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CELL SCIENCE AT A GLANCE

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Tenascin-C at a glance

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ABSTRACT

Tenascin-C (TNC) is a hexameric, multimodular extracellular matrix protein with several molecular forms that are created through alternative splicing and protein modifications. It is highly conserved amongst vertebrates, and molecular phylogeny indicates that it evolved before fibronectin. Tenascin-C has many extracellular binding partners, including matrix components, soluble factors and pathogens; it also influences cell phenotype directly through interactions with cell surface receptors. Tenascin-C protein synthesis is tightly regulated, with widespread protein distribution in embryonic tissues, but restricted distribution of tenascin-C in adult tissues. Tenascin-C is also expressed *de novo* during wound healing or in pathological conditions, including chronic inflammation and cancer. First described as a modulator of cell adhesion, tenascin-C also directs a plethora of cell signaling and gene expression programs by shaping mechanical and biochemical cues within the cellular microenvironment. Exploitment of the pathological expression and function of tenascin-C is emerging as a promising strategy to develop new diagnostic, therapeutic and bioengineering tools. In this Cell Science at a Glance article and the accompanying poster we provide a succinct and comprehensive overview of the structural and functional features of tenascin-C and its potential roles in developing embryos and under pathological conditions.

KEY WORDS: Tenascin-C, TNC, Chronic inflammation, Extracellular matrix, Matricellular molecule, Tissue repair, Cancer

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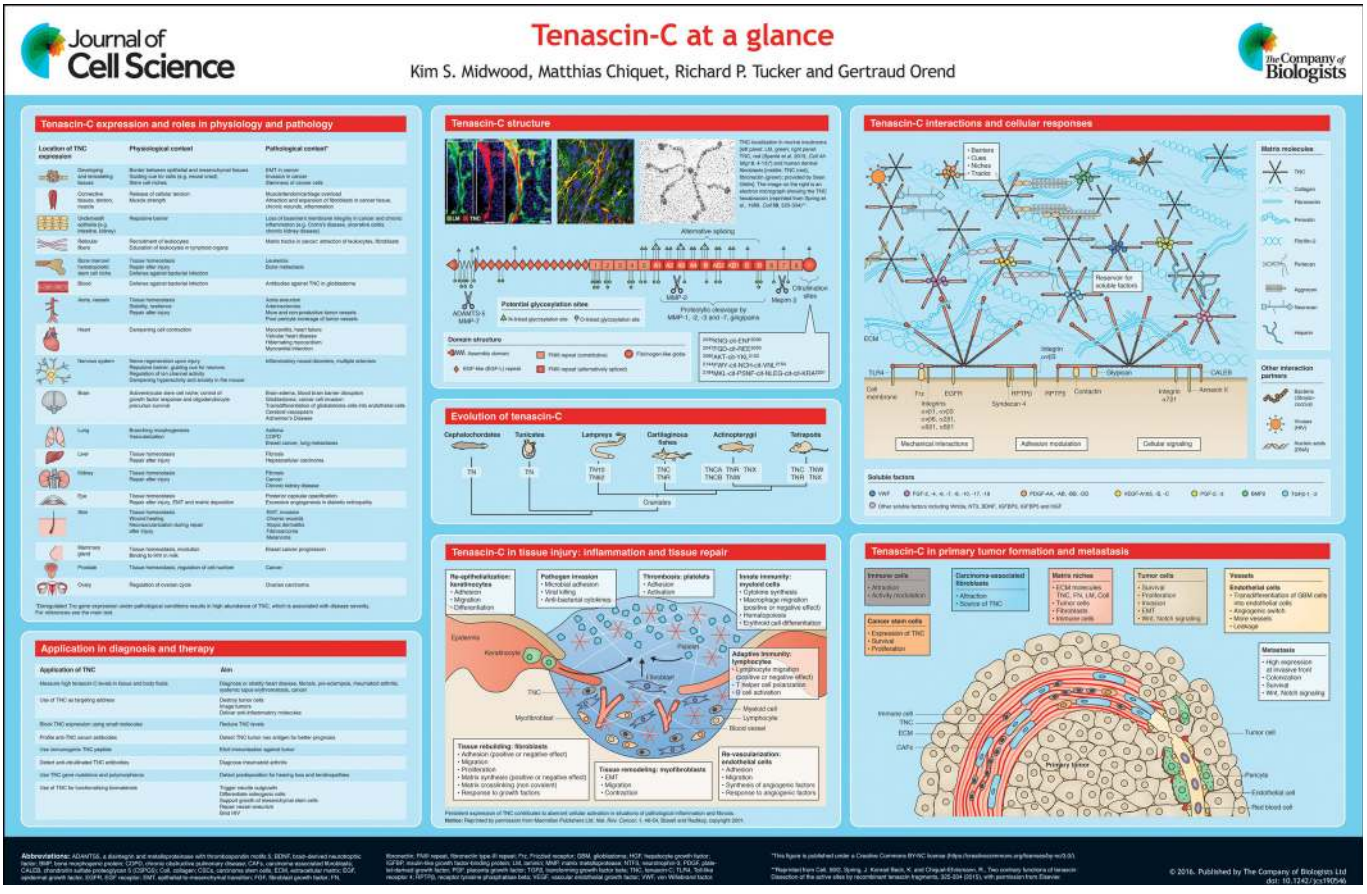
Introduction

