Tenascins and the Importance of Adhesion Modulation

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Tenascins are a family of extracellular matrix proteins that evolved in early chordates. There are four family members: tenascin-X, tenascin-R, tenascin-W, and tenascin-C. Tenascin-X associates with type I collagen, and its absence can cause Ehlers-Danlos Syndrome. In contrast, tenascin-R is concentrated in perineuronal nets. The expression of tenascin-C and tenascin-W is developmentally regulated, and both are expressed during disease (e.g., both are associated with cancer stroma and tumor blood vessels). In addition, tenascin-C is highly induced by infections and inflammation. Accordingly, the tenascin-C knockout mouse has a reduced inflammatory response. All tenascins have the potential to modify cell adhesion either directly or through interaction with fibronectin, and cell-tenascin interactions typically lead to increased cell motility. In the case of tenascin-C, there is a correlation between elevated expression and increased metastasis in several types of tumors.

THE DISCOVERY OF TENASCIN-C

The first member of the tenascin family, tenascin-C, was discovered independently in laboratories studying subjects as different as the extracellular matrix in brain cancer (glioma mesenchymal extracellular matrix antigen), the components of myotendinous junctions (myotendinous antigen), or the embryonic development of the nervous system (cytotactin) and J1 glycoprotein (for references, see Table 1). Important functions were postulated for the protein, ranging from a structural role

in muscle-tendon attachment to cell migration and cell-cell interactions in organ development. However, the first description of a function of tenascin-C was actually published long before anything was known about the existence of this protein when Ken Yamada and coworkers described the hemagglutinating activity of the major cell surface protein of chick embryo fibroblasts (Yamada et al. 1975). Almost a decade later Erickson and Iglesias used electron microscopy to analyze similar cell surface protein preparations, which were known to contain fibronectin, and found six-armed

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Table 1. The tenascins.

Name	Discovery and synonyms	References
Tenascin-C	Glioma mesenchymal extracellular matrix antigen (GMEM) Myotendinous antigen Cytotactin J1 glycoprotein	Bourdon et al. 1983 Chiquet and Fambrough 1984 Grumet et al. 1985 Kruse et al. 1985
Tenascin-R	J1 160/J1 180 Restrictin	Pesheva et al. 1989; Fuss et al. 1993 Rathjen et al. 1991; Norenberg et al. 1992; Brummendorf et al. 1993
Tenascin-X	Human gene X	Morel et al. 1989
Tenascin-Y		Hagios et al. 1996
Tenascin-W	Tenascin-W	Weber et al. 1998; Scherberich et al. 2004; Degen et al. 2007
	Tenascin-N*	Neidhardt et al. 2003

*Tenascin-W was first described in zebrafish (Weber et al. 1998) and later in mouse, where the orthologous protein was named tenascin-N (Neidhardt et al. 2003) before its relationship to tenascin-W was clarified (Scherberich et al. 2004; Tucker et al. 2006). The mouse and human tenascin-W genes, but not the genes in other species, are named *tnn* for this reason.

“hexabrachions” in addition to two-armed fibronectin molecules (Erickson and Inglesias 1984). Shortly thereafter, Chiquet-Ehrismann and coworkers showed that the hemagglutinating activity originally attributed to fibronectin was actually the function of the hexabrachions, which they named tenascin (Chiquet-Ehrismann et al. 1986). When other members of this gene family were eventually identified (tenascin-R, tenascin-W, and tenascin-X), the original tenascin was renamed tenascin-C, the “C” representing “cytotactin”. It was certainly not by chance that tenascin-C was isolated together with fibronectin: the two proteins not only bind to each other, they also are similar in size and structure and are often coexpressed. As shown in Figure 1, tenascins and fibronectins are only found in chordates, and the two proteins influence each other’s effects on cell behavior.

EVOLUTION AND EXPANSION OF THE TENASCIN FAMILY

Tenascins appear to have evolved early in the chordate lineage (Fig. 1); that is, at a time roughly corresponding to the appearance of organisms belonging to the phylum to which vertebrates and a few invertebrates, such as sea

