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INVITED REVIEW

Tenascins and inflammation in disorders of the nervous system

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Abstract In vitro and in vivo studies on the role of tenascins have shown that the two paradigmatic glycoproteins of the tenascin family, tenascin-C (TnC) and tenascin-R (TnR) play important roles in cell proliferation and migration, fate determination, axonal pathfinding, myelination, and synaptic plasticity. As components of the extracellular matrix, both molecules show distinct, but also overlapping dual functions in inhibiting and promoting cell interactions depending on the cell type, developmental stage and molecular microenvironment. They are expressed by neurons and glia as well as, for TnC, by cells of the immune system. The functional relationship between neural and immune cells becomes relevant in acute and chronic nervous system disorders, in particular when the blood brain and blood peripheral nerve barriers are compromised. In this review, we will describe the functional parameters of the two molecules in cell interactions during development and, in the adult, in synaptic activity and plasticity, as well as regeneration after injury, with TnC being conducive for regeneration and TnR being inhibitory for functional recovery. Although not much is known about the role of tenascins in neuroinflammation, we will describe emerging knowledge on the interplay between neural and immune cells in autoimmune diseases, such as multiple sclerosis and polyneuropathies. We will attempt to point out the directions of experimental approaches that we envisage would help gaining insights into the complex interplay of TnC and TnR with the cells that express them in pathological conditions of nervous and immune systems.

Keywords Extracellular matrix · Nervous system disorders · Neuroinflammation · Regeneration · Tenascin-C · Tenascin-R

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Introduction

Tenascins belong to a family of closely related extracellular matrix (ECM) glycoproteins, which consists of six members: tenascin-C (Bourdon and Ruoslahti, 1989; Chiquet and Fambrough, 1984), tenascin-R (Fuss et al., 1991, 1993; Pesheva et al., 1989; Rathjen et al., 1991), tenascin-X (Bristow et al., 1993), tenascin-Y (Hagios et al., 1996) and tenascin-W in zebrafish (Weber et al., 1998), with its mouse homolog designated tenascin-N (Neidhardt et al. 2003). Among them, tenascin-R is expressed exclusively in the nervous system, whereas tenascin-C, tenascin-Y, tenascin-W and tenascin-N are expressed in and outside the

nervous system. Tenascin-C and tenascin-R have been most widely studied in nervous system functions, and it thus deems appropriate to focus our review on these two molecules.

Tenascin-C

Structure Tenascin-C (TnC) is a large, oligomeric molecule of 1,900 kDa (Taylor et al., 1989), and consists of six identical polypeptide arms that are attached to a central globular core, thus forming a hexabrachion, as it had also been called. The arms are linked at their amino termini via a tenascin assembly (TA) domain (Jones and Jones, 2000), containing cysteine residues and three to four α-helical heptad repeats (Conway and Parry, 1991). The individual arms consist of epidermal growth factor-like (EGFL) repeats followed by domains similar to the type III units found in fibronectin (FNIII). The distal parts of the polypeptide arms end in a terminal knob resembling the carboxyl terminal portion of the beta and gamma chains of fibrinogen (Jones et al., 1988; Nies et al., 1991; Siri et al., 1991).

Alternative RNA splicing yields various isoforms of TnC with different numbers of domains (Nies et al., 1991; Spring et al., 1989). Alternatively spliced domains of TnC include FNIII A1, A2, A4, B, C and D domains, inserted between the 5th and 6th FNIII domains (Dörries and Schachner, 1994; Joester and Faissner, 1999, 2001). By the multiple variations of these alternatively spliced polypeptides, the tenascins are predisposed to interact with different types of cellular receptors or components of the ECM, thereby generating an impressive level of diversity in the function of the tenascins (Jones and Jones, 2000). The functions of the different domains have been extensively studied over many years. The FNIII domains at the proximal splice site influence neuronal and neural stem cell migration and FNIII domains at the distal splice site promote neurite outgrowth (Doerries et al., 1996; Faissner et al., 1994; Faissner and Steindler, 1995). The EGFL repeats play a role in neuronal and neural stem cell migration and pathfinding during development and in the adult central nervous system (Jones and Jones, 2000; Wiese et al., 2012). Cell surface receptors for TnC include members of the integrin family (Prieto et al., 1990), cell adhesion molecules (CAMs) of the immunoglobulin superfamily, a transmembrane receptor called phosphacan/receptor protein tyrosine phosphatase beta/zeta (RPTP z/b) (Barnea et al., 1994; Milev et al., 1997), and annexin II (Chung und Erickson, 1994; Chung et al., 1996). TnC is also known to interact with other ECM components, including fibronectin (Chiquet-Ehrismann, 1991; Chung et al., 1995), and chondroitin sulfate proteoglycans (Chiquet and Fambrough, 1984; Vaughan et al., 1987).

Expression TnC is highly expressed during ontogenetic development of almost every tissue. In the central nervous system, TnC is widely expressed at early stages of development in many species (Bartsch et al., 1992, 1995; Becker et al., 1995; Crossin et al., 1989; Götz et al., 1997; Joester and Faissner, 1999; Metzger et al., 2006; Mitrovic et al., 1994; Tongiorgi et al., 1995; Treloar et al., 2009). TnC is mainly synthesized by immature astrocytes, in particular radial glial cells during neuronal differentiation and migration in the cortex, retina and cerebellum (Crossin et al., 1986; Prieto et al., 1990; Tucker et al., 1994; Yuasa, 1996). It is also produced by neuronal subpopulations of the hippocampus, barrel cortex, olfactory bulb, spinal cord and retina (Bartsch, 1996; Götz et al., 1996; Mitrovic et al., 1994; Treloar et al., 2009).