Tenascin-C (TNC) is the founding member of the tenascin gene family. Discovered independently by researchers studying



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glioblastomas, the myotendinous junction and the developing central nervous system (Chiquet-Ehrismann and Tucker, 2011), its name reflects two sites where tenascin-C is prominently expressed: tendons (from Latin verb 'tenere' to hold) and embryos (from Latin 'nasci' to be born) (Chiquet-Ehrismann et al., 1986). The 'C' – derived from the previous name cytotactin – was assigned when additional members of the tenascin gene family were identified.

Tenascin-C exhibits a number of remarkable features that are related to its structure, expression and function. All tenascins share the same molecular architecture. Heptad repeats near the N-terminus of each tenascin chain support trimerization; in tenascin-C, two trimers can join to form a hexabrachion. The heptad repeats are followed – from N- to C-terminus – by one or more epidermal growth factor (EGF)-like domains, a string of fibronectin-type III (FNIII) repeats and a fibrinogen-like globe (see poster). This multimodular structure enables the tenascins to interact with a high number of highly diverse ligands. Another striking feature of tenascin-C is its tightly controlled gene expression pattern. In the embryo, tenascin-C is found around motile cells, at sites of epithelial-mesenchymal interactions and branching morphogenesis, and in dense connective tissue, such as bone, cartilage and tendons, as well as in the central nervous system (Akbareian et al., 2013; Sahlberg et al., 2001; Wiese and Faissner, 2015). However, little tenascin-C is found in the adult, where it is most prominent in stem cell niches and tendons (Chiquet-Ehrismann et al., 2014), and at sites of inflammation and trauma (Midwood et al., 2011); it is also particularly abundant in the stroma of solid tumors (Brösicke and Faissner, 2015; Lowy and Oskarsson, 2015; Midwood et al., 2011; Orend et al., 2014). Finally, tenascin-C exhibits an extraordinarily wide range of functions. Tenascin-C knockout mice show abnormalities regarding their behavior, brain cytoarchitecture, branching morphogenesis, stem cell niches and trauma responses (Chiquet-Ehrismann and Tucker, 2011). *In vitro* studies have also shown that tenascin-C can influence cell behavior in a number of ways. It is perhaps best known as an adhesion-modulating extracellular matrix protein owing to its ability to bind to fibronectin, and to alter cell spreading and signaling mediated by fibronectin and integrins (Chiquet-Ehrismann et al., 1986; Huang et al., 2001; Midwood et al., 2004). However, tenascin-C itself also acts directly as an integrin ligand (Tucker and Chiquet-Ehrismann, 2015; Yoshida et al., 2015), as well as performing a whole host of other functions.