squirts (Subphylum Urochordata, also known as tunicates) and the lancelet *Branchiostoma floridae* (Subphylum Cephalochordata, also known as amphioxus) belong. Both sea squirts and lancelets have tenascins with the identical general domain organization (heptad repeats, EGF-like repeats, FN3 domains, and a fibrinogen-related domain) as vertebrate tenascins, but no such genes could be found using similar approaches in echinoderms (e.g., sea urchins), protostomes like *Drosophila* or *Caenorhabditis elegans*, or cnidarians (the phylum to which *Hydra* and sea anemones belong) (Tucker and Chiquet-Ehrismann 2009a). Thus, tenascins are relatively new additions to the extracellular matrix, appearing in the first organisms with a dorsal hollow nerve cord and neural crest cells or neural crest-like properties, as well as a pharyngeal apparatus and notochord. This is intriguing, as tenascin-C is prominently expressed by neural crest cells (Tucker and McKay 1991) and can be required for their normal migration (Tucker 2001), and tenascin-C and its relative tenascin-W are expressed in dense connective tissues like cartilage and bone (e.g., see Mackie et al. 1987; Scherberich et al. 2004), which may have their origins in the notochord (Zhang and Cohn 2006) and pharyngeal arch mesenchyme (Hecht et al. 2008). Thus,

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Figure 1. Tenascins and fibronectin are only found in Chordates. The tenascin gene from amphioxus (Cephalochordata) encodes a predicted protein with the characteristic organization of tenascins: one or more EGF-like repeats near the amino terminus (yellow pentagons), FN3 domains (circles), and a carboxy-terminal fibrinogen-related domain (purple rectangle). FN3 domains with an RGD or KGD motif appropriately exposed for integrin binding are orange and those without are green. No fibronectin gene has been identified in amphioxus. In contrast, tunicates (Urochordata) have both a tenascin and a fibronectin-like gene. In mammals (adapted from human sequences here), there are four tenascin genes and a single fibronectin gene. In contrast, bony fish (Actinopterygii) have two fibronectin genes and the tenascin-C gene has duplicated. Representative proteins are illustrated here. Some are only predicted. In addition, some tenascins are known to have multiple splice variants that can result in different numbers of FN3 domains (see Fig. 2).

the evolution of tenascins is closely tied to the appearance of chordates, and may have played a key role in the development of their novel, defining structures.

The lancelet *Branchiostoma floridae* has a tenascin gene that is remarkably similar to a vertebrate tenascin. In addition to heptad repeats near the amino terminus that may support multimerization, it encodes five tenascin-type EGF-like repeats, 38 FN3 domains and a carboxy-terminal fibrinogen-related domain. Seven of the FN3 domains have RGD motifs that are predicted to be exposed and available for integrin binding, which is suggestive or presumptive

evidence that integrin-mediated signaling may be a fundamental tenascin function (Tucker and Chiquet-Ehrismann 2009a). Another early chordate, the sea squirt *Ciona intestinalis*, also has a tenascin gene. The predicted protein has heptad repeats, eight tenascin-type EGF-like repeats, 19 FN3 domains and a carboxy-terminal fibrinogen-related domain (Tucker et al. 2006; Tucker and Chiquet-Ehrismann 2009a).

As will be described below, tenascin-C is able to influence cell spreading and proliferation via its interactions with fibronectin (Huang et al. 2001; Midwood et al. 2004), which led to the hypothesis that tenascins may have evolved,

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in part, to modulate fibronectin function. If true, one would expect that fibronectins evolved either before tenascins or at roughly the same time. Surprisingly, attempts to identify genes encoding FN1, FN2 and FN3 domains in a number of genomes reveal that fibronectin, though highly conserved in domain organization in vertebrates, is only found in organisms belonging to the Phylum Chordata (Tucker and Chiquet-Ehrismann 2009a; see also Whittaker et al. 2006). A fibronectin-like gene is found in the genome of the sea squirt *Ciona savignyi* (Tucker and Chiquet-Ehrismann 2009a), but no fibronectin-like genes could be found in the *Branchiostoma floridae* genome, even though it contains a tenascin gene. If amphioxus is more distantly related to vertebrates than the sea squirts, which is becoming more widely accepted (e.g., see Putnam et al. 2007), then tenascin may have evolved before fibronectin, not the other way around. Regardless of their precise origins, the first organisms that express both fibronectin and tenascin are the vertebrates, and their coexpression and interactions may have been fundamental to vertebrate evolution.

The literature contains a number of names for tenascins (Table 1). Some of these names were assigned before the relationship to the tenascin family was known, whereas others were named before it was recognized that the orthologous tenascin had already been described in another species. Studies of the evolution of tenascin genes have helped clarify the relationships between members of the gene family and have led to simplification of the tenascin nomenclature (Tucker et al. 2006). Therefore, in most vertebrates there are four tenascins: tenascin-C, which is the original “tenascin”; tenascin-R, with the “R” standing for “restriction”; tenascin-X, named after “human gene X”; and tenascin-W, named after its discoverer. Bony fish (Class Actinopterygii) have five tenascins (Fig. 1). The fifth tenascin in bony fish is a duplication of tenascin-C; the two paralogs are called tenascin-Ca and tenascin-Cb (Tucker et al. 2006). Note that an unexpressed tenascin pseudogene (tenascin-XB) found in mammalian genomes appears to have resulted from a