Function The mechanisms by which TnC acts during development relate to its ability to function as an adhesive (Aukhil et al., 1990; Bourdon and Ruoslahti, 1989; Grumet et al., 1985; Prieto et al., 1990) and anti-adhesive (Faissner und Kruse, 1990; Prieto et al., 1990) molecule. These opposing activities have been attributed to the multidomain structure of TnC, in which the adhesive and anti-adhesive activities are mapped, respectively, to different FNIII domains and EGFL repeats (Doerries et al., 1996; Götz et al., 1996; Lochter and Schachner, 1993; Lochter et al., 1995). The duality of adhesive and repulsive properties predisposes TnC to participate in the control of cell migration, which is characterized by the dichotomy of bond formation and subsequent release (Faissner, 1997). In agreement with this assumption, the protein has been found to modulate the motility of many cell types, including neurons, fibroblasts and cancer cells (Jankovski and Sotelo, 1996; Paron et al., 2011; Trebaul et al., 2007). In addition, TnC is involved in axonal growth and guidance. Both the promotion of neurite outgrowth as well as the deflection of growth cones resulting from anti-adhesive features of TnC, have been documented (Crossin et al., 1989; Faissner and Steindler, 1995; Husmann et al., 1992; Lochter and Schachner, 1993; Taylor et al., 1993). The influence of TnC on growth cone motility and direction depends on the neuronal cell type and the geometry of its presentation in vitro, i.e. if TnC is offered as a uniform substrate or as a substrate boundary. When offered as substrate boundary with a conducive molecule, such as laminin, growth cones stall at the boundary, being deflected in most cases and only when a solitary growth cone overcomes the inhibitory boundary, it propels on the TnC substrate with a speed higher than on the laminin substrate (Taylor et al., 1993). Thus, when offered as a uniform substrate, TnC allows growth cones to advance at least as swiftly as on laminin. Again, this property depends on the neuronal cell type and developmental stage. In addition, because TnC is strongly expressed in the optic nerve head, it has been suggested to

inhibit the migration of oligodendrocytes from the optic nerve into the retina (Bartsch et al., 1994). Adhesive and anti-adhesive properties enable TnC to modulate cell proliferation. In vitro, it stimulates cell proliferation, e.g. of smooth muscle cells (Cleek et al., 1997; Cowan et al., 2000) or astrocytes (Ikeshima-Kataoka et al., 2007), but it has also been found to inhibit cell proliferation (Crossin, 1991). It is documented, on the one hand, to act as a survival factor by suppressing apoptosis (Cowan et al., 2000), while, on the other hand, studies on tenascin-C deficient (TnC−/−) mice report that TnC deficiency leads to reduced levels of programmed cell death, suggesting that it is also involved in the induction of physiological apoptosis, important for normal brain development (Garcion et al., 2001). Of particular note, there are several lines of evidence that TnC is involved in synaptic plasticity (Dityatev and Schachner, 2003; Gurevicius et al., 2009; Šekeljić and Andjus, 2012).

Tenascin-R

Structure Similar to TnC and other tenascin family members, TnR has a cysteine-rich N-terminal region, followed by EGFL domains, FNIII like repeats and a fibrinogen-homologous C-terminus (Jones and Jones, 2000). Two isoforms, one with molecular weight of 160 kDa, which forms both monomers and dimers, and another of 180 kDa, which forms trimers, are generated by alternative splicing of the sixth FNIII domain (Bartsch et al., 1993; Pesheva et al., 1989; Fuss et al., 1993).

Expression Tenascin-R (TnR) is expressed exclusively in the central nervous system by oligodendrocytes and some neuronal subpopulations (Bartsch et al., 1993; Fuss et al., 1993; Schachner et al., 1994). During mammalian brain development, TnR is first detectable around birth. It is expressed by oligodendrocyte progenitors and type-2 astrocytes and is most abundantly synthesized during myelination, being downregulated to low levels in the adult (Bartsch et al., 1993; Wintergerst et al., 1993), when it is localized at nodes of Ranvier and on the outer aspects of myelin sheaths (Bartsch et al., 1993). In adult rodents, TnR is produced by subpopulations of neurons and released into the extracellular matrix around the cell bodies and proximal dendrites of motoneurons in the spinal cord and brain stem, as well as interneurons in the cerebellum, hippocampus and olfactory bulb. This intriguing assembly of the extracellular matrix to which TnR contributes has been called ‘perineuronal net’.