The complex interplay of tissue-specific interactions and functions makes it difficult to define the actions of tenascin-C because it possesses an exquisite context-specific mode of action that defies neat classification. Most often identified at disease sites, tenascin-C has been implicated in the pathogenesis of a large number of conditions. However, tenascin-C evolved in early chordates (see poster and Box 1), suggesting a highly selective pressure for this molecule, thereby raising the questions: why do we have tenascin-C and what good does it do? In this Cell Science at a Glance article and its accompanying poster, we summarize many of the features of tenascin-C, including its appearance during evolution, its structure and binding partners, and the regulation of tenascin-C gene expression. We also highlight its roles under a number of physiological and pathological conditions before concluding with future directions for tenascin-C research (see poster and Box 2).

The many molecular variants of tenascin-C

Tenascin-C can exist in a number of different isoforms that are created by modifications occurring between transcriptional to post-translational levels (see poster). In human tenascin-C, eight of the FNIII repeats (FNIII 1–8) are always present, but the nine FNIII repeats located between FNIII 5 and FNIII 6 are subject to alternative splicing (FNIII A–D), potentially giving rise to 511 different isoforms. This complexity has significant impact on tenascin-C function because distinct FNIII repeats have specific binding partners, proteolytic cleavage sites and post-translational modification sites. Furthermore, new binding sites can be created that exist only across the boundaries of specific FNIII repeats. Splicing of tenascin-C can be extraordinarily dynamic, and has been best studied during development and in cancer, where the temporal and spatial expression of different isoforms is used to direct distinct cellular processes that drive embryogenesis and tumorigenesis (Giblin and Midwood, 2015).

Tenascin-C contains several predicted glycosylation sites (see poster), and tenascin-C purified from human glioma cells and chicken embryonic fibroblasts or that secreted in human breast milk is glycosylated. However, the extent and pattern of modification, and how this impacts tenascin-C function, is not well characterized. One study reports that glycosylated tenascin-C promotes proliferation of murine neuronal stem cells (Yagi et al., 2010). However, this modification is also expected to regulate the binding capabilities of tenascin-C, confer protection from proteolytic cleavage and/or interfere with hexamer assembly (Giblin and Midwood, 2015). Tenascin-C can also be modified post-translationally through citrullination, where a positively charged arginine residue is converted into a neutral citrulline residue. Five distinct citrullination sites were identified within the fibrinogen-like globe, with additional sites likely to be distributed throughout the molecule (see poster). This modification increases the immunogenicity of the C-terminal residues of tenascin-C, leading to the generation of autoantibodies in patients with rheumatoid arthritis, where their presence accurately predicts disease development (Schwenzer et al., 2015).

Box 1. The evolution of tenascin-C

Prior to the ability to analyze genomic sequences, a number of attempts were made to identify tenascins in non-chordate model organisms by screening cDNA libraries with antibodies or nucleic acid probes. Although this approach did result in the serendipitous discovery of the teneurin family of transmembrane proteins (Baumgartner and Chiquet-Ehrismann, 1993; Baumgartner et al., 1994), it was doomed to fail because tenascins are only found in chordates (Tucker and Chiquet-Ehrismann, 2009). The phylum Chordata is usually subdivided into the cephalochordates, tunicates and craniates. The cephalochordates, the subphylum to which the Florida lancelet (also known as amphioxus) *Branchiostoma floridae* belongs, are widely regarded to be the first chordates to have evolved. A predicted tenascin is found in the *B. floridae* genome and it has all of the characteristics of tenascins found in vertebrates (Tucker and Chiquet-Ehrismann, 2009). At least seven of the FNIII repeats of this tenascin have an RGD tri-peptide motif within the same exposed loop in which integrin-binding RGD motifs are found within fibronectin and human tenascin-C, making this tenascin likely to be an integrin ligand. To date, there is no evidence of a tenascin or tenascin-like precursor in the genomes of echinoderms or hemichordates, the two phyla that are most closely related to the chordates. In vertebrates, the glycoprotein fibronectin is an important binding partner of tenascin-C, but the genome of *B. floridae* lacks a fibronectin gene. This suggests that the first tenascins have evolved as independent integrin ligands and not as fibronectin modulatory proteins. Thus, although tenascins evolved early in the chordate lineage, current evidence suggests that tenascin-C first appeared in jawed vertebrates (Adams et al., 2015).

