastoma (Pezzolo et al., 2011) and melanoma oncospheres (Fukunaga-Kalabis et al., 2010) upon knock down of tenascin-C. In the breast cancer oncosphere model, tenascin-C induced enhanced survival and increased lung metastasis was linked to enhanced expression of the pluripotency markers Sox2, Oct4 and Nanog and the adult stem cell markers Musahsi (Msh1) and Lgr5. The expression of these genes was lowered in tenascin-C knock down cells. However, while Lgr5 and Msh1 expression was tenascin-C dependent, tenascin-C did not directly regulate the expression of the putative pluripotency markers (Sox2, Oct4, Nanog) as a tenascin-C knock down had revealed (Oskarsson et al., 2011).

Given that tenascin-C has been shown to have immuno-modulatory functions (reviewed in Midwood et al., 2009; Midwood et al., 2011; and this article) the presented data might at best be incomplete since most studies have been done in immune deficient mice. As additional complication the stromal compartment in a murine host is different from that of the human tumor (Fantozzi and Christofori, 2006), and human cells are not fully adapted to grow in a murine environment (Kuperwasser et al., 2005). In this context the studies by O'Connell et al. (2011) and Saupe et al. (2013) are relevant. As mentioned above, O'Connell et al. (2011) had intravenously injected 4 T1 cells into an immune competent *Tnc* −/− host, and observed less metastatic lesions in the lung. Curiously, metastasis assessment was only documented 4 days after engraftment. Whether at later time points the absence of tenascin-C from the stroma had an impact on metastasis was not mentioned. It was also not addressed whether the complete and simultaneous absence of tenascin-C from the tumor cells and/or host cells had an impact on metastasis.

These questions were recently addressed in the PNET/Rip1Tag2 insulinoma model of multi stage tumorigenesis that we had generated with low or high tenascin-C abundance (Saupe et al., 2013). We demonstrated that the expression levels of tenascin-C had an impact on micrometastasis formation (these mice die before they can develop macrometastases). Whereas the lowest numbers of lung metastases were seen in *Tnc* −/− tumor mice as assessed by qRT-PCR for insulin, the highest numbers were observed in lungs from tumor mice with expression of transgenic tenascin-C (Saupe et al., 2013). Although this result was anticipated, this is the first study where an important impact of tenascin-C on metastasis was proven in an immune competent context with stochastic tumor and metastasis formation.

5. Conclusion and perspectives

As reviewed in the previous sections, recent published work points to an indispensable (non-redundant) function of tenascins primarily in stem cell niches during organ turnover, renewal and regeneration. Evidence for a role of both tenascin-C and tenascin-R in neural stem cell migration and proliferation has been summarized in Section 2, and the association of tenascin-W with bone forming periosteum and with epithelial stem cell niches (e.g. hair and tooth buds) is intriguing. The effect of tenascin-W gene ablation has not been reported yet. As

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for tenascin-X, it remains to be seen whether the Ehlers-Danlos phenotype caused by its deficiency in mice and humans is due mainly to a structural or in addition to a regulatory defect. For example, growth factor signaling could be changed like in the case of fibrillin mutations in Marfan's syndrome (Dietz et al., 2005). However, most information on a function in stem cell niches is still available for tenascin-C.

The findings presented in Section 3 indicate that tenascin-C is an integral part of the hematopoietic niche that, while dispensable for steady state hematopoiesis, is important in driving hematopoietic regeneration after stress. So far only the consequence of complete myeloablation has been studied in tenascin-C deficient mice; it will be interesting to analyze the effect of more physiological insult on tenascin-C mediated hematopoeisis, for example pathogenic infection or injury. In addition to a function in the hematopoietic niche, published work also supports a role for tenascin-C in facilitating T cell recruitment to lymphoid tissues including the thymus, spleen and lymph nodes, as well as implying a context dependent role in driving T cell proliferation and polarization upon activation. It will be of interest to try and assess how these specific roles are mediated. Moreover, given the abnormal tenascin-C expression in non-lymphoid organs with autoimmune lesions (de Sousa, 1994), it will be interesting to determine if this ectopic expression promotes T cell infiltration, proliferation and activity during disease. Finally, the data reviewed here suggest that tenascin-C deposition as part of a transient 'pro-inflammatory niche' upon injury and infection can exert a profound effect on immunity, just as it does when constitutively expressed within stem cell niches throughout the body.

Section 4 reviews the current evidence that tenascin-C is functionally associated with tumor angiogenesis and metastasis formation. Tenascin-C may play multiple roles through its net-forming as well as its anti-adhesive activities, which are still poorly understood and most likely context dependent. Tenascin-C promotes the angiogenic switch, which might play a role in activating dormant metastatic tumor cells, but tenascin-C does not promote the formation of productive tumor blood vessels. Possibly, the poorly functional vessels and tenascin-C positive matrix tracks provide niches for metastatic tumor cells. Most likely tenascin-C is collaborating with other ECM molecules in promoting angiogenesis and metastasis where the best knowledge has been gathered for interactions with fibronectin (Van Obberghen-Schilling et al., 2011) and periostin (Kii et al., 2010). In particular collaborative activation of Wnt signaling by periostin and tenascin-C is a very attractive possibility. Even without a complete understanding of how they promote metastasis, due to their prominent expression in tumors and their large absence in most healthy tissues, tenascin-C and tenascin-W are extraordinarily promising targets in cancer diagnosis and therapy, which are currently heavily exploited (Kitson et al., 2013).

In most cases the precise molecular mechanisms of action of the tenascins in stem cell niches remain to be established. It is likely that besides direct interaction of the tenascins with cellular receptors, their interaction with growth factors might be an important aspect. Tenascin-C has been demonstrated to bind several growth factors from different families that are known to affect stem cell differentiation, including the PDGF family, the FGF family, the TGF-β superfamily, neurotrophins, and IGF-BPs (De Laporte et al., 2013). One important mechanism by which tenascin-C promotes tumor angiogenesis involves downregulation of DKK1 and activation of Wnt signaling. Given the pleiotropic effects of DKK1, it is likely that multiple pro-angiogenic LRP5/6-dependent pathways (blocked by DKK1) are de-repressed due to DKK1 downregulation by tenascin-C. Interestingly, effects of tenascin-W on Wnt-signaling have been observed as well (Kimura et al., 2007). Similarly to tenascin-C, tenascin-W has been found in many stem cell niches as summarized in Section 2. In addition, tenascin-W is part of the microenvironment in a large number of tumors (Scherberich et al., 2005; Degen et al., 2007, 2008), especially also around tumor blood vessels (Martina et al., 2010). Since tenascin-W expression often correlates with poor prognosis (Brellier et al., 2012), a function for tenascin-W in the metastatic niche will need to be investigated in future studies. Since stem cell niches are unusually rich in growth factors and many signaling pathways are activated, one of the ways by which tenascins may affect stem cells is by influencing growth factor signaling positively or negatively, by sequestering the factors in the matrix and/or presenting them as localized reservoirs to the stem cells. This venue clearly deserves to be investigated more thoroughly, since it might have an important impact on the use of tenascins for tissue engineering approaches (Chatakun et al., 2013).

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