Function Similar to TnC, TnR has inhibitory functions in the outgrowth and guidance of optic axons in vivo (Becker et al., 2000, 2003). TnR can, like TnC, both inhibit and promote neurite outgrowth depending on the cell type and on the way it is presented to the cells, i.e. as a uniform substrate or a substrate boundary (Becker et al., 2000; Faissner 1997; Pesheva et al., 1994; Schachner, 1994; Schachner et al., 1994). Furthermore, TnR can be adhesive or anti-adhesive to different cell types, depending on the partner cell type and developmental stage (Morganti et al., 1990; Pesheva et al., 1993; Schachner et al., 1994). During the first phase of interaction (shorter than 1 h), TnR is adhesive and thereafter becomes anti-adhesive: the initial recognition between TnR and a partner molecule TnR is adhesive to cells, and thereafter it becomes anti-adhesive, i.e. repellent. We therefore prefer the term “recognition” in the context of cell interactions, since after a short recognition phase the molecules can become adhesive or repellent. TnR supports the adhesion of oligodendrocytes and enhances oligodendrocyte process formation mediated by its binding to sulfogalactose-containing glycosphingolipids expressed on the oligodendrocyte surface (Pesheva et al., 1997). Finally, a function not obviously related to recognition was discovered: TnR is a functional modulator of the beta-subunit of voltage-gated sodium channels (Srinivasan et al., 1998; Xiao et al., 1999). Similarly, TnR is involved in functions that are also not obviously related to recognition between cells, namely synaptic functions, by being an important modulator of plasticity at central nervous system synapses (for reviews see Dityatev et al., 2010a,b). TnR regulates inhibitory perisomatic inhibition via interactions of its HNK-1 (human natural killer cell) carbohydrate epitope with GABA-B receptors and thus influences synaptic transmission and plasticity in the hippocampus (Brenneke et al., 2004; Bukalo et al., 2001; Dityatev and Schachner, 2003; Morellini et al., 2010; Saghatelyan et al., 2000, 2001). It is thus also an important ingredient in neural homoestasis. TnR cooperates with other extracellular matrix components in perineuronal nets in an arrangement similar to that of TnC, in that it surrounds cell bodies and proximal dendrites of some excitatory (e.g. motoneurons) and inhibitory, mostly GABAergic neuronal subpopulations. This assembly is achieved by TnR’s interactions with other glycoproteins, such as TnC, chondroitin sulfate proteoglycans, phosphacan or lecticans, such as brevican and versican as well as the glycan hyaluronic acid (Angelov et al., 1998; Brückner et al., 2000; Celio and Blümcke 1994; Celio and Chiquet-Ehrismann 1993; Hagihara et al., 1999; Haunso et al., 2000; Weber et al., 1999). Importantly for the relevance of TnR in the immune system, microglial cells are influenced by TnR in migration and secretion of cytokines and growth factors (Angelov et al., 1998; Liao et al., 2005), and, interestingly, adhesion of microglia is reduced by TnR (Angelov et al., 1998).

Tenascins in disorders of the nervous system

TnC plays a role in various regenerative processes, such as peripheral nerve regeneration and focal brain injury

(Brodkey et al. 1995; Irintchev et al. 1993; Martini 1994). It also induces a quiescent (inactive) phenotype in cultured astrocytes; thus, possibly regulating astrocytic scar formation after spinal cord injury (Holley et al. 2005). Upregulation of TnC after injury was described in various experimental paradigms, including various mechanical brain injuries, kainic acid-induced seizures, and spinal cord and femoral nerve injuries (Deller et al., 1997; Fruttiger et al., 1995; Laywell et al., 1992; Nakic et al., 1996; Zhang et al., 1997), thus implicating it in, yet to be fully described, mechanisms relevant for functional recovery. First indications as to its functional role in injury paradigms have been obtained by analyzing locomotor recovery after spinal cord injury (Chen et al., 2010). Recovery after spinal cord injury in homozygous TnC deficient (TnC−/−) mice was found to be reduced when compared with their wild-type (TnC +/+) littermates, indicating an overall positive impact of TnC on regeneration. Furthermore, treatment of injured wild-type spinal cords with a beneficial domain of TnC, TnC-FND, markedly improved regeneration (Chen et al., 2010). These findings were in agreement with the previous observations that TnC enhances neurite outgrowth and supports neuronal survival (Lochter and Schachner, 1993; Meiners et al., 2001). In addition to its growth-promoting effects, different mechanisms may be involved in the regeneration-conducive effects of TnC. In TnC−/− mice both the synaptic rearrangements in the lumbar spinal cord and the H-reflex response after injury were attenuated compared with wild-type littermates. It is thus likely that TnC exerts its beneficial effects by modifying synaptic response to damage in the central nervous system (Chen et al., 2010). Because it is known that inflammation is an important element of pathology in regeneration after nervous system injuries (Ankeny and Popovich 2009; David and Kroner, 2011; Wu et al., 2012), it is noteworthy that blood–spinal cord barrier remains open for longer time after spinal cord injury in TnC−/− mice than in their wild-type littermates (Peter et al., 2012). The repair of the blood–spinal cord barrier after injury is accomplished by the activation of astrocytes and microglia as well as macrophages infiltrating the injured tissue due to the breakdown of the blood–central nervous system barrier. In addition, astrocytes contribute to the pathology of the injured central nervous system through glial scar formation (Bradbury and Carter, 2011; Devanathan et al., 2010; Jakovcevski et al., 2007; Lee et al., 2012; Rolls et al., 2009). The relationship of TnC in the nervous and immune systems and their interdependence thus needs to be studied in different injury constellations and in the context of acute and chronic inflammatory responses.

Similar to TnC, TnR expression is upregulated after spinal cord injury in the lesion area (Deckner et al., 2000), thus implicating TnR in inhibiting axonal regrowth after injury (Pesheva and Probstmeier, 2000; Sandvig et al., 2004). Indeed, TnR−/− mice recover better after spinal cord than their wild-type littermates on the same genetic background, indicating an inhibitory role of TnR in recovery after injury by reducing axonal regrowth and remodeling of perineuronal nets leading to increased synaptic plasticity. We propose that, due to the reduction of perineuronal nets, synaptic rearrangements around motoneurons are enhanced, resulting in, as compared to wild-type mice, higher numbers of GABAergic and lower numbers of glutamatergic synaptic terminals after injury (Apostolova et al., 2006). As a functional correlate, the H-reflex response after spinal cord injury in TnR−/− mice is enhanced compared with wild-type littermates, suggesting that in the absence of TnR remodeling of synapses on spinal motoneurons is enhanced (Lee et al., 2009). Enhanced structural plasticity may also contribute to the better functional outcome of facial nerve repair in TnR−/− mice (Guntinas-Lichius et al., 2005). Improved recovery from spinal cord injury after application of chondroitinase ABC (Bradbury et al., 2002) is possibly also attributable to enzymatic degradation of the perineuronal nets and concomitant removal of growth-inhibiting chondroitin sulfate proteoglycans (Rhodes and Fawcett, 2004).