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Box 2. Application in diagnosis and therapy

Tenascin-C gene expression is often used as a read-out for successful tissue repair, and has also been used in approaches of tissue-repair and stem-cell-based tissue replacement. For example, incorporation of an integrin-α7β1-activating tenascin-C peptide into bioengineered gels supports triggered neurite outgrowth and osteogenic lineage differentiation (Berns et al., 2016; Mercado et al., 2004; Sever et al., 2014). Similarly, when tenascin-C is used to coat modified platinum coils placed into experimentally injured arteries, the coils are more effective at inducing vessel repair (Miura et al., 2016). Other biomaterials enriched in tenascin-C may also be useful to enhance mesenchymal stem cell survival during tissue repair (Rodrigues et al., 2013). Mutations and polymorphisms in the tenascin-C gene have been implicated in hearing loss (Zhao et al., 2013) and tendinopathies (Saunders et al., 2013), respectively, a fact that might be useful in the diagnosis of these conditions. As tenascin-C is a neoantigen in cancer and rheumatoid arthritis, there is scope to profile serum antibodies that recognize tenascin-C (Mock et al., 2015; Schwenzer et al., 2015) and to exploit tenascin-C as an antigen for immunization. Indeed, amongst 11 highly immunogenic peptides that have been delivered within an immunization cocktail to glioblastoma patients (clinical trial phase I), one represented tenascin-C (Dutoit et al., 2012; Rampling et al., 2016). Moreover, aptamers and antibodies that specifically bind to tenascin-C were applied to deliver drugs or immune stimulatory chemokines, such as IL2, into the tumor microenvironment of patients with different cancers (Catania et al., 2015; Gutbrodt et al., 2013 ; reviewed in Spenle et al., 2015b). Furthermore, tenascin-C gene expression negatively influences the cytotoxicity of doxorubicin in breast cancer and melanoma spheroids, as well as pancreatic cancer cells (Fukunaga-Kalabis et al., 2010; Oskarsson et al., 2011), suggesting that tenascin-C is a good target for adjuvant chemotherapy. Accordingly, downregulation of tenascin-C gene expression has also been a goal of RNA-based technologies (Rolle et al., 2010). In addition, anti-tenascin-C antibodies coupled to radioisotopes might be useful to image tissues and tumors of high tenascin-C gene expression (reviewed in Gu et al., 2015; Jacobson et al., 2015; Orend et al., 2014; Spenle et al., 2015b). Detection of high protein levels of tenascin-C within pathological tissues as well body fluids could be of diagnostic value and might provide a means to earlier detect associated conditions, including heart disease, fibrosis, pre-eclempsia, rheumatoid arthritis, systemic lupus erythematosus and cancer (Orak et al., 2016; Orend et al., 2014; Schwenzer et al., 2015; Ulusoy et al., 2015, Franz et al., 2015, Imanaka-Yoshida, 2012). Finally, the high levels of tenascin-C found in breast milk of HIV-infected mothers can potentially be exploited in a HIV-prevention strategy 'designed by nature' as their breast-fed infants are protected from contracting HIV (Fouda et al., 2013).