duplication of the carboxy-terminal part of the tenascin-X gene. The main features of the four mouse and human tenascins are summarized in Figure 2. The models depicted in Figure 2A are based on the protein accession numbers given in Figure 2B, which also includes the chromosomal locations, major sites of expression, and human disease associations. Further variations in tenascins are obtained by alternative splicing, which is frequently observed in tenascin-C and also occurs in tenascin-R (Joester and Faissner 2001). The FN3 repeats subject to alternative splicing are colored in light green in Figure 2A. Alternative splicing has not been described for tenascin-W or tenascin-X.

TENASCINS IN CELL ADHESION MODULATION

One of the first observations testing tenascin-C as a substratum for cells in culture revealed that cells did not adhere well and proliferation was increased (Chiquet-Ehrismann et al. 1986). Tenascin-C even inhibited cell adhesion to fibronectin (Chiquet-Ehrismann et al. 1988; Lotz et al. 1989). This provided the basis for the new classification of a subgroup of extracellular matrix proteins as antiadhesive or adhesion-modulating extracellular matrix proteins (reviewed in Chiquet-Ehrismann 1991). Adhesion modulation has, in the meantime, become a well-recognized mechanism to influence cell proliferation, migration, differentiation, and anoikis (Murphy-Ullrich 2001). This theme is now very much under discussion in the fields of stem cell research as well as tissue engineering (for a recent review, see Guilak et al. 2009). Several mechanisms were found to be responsible for the antiadhesive effects of tenascin-C depending on the cells and the experimental paradigms used. In mixed substrata of fibronectin and tenascin-C the antiadhesive effect is mediated by binding of tenascin-C to the HepII/syndecan-4 binding site in the FN3-13 repeat of fibronectin, thereby inhibiting the coreceptor function of syndecan-4 in fibronectin-mediated cell spreading

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Figure 2. Main features of the four vertebrate tenascins. (A) *Top left* shows a tenascin-C hexabrachion revealed in an electron micrograph after rotary shadowing. Domain models of each tenascin family member are depicted for human and mouse orthologs as indicated by h (human) or m (mouse) within their fibrinogen-related domains (FReD). Heptad repeats for oligomerization are present close to the amino terminus indicated by a short black line in front of the EGF-like repeats shown in yellow and FN3 domains in dark green for the constant repeats, light green for FN3 repeats prone to alternative splicing, and orange for RGD-containing FN3 repeats. (B) Accession numbers on which the models in (A) are based and the chromosomal locations of the genes are given in the first column. Note that these protein sequences do not include certain extra repeats existing in rare splice variants. Main sites of expression are summarized as well as the major human or mouse disease associations found in the literature and cited in the main text.

(Huang et al. 2001; Midwood et al. 2004). In consequence, the activities of RhoA and focal adhesion kinase are compromised: cells redistribute their actin to the cell cortex and down-regulate focal adhesion formation (Wenk et al. 2000; Midwood and Schwarzbauer 2002; Ruiz et al. 2004; Lange et al. 2007). This might be a general mechanism for adhesion modulation,

because fibulin-1 was also shown to modulate cell adhesion to fibronectin in this way (Williams and Schwarzbauer 2009). Additional mechanisms of adhesion modulation by tenascin-C have been described that require cyclic GMP-dependent protein kinase (Murphy-Ullrich et al. 1991, 1996). Furthermore, tenascin-C can directly interact with various cell

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adhesion receptors and influence their activities (for extensive reviews, see Orend and Chiquet-Ehrismann 2006; Midwood and Orend 2009). The FN3 repeats subject to alternative splicing are also involved in the modulation of cell adhesion, and tenascin-C with extra repeats was shown to be more active than tenascin-C without extra repeats in inducing irregular cell spreading with formation of cortical membrane ruffles and cellular protrusions that contain filamentous actin and fascin (Fischer et al. 1997). A possible receptor mediating this effect could be annexin II, which was found to bind to the extra repeats of tenascin-C (Chung and Erickson 1994), and annexin II receptors on endothelial cells were shown to mediate several cell regulatory functions induced by tenascin-C, such as mitogenesis, cell migration, and loss of focal adhesions (Chung et al. 1996). Figure 3 shows two examples of cells plated on tenascin-C versus fibronectin demonstrating the morphological differences that result from culture on the respective extracellular matrix proteins.