Finally, it is worth mentioning in the context of regeneration that similar functions of TnC and TnR appear to be operant in injury of the peripheral nervous system as in the central nervous system: functional recovery was reduced in TnC−/− mice, whereas it was enhanced in TnR−/− mice, in comparison to their respective wild-type controls (Guntinas-Lichius et al., 2005). Interestingly, TnC and TnR doubly deficient mice behaved similarly to TnC−/− mice, emphasizing a more prominent role of TnC than TnR in regeneration in this injury paradigm (Guntinas-Lichius et al., 2005). In conclusion, we expect that these null mutant mice may allow first insights into the mechanisms of tenascin functions in other pathological conditions of the central and peripheral nervous systems.

Tenascins and inflammation

There appear to be two essential clues implying an important role of TnC in inflammation. First, this molecule is constitutively expressed in peripheral lymphoid organs, i.e. lymph nodes and spleen, with preferential expression in T cell-dependent zones of these organs (Chilosi et al., 1993). Second, TnC expression has been observed, in addition to the nervous system, in various tissues and organs affected by inflammation, including stomach (Tiitta et al., 1994), skin (Knaggs et al., 1994; Soini et al., 1997), oral mucosa (Tiitta et al., 1995), kidney (Truong et al., 1996), lungs (Hisatomi et al., 2009; Laitinen et al., 1996; Zhao et al., 1998), joints (Hasegawa et al., 2007; Patel

et al., 2011; Veje et al., 2003; Yoshida et al., 1996), eyes (Abu El-Asrar et al., 2003; Maseruka et al., 1997), blood vessels (Satta et al., 1997; Wallner et al., 1999), liver (Koukoulis et al., 1999), pleura (Kaarteenaho-Wiik et al., 2000), bowels (Riedl et al., 2011; Salas et al., 2003), and heart (Imanaka-Yoshida et al., 2002, 2004). Interestingly, TnC serum levels correlated with serum levels of a classical inflammation marker, C-reactive protein (Schenk et al., 1995).

The relationship between TnC and components of the immune system is bidirectional: TnC affects T cell activation as well as adhesive properties of T cells, B cells and monocytes. Specifically, it was shown that TnC inhibited T cell activation induced by a soluble antigen, alloantigens or by the mitogen concanavalin A, furthermore it enhanced clustering of B cells (Rüegg et al., 1989). Vice versa, TnC expression is regulated by cytokines released by the immune system in various cell types, as shown in numerous in vitro studies. For instance, interferon (IFN)- γ and tumor necrosis factor (TNF) stimulate its expression in bronchial epithelial cells (Härkönen et al., 1995). On the other hand, IFN-γ antagonizes fibroblast growth factor (FGF)2-induced TnC synthesis in astrocytes (DiProspero et al., 1997). Interleukin (IL)-4 induces and dexamethasone reduces TnC expression in type 2 macrophages (Gratchev et al., 2005). The combination of hypoxia and IL-1β increases TnC protein and mRNA levels of synovial fibroblasts (Tojyo et al., 2008). TNF stimulates TnC gene expression in adipose tissue (Catalán et al., 2012). The treatment of human fibroblasts with TNF and IFN-γ induces the expression of TnC (Meuronen et al., 2011). Accordingly, it was shown that the expression of TnC is attenuated in the respiratory epithelium of mice with impaired Th1 immunity, i.e. of mice that are deficient for the transcription factor STAT4 (Meuronen et al., 2011). As a consequence, these mice show reduced secretion of TNF and IFN-γ, suggesting that these cytokines increase TnC expression in vivo.

Toll-like receptors (TLR) are prototypical pattern recognition receptors. These receptors are specific for ligands that are cognate conserved molecular markers of infection and tissue damage. Typical TLR ligands are pathogen-associated molecular patterns (PAMP), i.e. microbial products, such as lipopolysaccharide, lipomannan or double-stranded RNA. Importantly, PAMPs and signaling that they induce through engagement of TLRs have been implicated in the regulation of TnC expression (Fig. 1). Various TLR ligands stimulate human monocyte-derived dendritic cells to express TnC. These molecules include lipopolysaccharide-LPS (for TLR4), 5,6-oxido-7,9,11,14-eicosatetraenoic acid - LTA (for TLR1/2), lipopeptide PAM3 (for TLR2/6) and flagellin (for TLR5) (Goh et al., 2010). Moreover, LPS also increases TnC gene expression in non-immune stromal vascular fraction cells of adipose tissue, i.e. endothelial cells, smooth muscle cells, pericytes, fibroblasts, mast cells, and preadipocytes, while TnC and TLR4 expression are both induced by TNF-α in these cells (Catalán et al., 2012). Vice versa, TnC induces synthesis of pro-inflammatory cytokines via activation of TLR4 in human macrophages and fibroblasts from synovia of rheumatoid arthritis patients (Midwood et al., 2009). Furthermore, TnC was also shown to induce expression of TLR4 protein, and CCL2 mRNA in human adipocyte cultures (Catalan et al., 2012).