Finally, tenascin-C can be cleaved by matrix metalloproteases (MMPs) (Giblin and Midwood, 2015) and gingipain cysteine proteases (Ruggiero et al., 2013), which contributes to tenascin-C turnover in tissue. *In vitro* cleavage of purified tenascin-C through MMP-1,-2, -3 and -7 demonstrated that the majority of cleavage sites are located within the alternatively spliced domains, although MMP-7 and the proteinase ADAMTS5 (a disintegrin and metalloproteinase with thrombospondin motifs 5) both also cleave within the assembly domain. Although degradation is an important mechanism to control the levels of tenascin-C in tissue, it can also pro-actively impact on tenascin-C function by releasing soluble fragments that have unique functions compared to the full, intact molecule. For example, cleavage can uncover cryptic pro-apoptotic activity, hidden fibronectin-binding sites and concealed heparin-sulphate-binding sites that promote cell spreading (Giblin and Midwood, 2015).

The cellular and molecular interactions of tenascin-C

Tenascin-C binds to a high number of different ligand types (see poster). It interacts with other extracellular matrix (ECM) components – the first and best characterized of which is fibronectin – through a number of binding sites that are distributed throughout its FNIII repeats. Tenascin-C also binds to collagen, periostin and fibrillin-2 – although binding sites for these molecules have not yet been mapped – as well as to proteoglycans of the lectican family and to perlecan, which use binding sites within FNIII 3–5 and the fibrinogen-like globe (Orend et al., 2014). Tenascin-C also binds to receptor-type protein tyrosine phosphatase beta zeta (RPTPβζ), contactin, CALEB (officially known as CSPG5) and glypican; the binding maps have been published elsewhere (Midwood et al., 2011). These inter-matrix interactions are likely to play a structural role – for example, by defining the stiffness of the cellular environment – but they can also modulate how ECM components signal to the cell. Interactions of tenascin-C with cell surface receptors enable direct communication with the cell. Human tenascin-C binds to six different integrins through its RGD-containing FNIII 3 repeat, but integrin-binding sites are also located in the alternatively spliced FNIII repeats and the fibrinogen-like globe (Tucker and Chiquet-Ehrismann, 2015; Yoshida et al., 2015). Some controversy about integrin specificity has been discussed elsewhere (Tucker and Chiquet-Ehrismann, 2015). Tenascin-C can also impact on cell proliferation through activation of the epidermal growth factor (EGF)-receptor (Swindle et al., 2001) and inflammatory signaling pathways through activation of Toll-like receptor TLR-4 (Midwood et al., 2009). More recently, tenascin-C interactions with soluble factors have emerged, e.g. with Wnt/wingless 3a (Wnt3a), transforming growth factor beta (TGFβ) and vascular endothelial growth factor (VEGF); many growth factors use binding sites located in FNIII repeats 3–5. This sequestration of soluble factors might prolong their half-life, increase their local concentrations and/or affect their conformation, all of which will affect their ability to signal to the cell (De Laporte et al., 2013; Hendaoui et al., 2014; Martino et al., 2014). Finally, tenascin-C can bind to pathogens, including *Streptococcus* and human immunodeficiency virus (HIV); here, tenascin-C may serve as a conduit for, or structural barrier to, infectious agents, and/or may actively participate in host defence. For example, tenascin-C binding to the HIV-1 chemokine receptor site neutralizes viral activity (Fouda et al., 2013).

Tenascin-C in tissues

In contrast to other ECM glycoproteins, tenascin-C has a restricted protein distribution that can rapidly change. In embryos, tenascin-C appears at many sites of tissue morphogenesis (Chiquet, 1992). For example, in limb buds, tenascin-C is a marker for organization of the perichondrium and periosteum, ligaments and tendons (Chiquet and Fambrough, 1984). Tenascin-C also accumulates around budding epithelia in developing kidneys, lung, mammary glands, teeth and hair follicles (Chiquet, 1992), and is expressed around neurons and glial cells in some regions of the developing central nervous system (Faissner, 1997). In the normal, healthy adult organism, tenascin-C expression is sparse; it is found only in a few connective tissues that bear tensile strength (Flück et al., 2000), underneath some epithelia (Aufderheide et al., 1987; Talts et al., 1997) and in certain stem cell niches – including the bulge of hair follicles, crypts of the intestine and bone marrow (Chiquet-Ehrismann et al., 2014).