Adhesion modulation effects have also been reported for the other tenascins. Tenascin-R

inhibits adhesion of mesenchymal and neural cells to fibronectin (Pesheva et al. 1994). Osteosarcoma and bladder carcinoma cells adhere to a tenascin-X substratum, but they did not spread or assemble stress fibers (Elefteriou et al. 1999) and p38 MAPK was identified as the major mediator of tenascin-X-induced cell detachment of mouse L cells (Fujie et al. 2009). Addition of tenascin-W to the culture medium of cancer cells (Scherberich et al. 2005; Degen et al. 2007) as well as primary osteoblasts (Meloty-Kapella et al. 2006; Meloty-Kapella et al. 2008) stimulated their migration toward a fibronectin substratum in vitro. Thus, a common activity of all tenascins seems to be their ability to modulate cell adhesion and migration.

REGULATION OF TENASCIN EXPRESSION

From the very different expression patterns of the four tenascins, it follows that the regulation of expression must be very different (for recent reviews, see Chiquet-Ehrismann and Chiquet 2003; Tucker and Chiquet-Ehrismann 2009b). There seem to be two types of tenascins: those with widespread and steady expression

Figure 3. Adhesion modulation by tenascin-C. Cells adopt different morphologies depending on the substratum to which they are adhering. Although the MCF7 epithelial cancer cells form cell layers with close cell–cell contacts typical of epithelia on fibronectin, they disperse and lose their cell–cell contacts on a tenascin-C substratum, a process termed epithelial–mesenchymal transition (or EMT) that is important in cancer invasion. In addition, the myogenic/osteogenic mouse cell line C2C12 reacts differently to these two substrata. As revealed by phalloidin staining the cells elaborate stress fibers on fibronectin while they concentrate F-actin in cell protrusions when plated on tenascin-C.

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throughout development and in the adult, and those with highly fluctuating expression patterns depending on the developmental stage and on intrinsically or extrinsically changing environments. Tenascin-X and tenascin-R belong to the former group; tenascin-X is expressed primarily by muscle and in loose connective tissues, whereas tenascin-R expression is limited to the nervous system. Tenascin-C and tenascin-W belong to the latter group. During development, tenascin-C is expressed during organ morphogenesis, and both tenascin-C and tenascin-W are expressed in the developing and adult skeleton. Tables summarizing the reported expression patterns of all tenascins can be found in Brellier et al. (2009). In addition, many pathological conditions including tumorigenesis, infection, and inflammation trigger tenascin-C expression (for a review, see Chiquet-Ehrismann and Chiquet 2003). Many different growth factors and cytokines are able to induce tenascin-C expression (for a review, see Orend and Chiquet-Ehrismann 2006; Tucker and Chiquet-Ehrismann 2009b), whereas less is known about the regulation of tenascin-W. There exist some common factors that lead to tenascin-C and tenascin-W expression in cultured cells, such as transforming growth factor α and transforming growth factor β although the latter is more potent in inducing tenascin-C than tenascin-W, whereas the opposite is the case for BMP2 (Scherberich et al. 2005). Activation of many of the major signaling pathways can lead to induction of

tenascin-C and/or tenascin-W expression (Table 2). In turn, plating cells on tenascin-C-containing substrata can affect several signaling pathways, such as induction of signaling through 14-3-3 tau (Wang et al.; Martin et al. 2003) MAPK and Wnt (Ruiz et al. 2004) or inhibition of the small GTPase RhoA known to induce actin stress fiber formation (Wenk et al. 2000). Thus, some of the same pathways that initially trigger tenascin-C expression potentially lead to negative (in the case of RhoA) or positive (in the case of MAPK and Wnt signaling) feedback loops. Another positive feedback loop may be the basis of chronic inflammation in arthritis, where inflammatory cytokines induce tenascin-C expression, which in turn activates TLR4 signaling in fibroblasts and myeloid cells leading to more cytokine production and more tenascin-C secretion. This establishes a vicious cycle causing chronic inflammation (Goh et al. 2010; Midwood et al. 2009).

Consistent with the many signaling pathways known to induce tenascin-C expression many transcription factors are known to stimulate tenascin-C transcription (Table 2) whereas GATA-6 was identified as a transcriptional repressor of tenascin-C (Ghatnekar and Trojanowska 2008). In addition, tenascin-C can also be regulated at the transcript level by miR-335 (Tavazoie et al. 2008).

The least investigated aspect of tenascin-C regulation is its turnover at the protein level, although several proteases have been found to

Table 2. Signaling pathways and transcription factors that induce tenascin-C expression.