Regulation of TnC activity in inflammation is achieved through control of its production and availability in the extracellular milieu. It was shown that TnC synthesis induced through TLR in dendritic cells is transcriptionally regulated and that it requires the specific activation of AKT/PI3 K and NF-κB signaling pathways (Goh et al., 2010). Furthermore, proteolytic degradation and, thus, inactivation of TnC plays an important role in control of its effect on inflammation. For example, TnC protein accumulation in peribronchial areas is considered to be a pathological feature of airway hyperreactivity to allergens in asthma and such accumulation is typically seen in MMP19-deficient mice, implying that MMP19 is a major regulator of this inflammatory process (Gueders et al., 2010). In parallel, Th2-driven airway eosinophilia and airway hyperreactivity is exacerbated in MMP19-deficient mice. Thus, it is suggested that by preventing TnC accumulation, MMP19 controls Th2-mediated inflammatory response in asthma (Gueders et al., 2010). However, in some instances, proteolytic cleavage of ECM molecules produces their fragments which are recognized by immune receptors and act upon immune cells (reviewed in Sorokin, 2010). Fragments obtained in this way may have different effects on immunity than their parental molecule, e.g. high-molecular weight hyaluronan has anti-inflammatory, while its low-molecular weight fragments have pro-inflammatory effects (Sorokin, 2010). Interestingly, thrombin-cleaved forms of TnC and osteopontin, another inflammation-related ECM component, share α9β1 integrin as a common receptor. α9β1 integrin-mediated signaling is involved in the pathogenesis of various autoimmune diseases (Uede, 2011), implicating this integrin as a key receptor for TnC effects in (auto)immunity. Indeed, it was shown in a collagen-induced arthritis model that TnC and osteopontin produced by dendritic cells and macrophages act through α9β1 integrin in cooperation with TLR ligands which act on TLR to stimulate the generation of Th17 promoting cytokines in the same cells (Fig. 1; Kanayama et al., 2011). In agreement with these observations is the finding that dendritic cells from TnC−/− mice exhibit specific deficits in differentiation of Th cells towards the Th17 cell phenotype in an antigen-induced arthritis model (Ruhmann

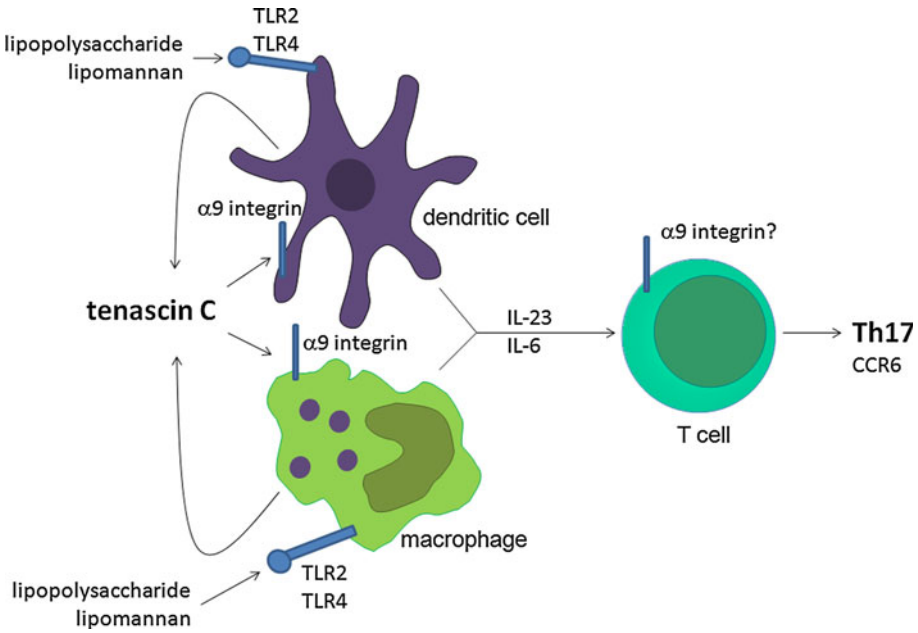

Fig. 1 TnC is an important mediator of Th17 differentiation. Antigen-presenting cells (macrophages and dendritic cells) produce TnC in response to various stimuli, including ligands for TLR (TLR2 and TLR4). Vice versa, TnC stimulates expression of TLR on antigen-presenting cells. TnC produced by dendritic cells and macrophages acts through α9β1 integrin and cooperates with TLR ligands (i.e. microbial products, such as lipopolysaccharide and lipomannan) to stimulate synthesis of cytokines IL-6 and IL-23 which direct differentiation of Th cells towards the Th17 phenotype. The possibility that TnC directly affects Th cell differentiation through α9β1 integrin has not yet been explored (note "?" in "α9 integrin" at the T cell)

et al., 2012). Namely, dendritic cells from TnC−/− mice have no defects in maturation, expression of MHC class II antigens or the co-stimulatory molecules CD40 and CD86, but they have reduced ability to produce inflammatory cytokines important for Th17 induction. Consequently, IL-17 levels in the arthritic joints of TnC−/− mice are almost annulated. Thus, it appears that through α9β1 integrin engagement TnC affects the generation of Th17 cells, which constitute a major auto-immunity inducing population (Fig. 1). The possibility that TnC affects Th17 differentiation by acting directly through α9β1 integrin expressed on T cells have not been explored so far. Interestingly, it is known that T cells recognize tenascin and that tenascin has a supportive role in T cell rolling (Clark et al., 1997). In the same study, however, numerous integrins (including β1) were discarded as candidate-binding partners for TnC to promote the rolling process.