The most intriguing aspect of tenascin-C protein synthesis is its rapid induction in many tissues in response to pathological stress (Chiquet-Ehrismann and Chiquet, 2003). For example, patients with high levels of C-reactive protein, which is elevated upon infection and inflammation, also have high serum levels of tenascin-C (Schenk et al., 1995). Furthermore, tenascin-C appears after mechanical or chemical injury, including mechanical overload of

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muscle and tendons (Flück et al., 2000). Stromal cells (e.g. myeloid cells in cancer tissue) are the main tenascin-C source after injury, although inflammatory leukocytes also contribute (Goh et al., 2010; O'Connell et al., 2011). Indeed, tenascin-C is induced during chronic inflammation, for instance in rheumatoid arthritis; (Midwood et al., 2011). Moreover, many articles have described increased protein levels of tenascin-C in human cancers (reviewed in Lowy and Oskarsson, 2015, Orend et al., 2014). Tenascin-C protein synthesis is often used as a readout for successful tissue repair, and has also been used in tissue repair and stem-cell-based approaches of tissue replacement. Increased levels of tenascin-C in chronic inflammation and cancer can also be exploited for diagnosis and targeting (see poster and Box 2).

Regulation of *Tnc* gene expression

As expected for highly regulated genes, the promoter of the tenascin-C gene (*Tnc*) contains a TATA box (Chiovaro et al., 2015), and a number of specific transcription factors that contribute to driving the distinct patterns of *Tnc* expression in the embryo and the adult. For instance, the product of the patterning gene paired mesoderm homeobox protein 1 (*Prrx1*) directly regulates the *Tnc* promoter (Martin et al., 1995); it transactivates the mouse *Tnc* gene by interacting with a conserved homeodomain-binding sequence in its promoter (Ihida-Stansbury et al., 2004). In contrast, homeobox even-skipped homolog protein 1 (Evx1) indirectly stimulates *Tnc* expression by synergizing with transcription factors Jun and/or Fos (Jones et al., 1992). At least two more homeobox transcription factors, Pou3F2 and Otx2, regulate *Tnc* expression through direct binding to conserved sequences in its promoter (Copertino et al., 1997; Gherzi et al., 1997). Finally, *Tnc* was shown to be a target gene of Sox4, which is overexpressed (together with *Tnc*) in many human tumors (Scharer et al., 2009).

Although *de novo* expression of *Tnc* is a hallmark of inflammation, and a number of cytokines were shown to induce the gene (Chiquet-Ehrismann and Chiquet, 2003), it is not yet known how cytokines control *Tnc* transcription. However, two potential binding sites for SMAD2 and SMAD3 have been shown to be responsible for activation of the *Tnc* promoter through TGFβ in human fibroblasts (Jinnin et al., 2004). Platelet-derived growth factor (PDGF) regulates *Tnc* expression via the phosphoinositide 3-kinase (PI3K)–AKT signaling pathway, which induces the binding of transcription factor specificity protein 1 (SP1) and of transcription factors ETS1 and ETS2 to specific promoter sequences (Jinnin et al., 2006). The cell-bound ligands Delta and Jagged have also been shown to induce *Tnc* through their transmembrane receptor Notch, whereby the cleaved intracellular domain of Notch2 acts in a manner that is dependent on binding sites for transcription factor RBPJk within the *Tnc* promoter (Sivasankaran et al., 2009).

Moreover, *Tnc* expression is strongly suppressed through glucocorticoids (Ekblom et al., 1993) but the mechanism is still unknown.

Tnc expression can be regulated by mechanical stress, for instance, in arterial smooth muscle through hypertension (Mackie et al., 1992) or by mechanical overload in skeletal muscle (Flück et al., 2000). In cultured fibroblasts that are subjected to tensile strain, β1-integrin-mediated activation of the small GTPase RhoA induces actin assembly and contraction (Lutz et al., 2010); this results in nuclear translocation of the transcriptional regulator megakaryocytic leukemia-1 (MKL1) to activate *Tnc* expression (Asparuhova et al., 2009). Alternative mechanotransduction pathways controlling *Tnc* expression have been discovered in other cell types, for example, in arterial smooth muscle cells, stretch was found to induce the synthesis of the nuclear factor of activated T-cells 5 (NFAT5), a transcription factor that stimulates *Tnc* transcription (Scherer et al., 2014).