Signaling pathway	Reference	Transcription factor	Reference
ROS/NFkB	Yamamoto et al. 1999	Brn2	Copertino et al. 1997
ERK1/2	Jones et al. 1999	c-Jun, NFkB	Mettouchi et al. 1997
Ras/MAPK	Maschler et al. 2004	Prx1	Jones et al. 2001
Rho/ROCK	Chiquet et al. 2004; Sarasa-Renedo et al. 2006	Smad3/4, Sp1, Ets1,2 CBP/p300	Jinnin et al. 2004; Jinnin et al. 2006
β -catenin/Wnt	Beiter et al. 2005; Cohen et al. 2008	Sox4	Scharer et al. 2009
Notch	Sivasankaran et al. 2009	RBPJk	Sivasankaran et al. 2009
AKT/PI3K	Goh et al. 2010	MEF2c with scleraxis	della Gaspera et al. 2009
TLR4/NFkB	Goh et al. 2010	EWS-ETS	Watanabe et al. 2003

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cleave tenascin-C (Mai et al. 2002; Imai et al. 1994; Siri et al. 1995). In the case of meprin β and plasmin, digestion of tenascin-C converts it from an antiadhesive to an adhesive substratum (Gundersen et al. 1997; Ambort et al. 2010).

The promoter and the transcriptional regulation of tenascin-W remain to be determined. However, the promoters of tenascin-R and tenascin-X have been identified and studied. The promoters of human (Gherzi et al. 1998), rat (Leprini et al. 1998), and mouse tenascin-R (Putthoff et al. 2003) lack a TATA or CAAT box, GC-rich regions or initiator element. Sequences required for the neuronal expression of tenascin-R were identified within 57bp upstream of the transcription start site and in the first exon (Leprini et al. 1998; Putthoff et al. 2003), but the transcription factors involved are unknown. Several regions of the tenascin-X promoter were found to bind proteins by mobility shift assays and functionally important Sp1 binding sites were identified (Minamitani et al. 2000; Wijesuriya et al. 2002). Glucocorticoids inhibit tenascin-X expression in fibroblasts (Sakai et al. 1996). In this respect tenascin-X is similar to tenascin-C, which is also negatively regulated by glucocorticoids (Chiquet-Ehrismann et al. 1995; Sakai et al. 1995).

TENASCINS IN CELL MIGRATION, CANCER CELL INVASION, AND METASTASIS

One of the main sites of expression of tenascin-C and tenascin-W is the tumor microenvironment (for recent reviews, see Martina et al. 2010; Orend and Chiquet-Ehrismann 2006). In most epithelial cancers, the cellular source of tenascin-C and tenascin-W is not the tumor cells themselves, but rather tumor-associated fibroblasts residing in the tumor microenvironment. Immunohistochemical analyses of these tumors usually reveal a fibrous network of tenascin-C and tenascin-W enclosing unstained tumor nests. Examples of breast and colon carcinomas are shown in Figure 4. In other cancers such as melanoma or glioblastoma, the cancer cells themselves are secreting tenascin-C (Natali et al. 1990; Herlyn et al. 1991; Sivasankaran et al.

2009) and both tenascin-C as well as tenascin-W are present in brain cancer blood vessels (Higuchi et al. 1993; Zagzag et al. 1995; Kim et al. 2000; Martina et al. 2009). Tenascin-W staining correlates with von Willebrand factor staining, which is consistent with tenascin-W production by endothelial cells (Fig. 4). In contrast, tenascin-C staining correlates with desmin-expressing cells, demonstrating that the source of tenascin-C may be pericytes (Martina et al. 2009). Both tenascins have been shown to stimulate angiogenesis in vitro (Martina et al. 2009). Perivascular staining of tenascin-C was found to correlate with a shorter disease-free time in astrocytoma patients suggesting that tenascin-C may serve as a prognostic marker for an earlier tumor recurrence (Herold-Mende et al. 2002). In contrast to oligodendrogliomas, glioblastomas are rich in tenascin-C throughout the tumor, and tenascin-C has been associated with local invasion of this aggressive tumor type and stromal tenascin-C expression is correlated with shorter patient survival (Leins et al. 2003). Tenascin-C is strongly implicated in mediating the invasive behavior of glioma cells, and early studies showed that tenascin-C stimulated fibronectin-mediated cell migration (Deryugina and Bourdon 1996). Similar observations have been made by several different research groups (Hirata et al. 2009; Sivasankaran et al. 2009); in one report, this migration was found to be dependent on the induction of metalloproteinase-12 (Sarkar et al. 2006). The connection between tenascin-C expression and invasion is, however, not restricted to brain tumors. Also, in breast cancer tenascin-C was observed at invasion borders and can serve as a predictor of both local and distant recurrence (Jahkola et al. 1998) and a higher risk of distant metastasis (Jahkola et al. 1996). A role for tenascin-C in metastasis promotion was also indicated by studies of a mouse xenograft model. It was found that miR335 suppresses metastasis by down-regulating Sox4 and tenascin-C (Tavazoie et al. 2008) and tenascin-C has recently been found to be a direct target of Sox4 (Scharer et al. 2009). Finally, tenascin-C was found among the signature genes that mediate breast cancer