Besides affecting immune cells directly through integrin receptors, TnC is also capable of interfering with the actions of other ECM molecules. For instance, if T cells recognize fibronectin through integrin α5β1 and α4β1 in vitro, ERK signaling is activated in T cells, resulting in elevated actin polymerization and amoeboid movement of T cells (Hauzenberger et al., 1999; Huang et al., 2010). However, if TnC is secreted in the vicinity of T cell fibronectin-interacting site, it blocks the interaction and inhibits motility of T cells. This mechanism of inhibition of T cell is utilized by glioblastoma cells, which in this way prevent infiltration of T cells into the tumor mass (Huang et al., 2010). TnC-imposed interference of T cell binding to fibronectin might have a broader implication for TnC-mediated regulation of leukocyte migration in general. In support of this assumption is the seminal report on TnC inhibition of monocyte adhesion to fibronectin (Rüegg et al., 1989).

When considering the importance of Th17 cells and IL-17 for rheumatoid arthritis pathogenesis (Li et al., 2010), it is conceivable that mice deficient in TnC would have impaired arthritis induction and/or its severity impediment. Indeed, TnC−/− mice showed rapid resolution of acute joint inflammation and they were protected from erosive arthritis, while intra-articular injection of TnC promoted joint inflammation in mice (Midwood et al., 2009). Data from arthritis studies in TnC−/− mice are corroborated by the finding that TnC is persistently highly expressed in the inflamed synovium of joints from rheumatoid arthritis patients (Goh et al., 2010) and that TnC induces cytokine synthesis in explant cultures from inflamed synovia of patients suffering from rheumatoid arthritis (Midwood et al., 2009).

Studies on TnC−/− mice have still not provided a clear view on the role of TnC in inflammation and autoimmunity. For instance, although TnC expression is elevated in the skin of mice suffering from contact dermatitis, in

TnC−/− mice dermatitis was more severe, while infiltration of polymorphonuclear cells persisted longer than in wild-type mice, suggesting that TnC is anti-inflammatory in dermatitis (Koyama et al., 1998). Similar results were obtained for unilateral stab injury in the cerebral cortex, with the expression of the pro-inflammatory cytokines IL-1β, TNF-α, and IL-6 being higher and levels of IL-4 and granulocyte colony-stimulating factor being lower in TnC−/− mice than in wild-type controls (Ikeshima-Kataoka et al., 2008).

Although there are no published data on the relevance of TnC in neuroinflammation, it is tempting to speculate that this molecule might have an important role in the pathogenesis of a prototypical inflammatory disease of the central nervous system – multiple sclerosis (MS). An obvious argument to support this claim would be that TnC directs naive $CD4^+$ cells towards the Th17 phenotype, since Th17 cells are among the most important and pathogenic populations of immune cells in MS (Jadidi-Niaragh and Mirshafiey, 2011). These cells have been indicated to initiate and orchestrate auto-aggressive immune responses which lead to demyelination and axonal damage. At later phases of the immunopathology of MS, other cell types, mostly macrophages and cytotoxic T cells perform effector functions directed against central nervous system tissue (Agrawal and Yong, 2006), leading to the formation of sclerotic plaques. These lesions may be acutely or chronically active (with ongoing inflammation) or inactive (post-inflammatory). It is noteworthy in this context that TnC and TnR expression is reduced in acute MS lesions, while there is no difference in TnC and TnR levels between chronic lesions and normal white matter (Gutowski et al., 1999). The observed downregulation of tenascins could be explained by an overall destruction of ECM components during inflammation, which would not have to be associated with a role of TnC in the regulation of inflammation. In a study on experimental autoimmune encephalomyelitis (EAE), an animal model of MS, upregulation of the two molecules in EAE lesions was observed (Zhao et al., 2009). It thus appears important to perform extensive investigation on the roles of TnC and TnR in MS initiation and progression. Because the immune response towards central nervous system tissue in MS is shaped in the lymphoid organs it deems necessary to investigate effects of TnC on the generation of the autoimmune response not only in the central nervous system, but also in tissues of the immune system. Much of our knowledge about MS pathogenesis stems from studies on EAE model (Krishnamoorthy and Wekerle, 2009). For instance, data about the importance of IL-17-producing Th17 cells in neuroinflammation (Hofstetter et al., 2005; Miljkovic et al., 2006; Miljković et al., 2011), or essential facts about transmigration of T cells across the blood–brain barrier (Bartholomäus et al., 2009). Thus, it seems reasonable to analyze TnC and TnR in the context of EAE model as a basis for further research in MS.