Physiological and pathological cell responses mediated by tenascin-C

Tenascin-C exerts different effects on many different cell types and can stimulate multiple signaling events at once. Cells respond in a context-specific manner to tenascin-C, and tenascin-C often triggers the opposite effect in two cell types (Chiquet-Ehrismann et al., 2011; Midwood and Orend, 2009; Orend et al., 2014). Below, we summarize some of the distinctly different means by which tenascin-C impacts on cell behavior (see also poster).

One of the earliest descriptions of tenascin-C function reported its ability to modulate cell adhesion to other matrix components (Chiquet-Ehrismann et al., 1986). For example, tenascin-C blocks fibronectin-mediated cell adhesion and spreading through competition with syndecan-4 (Huang et al., 2001). Tenascin-C itself can be a poor adhesive substrate for cells, and activation of annexin-II-mediated anti-adhesive signaling through its FNIII repeats A–D renders larger tenascin-C isoforms less adhesive than smaller ones (Giblin and Midwood, 2015). The anti-adhesive properties of tenascin-C can also be enhanced, reduced or even abolished by additional signaling that involves lysophosphatidic acid receptor (LPAR), platelet-derived-growth factor receptor (PDGFR), endothelin type A and B receptors (EDNRA and EDNRB, respectively), or cleavage through proteases (Ambort et al., 2010; Gundersen et al., 1997; Lange et al., 2007, 2008).

ECM networks that are tenascin-C-rich exert control over cellular movement. For example, tenascin-C promotes neural crest cell migration (Akbareian et al., 2013; Tucker, 2001), as well as migration of tumor cells and metastatic progression (Lowy and Oskarsson, 2015; Saupe et al., 2013). However, tenascin-C has also been shown to inhibit cell migration, especially in the case of growth cones (Faissner, 1997). Tenascin-C located in the reticular fibers of the thymus controls lymphocyte influx and appears to define places of leukocyte maturation (Drumea-Mirancea et al., 2006). Similar structures identified as poorly characterized bundles of matrix (matrix tracks) may exist throughout tumors (Kaariainen et al., 2006; Spenlé et al., 2015a) where they could have a role similar to that of reticular fibers in the thymus or other lymphoid tissues (Midwood et al., 2011) (see poster). Tenascin-C is a component of softer regenerative matrix (Chiquet-Ehrismann and Chiquet, 2003), suggesting that this matrix component actively modulates the mechanical properties of the ECM (Miroshnikova et al., 2016). Tenascin-C modulates cellular tension by dismantling actin stress fibers (Midwood and Schwarzbauer, 2002; Ruiz et al., 2004; Saupe et al., 2013). In contrast, tenascin-C promotes constriction of cerebral arteries, which involves activation of EGFR and extracellular signaling-related kinases 1 and 2 (ERK1/2), although it is unknown whether this involves effects of tenascin-C on matrix resilience (Fujimoto et al., 2016).

Tenascin-C promotes survival of oligodendrocyte precursor cells by enhancing fibroblast growth factor receptor (FGFR) and by blocking bone morphogenic protein (BMP4) signaling (Garcion et al., 2004) but has been shown to induce apoptosis in smooth muscle cells through its EGF-like repeats (Wallner et al., 2004). Tenascin-C also promotes and blocks proliferation of tumor cells (Huang et al., 2001) and fibroblasts (Orend et al., 2003), respectively, a process in which tenascin-C and fibronectin compete for binding to syndecan-4 and that, potentially, involves other not-yet-identified mechanisms. In cancer stem cells, tenascin-C

promotes proliferation (Fukunaga-Kalabis et al., 2010; Oskarsson et al., 2011), or their transdifferentiation into cells with endothelial properties (Pezzolo et al., 2011).