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Figure 4. Tenascin-C and tenascin-W in cancer stroma. Immunostaining for tenascin-W and tenascin-C of sections of colon carcinoma (colon Ca) and breast carcinoma (breast Ca) reveal stromal staining in both cancer types (brown staining corresponding to the areas poor in nuclei visible in the corresponding H&E stained adjacent sections). In brain cancer (oligodendroglioma and glioblastoma) tenascin-W is found around blood vessels while tenascin-C is in addition also detected throughout the entire glioblastoma tissue and is secreted by these highly invasive cancer cells. The lowest panels reveal that tenascin-W and tenascin-C are expressed by different blood vessel cells: tenascin-W seems to be made by endothelial cells, whereas tenascin-C is made by the surrounding desmin-positive pericytes.

metastasis to lung (Minn et al. 2005). A similar correlation has been found for tenascin-W in mouse models of mammary cancer, where stromal tenascin-W expression was particularly prominent in those cancers known to metastasize (Scherberich et al. 2005). So far such a correlation was not observed in human breast cancer where tenascin-W expression was higher in low-grade than in high-grade cancers (Degen et al. 2007). However, in colon cancer tenascin-W may correlate with the severity of

the disease because serum levels of patients with nonmetastatic colon cancers were higher in those patients that suffered a recurrence (Degen et al. 2008).

We mentioned above the existence of distinct tenascin-C isoforms (see Fig. 2). It is interesting to note that larger isoforms are often tumor-specific. For example, in high-grade astrocytomas large tenascin-C variants containing the FN3-C domain are abundant around vascular structures and proliferating cells

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(Carnemolla et al. 1999). Also, FN3-B domain containing isoforms are associated with invasion fronts in ductal breast cancer (Tsunoda et al. 2003) and those with FN3-A1 domain are found in the majority of lymphomas (Schliemann et al. 2009). Part of the reason for the distinct isoform expression pattern between healthy and tumor tissues could be because the extracellular pH influences the splicing of tenascin-C mRNA (Borsi et al. 1996). Thus, large tenascin-C isoforms might be expected to be enriched in tumors known to represent an acidic tissue. The presence of large tenascin-C variants in tumors can have additional functional consequences because this will also influence the susceptibility of tenascin-C to proteases (Siri et al. 1995; Ambort et al. 2010). The cancer-specific expression of large tenascin-C isoforms has also been exploited for targeted tumor therapy (Brack et al. 2006; Reardon et al. 2007). For tenascin-X and tenascin-R a connection to cancer has rarely been made. Thus, the tumor-specific functions described above are particularly important for tenascin-C and tenascin-W.

TENASCIN FUNCTION INFERRED FROM MOUSE MODELS

The initial studies of tenascin-C knockout mice did not report any obvious developmental abnormalities (Saga et al. 1992; Forsberg et al. 1996), but over time a number of important phenotypes have been observed (Table 3). The first of these described abnormal behavior (Fukamauchi et al. 1996; see also Kiernan et al. 1999), which was confirmed and thoroughly analyzed by Morellini and Schachner (2006). They found that the tenascin-C knockout mice have lower anxiety and increased activity, but normal coordination and cognitive skills. Detailed electrophysiological (Evers et al. 2002; Gurevicius et al. 2009) and morphometric (Irintchev et al. 2005; Gurevicius et al. 2009) studies of knockout mouse brains produced results that may help explain the behavioral changes. For example, the cerebral cortex of tenascin-C knockout mice has a higher neuronal

density than the controls and its pyramidal cells have abnormal dendritic morphology.

Some organs featuring epithelial-mesenchymal interactions and branching morphogenesis are also abnormal in the tenascin-C knockout mice. When lungs are cultured from fetal knockout mice they have fewer end buds than controls and the end buds are larger (Roth-Kleiner et al. 2004). This was confirmed in sections of the lungs of neonatal knockout mice, which also have larger air spaces than the controls. The prostates of the knockout mice are larger than in wild-type mice and feature multi-layered epithelia, some of which protrude into the lumens of the ducts (Ishii et al. 2008).