Astrocytes play a dominant role in the interaction between immune cells and central nervous system tissue (reviewed in Miljković et al., 2011), since they regulate another important feature in interactions of the central nervous system with immune cells—they are basic constituents of the blood–brain barrier and regulate its endothelial–astrocytic endfeet interface. Therefore, astrocytic processes interact with immune cells in the initial steps of an inflammatory invasion. In addition, astrocytes in the parenchyma produce several ECM components and ECM-related molecules which have been implicated in MS and EAE pathogenesis, including fibronectin, CS-1 (CS—connecting segment), osteopontin, MMPs and TIMPS (reviewed in Miljković et al., 2011). It is noteworthy that astrocytes not only generate TnC, but also respond to it (Fig. 2) Although the expression of α9β1 integrin on astrocytes has not yet been documented, it is known that astrocytes upregulate expression of various integrins in inflammatory environment, i.e. under the influence of inflammatory cytokines (Aloisi et al., 1992) and that astrocytomas express α9β1 integrin (Brown et al., 2008). Production of TnC by astrocytes is regulated by cytokines secreted by microglia and macrophages, such as transforming growth factor (TGF)-β and FGF-β (Smith and Hale, 1997). However, it is not known how pro-inflammatory cytokines, such as IFN-γ, TNF, and IL-17 regulate TnC synthesis in astrocytes. Interestingly, astrogliosis is delayed after stab injury to the brain in TnC−/− compared to wild-type mice, while the balance between production of pro-inflammatory and anti-inflammatory cytokines is shifted towards the inflammatory branch (Ikeshima-Kataoka et al., 2008). Thus, TnC may promote astrogliosis and inhibit generation of inflammatory cytokines by astrocytes. Importantly, both astrogliosis and cytokines production are involved in MS pathogenesis (Miller, 2012). Besides their role in interaction with immune cells, astrocytes play an important role in recovery from the inflammatory insult in MS, including remyelination (Moore et al., 2011). An in vitro correlate of these findings is that plating of astrocytes on TnC resulted in less myelinated fibers in dissociated rat spinal cord myelinating cultures when compared with plating of astrocytes on the control substrate poly-L-lysine (Nash et al., 2011). Whether TnC has a negative impact on remyelination in EAE will need to be studied with the hope to gain insights into the role of this extracellular matrix molecule in MS.

TnR is also able to stimulate generation of cytokines and growth factors, including TGF-β, TNF, CXCL2, brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in microglial cells (Liao et al., 2005; Liao

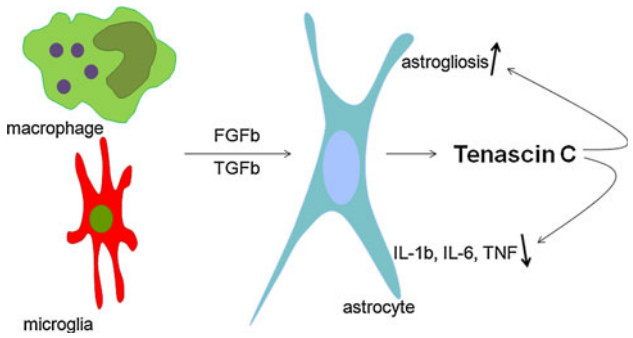

Fig. 2 TnC is produced by astrocytes and it affects astrocyte proliferation and cytokine production. Activated macrophages and/or microglia stimulate astrocytes by cytokine release (for instance, FGFb, TGFb) to produce TnC. By autocrine feedback TnC promotes astrogliosis and inhibits generation of pro-inflammatory cytokines (IL-1b, IL-6, TNF) in astrocytes

et al., 2008). When considering the importance of microglia and its soluble products for CNS inflammation, as well as for neural protection and repair (Ransohoff and Brown, 2012), effects of TnR on microglia promote it as a conceivable factor in the neuroinflammatory disorder MS and its experimental model EAE. Again, further studies are warranted regarding this issue.

Conclusions and outlook

TnC has been found to be beneficial for regeneration after injury of the adult central nervous system. It also induces the quiescent phenotype of cultured astrocytes in vitro, thus possibly regulating astrocytic scar formation after spinal cord injury. In addition to its neurotrophic potential TnC is also involved in synaptic plasticity in the adult central nervous system. TnR has been suggested to be among the oligodendrocyte-derived molecules inhibiting axonal regrowth after injury, a counterproductive function with regard to regeneration. Yet, it has also been implicated in remyelination of denuded axons and remodeling of perineuronal nets. Thus, inhibiting axonal regrowth in spinal cord injury may render the positive effect of TnR in remyelination obsolete. On the other hand, allowing perineuronal nets to remodel in TnR-deficient mice might take precedence in functional recovery. Although TnC is likely to be important for pathogenesis of neuroinflammatory disorders due to its involvement in non-neural inflammation, a role for TnR has yet to be explored in the pathogenesis of inflammatory responses to nervous system injury. Of special interest is the link between neuroinflammation and expression of TnC by astrocytes and antigen-presenting cells, such as dendritic cells and macrophages/microglia. The contribution of astrocytes to neuroinflammatory pathogenesis has become particularly pertinent to analyze further in view of their roles in astrogliosis/glial scar formation, remyelination and trophic support of neurons and in their interaction with immune cells to shape immune responses in the central nervous system. Considering that microglia/macrophages stimulate TnC expression in cultured astrocytes, this could then influence differentiation of Th cells and thus might affect the manner and intensity of an (auto)immune response within the central nervous system. Although such effect of astrocytic TnC is expected, antigen-presenting cell-produced TnC should have an effect on the immune response both in the nervous system and in the lymphoid tissue. A role of TnR in immune responses may be important in view of the in vitro observations that microglia/macrophages are repelled in their adhesion by this molecule and that it stimulates microglia to generate cytokines. Although changes in expression of TnC and TnR in sclerotic MS lesions have been reported, there is no clear evidence for a role of these molecules in neuroinflammation. Studies on EAE in TnC −/− and TnR−/− mice, as well as further screening for TnC and TnR and their respective antibodies in the cerebrospinal fluid of MS patients and mice with EAE appear therefore warranted.