The high conservation of tenascin-C throughout evolution, its lack of mutational hotspots and its tightly controlled expression all argue for an important role in physiology. However, tenascin-C is also persistently expressed in a high number of pathological conditions (see poster), two well-studied examples being chronic inflammation and cancer. Although *Tnc* is transiently induced during acute inflammation, its continued expression in several chronic inflammatory diseases has been shown to contribute to disease severity in humans as well as in mice (Udalova et al., 2011).

Hundreds of publications also indicate a role for tenascin-C in promoting cancer progression and metastasis (see poster). For example, a study using a mouse model, in which tumors express tenascin-C either in abundance or not at all, has demonstrated that tenascin-C promotes multiple events, such as survival, proliferation, invasion and metastasis (Saupe et al., 2013); this is consistent with reports studying cancer in humans (reviewed in Orend et al., 2014, Lowy and Oskarsson, 2015). Tenascin-C promotes the angiogenic switch and the formation of poorly functional blood vessels that may involve Wnt signaling (Saupe et al., 2013). Tenascin-C is also a strongly expressed molecule of the AngioMatrix (i.e. ECM and ECM-related proteins that are part of the angiogenic switch), whose expression correlates with worsened patient survival (Langlois et al., 2014). Tenascin-C exerts a dual role in angiogenesis. Whereas tenascin-C blocks pro-survival signaling in endothelial cells through direct contact, it also induces a pro-angiogenic secretome in glioblastoma cells (Rupp et al., 2016). Tenascin-C can also promote survival of circulating breast cancer cells and their colonization within lung parenchyma; this involves Notch and Wnt signaling, including stemness-promoting leucine-rich-repeat-containing G-protein-coupled receptor 5 (LGR5) (Oskarsson et al., 2011). Synthesis of tenascin-C protein at the invasive front of the tumor and in lung metastases correlates with poorer prognosis (reviewed in Orend et al., 2014). Here, Rho inhibition (through impairing syndecan-4 and integrin $\alpha5\beta1$) and activation of Cdc42 and Rac (involving fascin) could be instrumental (reviewed in Lowy and Oskarsson, 2015). Tenascin-C can promote migration through epithelial-to-mesenchymal-transition (EMT) and EGFR activation by the tenascin-C EGF-like repeats (reviewed in Lowy and Oskarsson, 2015; Shao et al., 2015). Finally, through regulating innate and adaptive immunity, tenascin-C can also contribute to tumor progression, although the mechanisms by which this occurs are not completely understood to date (Hauzenberger et al., 1999; Orend et al., 2014; Jachetti et al., 2015).

Conclusions and perspectives

Tenascin-C not only modulates cell behavior by acting as a ligand for cell surface receptors, such as integrins and TLR4, but also has important roles in modulating integrin signaling through fibronectin and by anchoring growth factors. Several potential ligands within the ECM have been found but the nature and purpose of these interactions are mostly unknown. Alternative splicing, post-translational modifications and proteolytic processing of tenascin-C have been identified, yet the distinct functions of the arising tenascin-C molecules are poorly understood. The combined findings summarized here indicate that, in addition to its little understood roles in physiology (e.g. in immunity and EMT), a main function of tenascin-C is that of a stress protein that serves to modulate cell adhesion, migration and proliferation. A better understanding of its roles might lead to the development of new applications in tissue repair, as well as to more appropriate therapies in the fight against chronic inflammation, tumor growth and metastasis. Challenges have to include the development of immune-competent animal models with tightly regulated, tissue-specific protein expression of tenascin-C and several of its more common variants.

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Competing interests

K.S.M. is the founder of, and consultant to, Nascient Ltd.

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A high-resolution version of the poster and individual poster panels are available for downloading at http://jcs.biologists.org/lookup/doi/10.1242/jcs.190546.supplemental

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