Tenascin-C is frequently encountered in stem cell niches, and hematopoiesis is abnormal in stem cells cultured from tenascin-C knockout mouse bone marrow (Ohta et al. 1998). Similarly, the tenascin-C found near glial precursors in the developing brain appears to be critical for their differentiation, migration, and survival (Garcion et al. 2001; Garcion et al. 2004; Garwood et al. 2004). However, the appearance of glial progenitors derived from the tenascin-C-rich subependymal zone of the adult mouse is unaffected by knocking out tenascin-C (Kazanis et al. 2007). The latter is an important example of close analysis of a region with abundant tenascin-C failing to show a phenotype in the knockouts, perhaps because its absence can be compensated for by other factors.

Some of the most interesting phenotypes observed in the tenascin-C knockout mice are seen in disease models or responses to trauma (Table 3). For example, tenascin-C knockout mice develop less severe asthma in a mouse model (Nakahara et al. 2006). This may be a reflection of the negative consequences of up-regulation of tenascin-C expression commonly associated with inflammation. This was nicely illustrated by (Midwood et al. 2009), who showed that tenascin-C knockout mice are protected from arthritis-like damage following the injection of an antigen into the knee joint. It seems that in the absence of tenascin-C mice are protected from chronic inflammation. A connection between tenascin-C and asthma has also been made in humans where it was

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Table 3. Tenascin knockout mouse phenotypes.

Tenascin knockout	Phenotypes	References
Tenascin-C	Abnormal behavior	
	Poor swimming, hyperlocomotion, coordination deficits	Fukamauchi et al. 1996; Kiernan et al. 1999
	Circadian rhythm defects, increased activity in novel environments, reduced anxiety, weak grip	Morellini and Schachner 2006
	Abnormal central nervous system development and organization	
	Increased migration and reduced proliferation of oligodendrocyte precursors	Garcion et al. 2001
	Accelerated maturation of oligodendrocyte precursors	Garwood et al. 2004
	Effects on numbers of neurons and glia in the hippocampus and cerebral cortex	Irintchev et al. 2005; Gurevicius et al. 2009
	Abnormal brain electrophysiology	Evers et al. 2002; Andjus et al. 2005; Gurevicius et al. 2009
	Effects on olfaction and olfactory bulb development	de Chevigny et al. 2006; Treolar et al. 2009
	Abnormal stem cell niches	
	Reduced colony forming capacity of bone marrow cells	Ohta et al. 1998
	Abnormal neuronal stem cell niche	Garcion et al. 2004
	Abnormal branching morphogenesis	
	Reduced airway branching and larger air spaces	Roth-Kleiner et al. 2004
	Abnormal prostate development	Ishii et al. 2008
	Abnormal responses to injury and stress	
	Susceptibility to glomerulonephritis	Nakao et al. 1998
	Prolonged dermatitis following application of hapten	Koyama et al. 1998
	Absence of migrating keratinocytes in corneal sutures	Matsuda et al. 1999
	Abnormal regeneration, sprouting and reinnervation following peripheral nerve crushes or exposure to neurotoxins	Cifuentes-Diaz et al. 1998; Cifuentes-Diaz et al. 2002; Guntinas-Lichius et al. 2005
	Reduced angiogenesis around grafted melanoma cells	Tanaka et al. 2004
	Attenuated response to vibrissotomy	Cybulska-Klosowicz et al. 2004
	Reduced recruitment of myofibroblasts after myocardial injury	Tamaoki et al. 2005
	Reduced neointimal cell migration and proliferation following aortotomy	Yamamoto et al. 2005
	Reduced bronchial asthma	Nakahara et al. 2006
	Attenuated fibrosis during hepatitis	El-Karef et al. 2007
	Atrophy of fast-muscle fibers following mechanical stress	Flück et al. 2008
	Altered expression of inflammatory cytokines following CNS injury	Ikeshima-Kataoka et al. 2008

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Table 3. (Continued from previous page)

Tenascin knockout	Phenotypes	References
Tenascin-R	Reduced joint inflammation and protection from arthritis	Midwood et al. 2009
	Delay in articular cartilage repair following ligament damage	Okamura et al. 2010
	Reduced fibrosis and myocardial stiffness following myocardial infarction	Nishioka et al. 2010
	Abnormal behavior	
	Increased anxiety, reduced coordination, cognitive defects, improved working memory	Montag-Sallaz and Montag 2003; Freitag et al. 2003; Morellini et al. 2010
	Abnormal central nervous system development and organization	
	Abnormal electrophysiology	Weber et al. 1999; Saghatelian et al. 2001; Bukalo et al. 2001; Brenneke et al. 2004; Gurevicius et al. 2004; Bukalo et al. 2007
	Abnormal organization of perineural nets	Weber et al. 1999; Haunso et al. 2000; Brueckner et al. 2000
	Reduced extracellular space in brain	Syková et al. 2005
	Abnormal hippocampus	Nikonenko et al. 2003
Tenascin-X	Abnormal response to injury	
	Improved recovery following spinal cord or peripheral nerve injury	Guntinas-Lichius et al. 2005; Apostolova et al. 2006; Lee et al. 2009
	Retarded progression of electrical stimulation-induced seizures	Hoffmann et al. 2009
	Ehlers-Danlos Syndrome-related phenotypes	
	Abnormal epidermal scars, hyperextensible skin, fragile skin, reduced dermal fibrillar collagen, abnormal fibrillar collagen	Mao et al. 2002; Minamitani et al. 2004a, 2004b; Egging et al. 2006, 2007
	Miscellaneous phenotypes	
	Abnormal vaginal plug location, rectal prolapse	Egging et al. 2008
	Abnormal accumulation of dermal lipids	Matsumoto et al. 2004
	Abnormal melanoma growth and metastasis	Matsumoto et al. 2002

found that a coding SNP within an alternatively spliced FN3 domain strongly associates with adult bronchial asthma (Matsuda et al. 2005).

The tenascin-R knockout mice have neuronal phenotypes, as one would expect from the restricted pattern of tenascin-R expression (Table 3). The behavioral phenotypes are diametrically opposed to those observed in the tenascin-C knockouts: the tenascin-R knockout mice display more anxiety in an open field test, are uncoordinated, and have deficits in associative learning. Tenascin-R and tenascin-C both seem to be critical for normal development of

the nervous system, but they appear to act on different parts of the brain.

The first morphological tenascin knockout phenotype came not from the mouse, but from a human: a 26-year-old man with Ehlers-Danlos Syndrome was shown to have a mutation that resulted in the loss of expression of tenascin-X (Burch et al. 1997). Ehlers-Danlos Syndrome is characterized as hyperextensible skin and joints, susceptibility to bruising, and poor wound healing. The role of tenascin-X in this syndrome, which previously was believed to be limited to collagens and enzymes that

help modify and assemble collagens, was shown convincingly by the phenotype of the tenascin-X knockout mouse (Table 3) (Mao et al. 2002; see also Egging et al. 2006). These mice have easily deformable skin and a significant decrease in the number of collagen fibrils in the dermis.

The expression of tenascins has also been shown to change when other genes are knocked out. Thus, the phenotypes associated with these mutants may, in part, be related to changes in tenascin expression. For example, knockout of Bcl-2 results in abnormal vascular development and angiogenesis; endothelial cells isolated from these mice are less migratory and make less tenascin-C (Kondo et al. 2008). Knockouts of Smad8, which is part of the BMP signaling pathway, have increased levels of tenascin-C expression in vascular smooth muscle and develop vascular pulmonary disease (Huang et al. 2009). Mice deficient in Msx2 show accelerated healing of skin wounds accompanied by increased tenascin-C expression in the granulation tissue (Yeh et al. 2009). Finally, tenascin-C levels are elevated when MMP-19, a protease that cleaves tenascin-C, is knocked out (Gueders et al. 2009). The MMP-19 knockouts are prone to airway inflammation after challenge with airborne allergens.

Phenotypes of tenascin-C, -R, and -X knockout mice reveal critical roles for these proteins. Both tenascin-C and -R are required for normal development of the nervous system, and tenascin-C is required for normal responses to certain types of trauma. Tenascin-C does not appear to be necessary for the gross development of most nonneuronal tissues, but careful study shows that certain organ systems develop abnormally at the cellular level in the absence of tenascin-C. Tenascin-X is clearly required for the normal assembly and/or maintenance of the structural matrix of the dermis and other connective tissues. Future studies with tenascin-W knockout animals may give insight into critical functions for this protein as well. Unfortunately, all tenascin knockout mice are “whole body” knockouts, which increases the likelihood that the genes of other extracellular matrix proteins or their receptors or any other type of compensatory machinery could be

up-regulated or down-regulated to compensate for the missing tenascin. It would be interesting to see if Cre-mediated ablation of tenascin expression in a specific tissue and/or at a specific time in development would improve our understanding of tenascin functions.

In summary, there is clear evidence from these studies that tenascins can have structural roles as well as roles in cell signaling. An example of the former is tenascin-X, which is necessary for the structural integrity of connective tissues. Tenascin-C is an example of the latter. It is highly induced by many different challenges such as trauma, inflammation, or cancer development, and it seems to be involved in regenerative processes as well. It appears that tenascin-C is important in regulating cell proliferation and migration, and it affects differentiation during development as well as during regeneration and healing after insults. In both cases, the structural as well as the signaling functions, the exact molecular mechanisms underlying these activities remain to be determined.

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