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References

Abu El-Asrar AM, Meersschaert A, Al-Kharashi SA, Missotten L, Geboes K (2003) Immuno-histochemical evaluation of conjunctival remodelling in vernal keratoconjunctivitis. Eye (Lond) 17:767–771

Agrawal SM, Yong VW (2006) Immunopathogenesis of multiple sclerosis. Int Rev Neurobiol 79:99–126

Aloisi F, Borsellino G, Samoggia P, Testa U, Chelucci C, Russo G, Peschle C, Levi G (1992) Astrocyte cultures from human embryonic brain: characterization and modulation of surface molecules by inflammatory cytokines. J Neurosci Res 32: 494–506

Angelov DN, Walther M, Streppel M, Guntinas-Lichius O, Neiss WF, Probstmeier R, Pesheva P (1998) Tenascin-R is antiadhesive for activated microglia that induce downregulation of the protein after peripheral nerve injury: a new role in neuronal protection. J Neurosci 18:6218–6229

Ankeny DP, Popovich PG (2009) Mechanisms and implications of adaptive immune responses after traumatic spinal cord injury. Neuroscience 158:1112–1121

Apostolova I, Irintchev A, Schachner M (2006) Tenascin-R restricts posttraumatic remodeling of motoneuron innervation and functional recovery after spinal cord injury in adult mice. J Neurosci 26:7849–7859

Aukhil I, Slemp CC, Lightner VA, Nishimura K, Briscoe G, Erickson HP (1990) Purification of hexabrachion (tenascin) from cell culture conditioned medium, and separation from a cell adhesion factor. Matrix 10:98–111

Barnea G, Grumet M, Milev P, Silvennoinen O, Levy JB, Sap J, Schlessinger J (1994) Receptor tyrosine phosphatase beta is expressed in the form of proteoglycan and binds to the extracellular matrix protein tenascin. J Biol Chem 269:14349–14352

Bartholomäus I, Kawakami N, Odoardi F, Schläger C, Miljkovic D, Ellwart JW, Klinkert WE, Flügel-Koch C, Issekutz TB, Wekerle H, Flügel A (2009) Effector T cell interactions with meningeal vascular structures in nascent autoimmune CNS lesions. Nature 462:94–98

Bartsch U (1996) The extracellular matrix molecule tenascin-C: expression in vivo and functional characterization in vitro. Prog Neurobiol 49:145–168

Bartsch S, Bartsch U, Dörries U, Faissner A, Weller A, Ekblom P, Schachner M (1992) Expression of tenascin in the developing and adult cerebellar cortex. J Neurosci 12:736–749

Bartsch U, Pesheva P, Raff M, Schachner M (1993) Expression of janusin (J1–160/180) in the retina and optic nerve of the developing and adult mouse. Glia 9:57–69

Bartsch U, Faissner A, Trotter J, Dörries U, Bartsch S, Mohajeri H, Schachner M (1994) Tenascin demarcates the boundary between the myelinated and nonmyelinated part of retinal ganglion cell axons in the developing and adult mouse. J Neurosci 14:4756–4768

Bartsch S, Husmann K, Schachner M, Bartsch U (1995) The extracellular matrix molecule tenascin: expression in the developing chick retinotectal system and substrate properties for retinal ganglion cell neurites in vitro. Eur J Neurosci 7:907–916

Becker T, Becker CG, Niemann U, Naujoks-Manteuffel C, Bartsch U, Schachner M, Roth G (1995) Immunohistological localization of tenascin-C in the developing and regenerating retinotectal system of two amphibian species. J Comp Neurol 360:643–657

Becker T, Anliker B, Becker CG, Taylor J, Schachner M, Meyer RL, Bartsch U (2000) Tenascin-R inhibits regrowth of optic fibers in vitro and persists in the optic nerve of mice after injury. Glia 29:330–346

Becker CG, Schweitzer J, Feldner J, Becker T, Schachner M (2003) Tenascin-R as a repellent guidance molecule for developing optic axons in zebrafish. J Neurosci 23:6232–6237

Bourdon MA, Ruoslahti E (1989) Tenascin mediates cell attachment through an RGD-dependent receptor. J Cell Biol 108:1149–1155

Bradbury EJ, Carter LM (2011) Manipulating the glial scar: chondroitinase ABC as a therapy for spinal cord injury. Brain Res Bull 84:306–316

Bradbury EJ, Moon LD, Popat RJ, King VR, Bennett GS, Patel PN, Fawcett JW, McMahon SB (2002) Chondroitinase ABC promotes functional recovery after spinal cord injury. Nature 416:636–640

Brenneke F, Bukalo O, Dityatev A, Lie AA (2004) Mice deficient for the extracellular matrix glycoprotein tenascin-r show physiological and structural hallmarks of increased hippocampal excitability, but no increased susceptibility to seizures in the pilocarpine model of epilepsy. Neuroscience 124:841–855

Bristow J, Tee MK, Gitelman SE, Mellon SH, Miller WL (1993) Tenascin-X: a novel extracellular matrix protein encoded by the human XB gene overlapping P450c21B. J Cell Biol 122: 265–278

Brodkey JA, Laywell ED, O'Brien TF, Faissner A, Stefansson K, Dörries HU, Schachner M, Steindler DA (1995) Focal brain injury and upregulation of a developmentally regulated extracellular matrix protein. J Neurosurg 82:106–112

Brown MC, Staniszewska I, Lazarovici P, Tuszynski GP, Del Valle L, Marcinkiewicz C (2008) Regulatory effect of nerve growth factor in alpha9beta1 integrin-dependent progression of glioblastoma. Neuro Oncol 10:968–980

Brückner G, Grosche J, Schmidt S, Härtig W, Margolis RU, Delpech B, Seidenbecher CI, Czaniera R, Schachner M (2000) Postnatal development of perineuronal nets in wild-type mice and in a mutant deficient in tenascin-R. J Comp Neurol 428:616–629

Bukalo O, Schachner M, Dityatev A (2001) Modification of extracellular matrix by enzymatic removal of chondroitin sulfate and by lack of tenascin-R differentially affects several forms of synaptic plasticity in the hippocampus. Neuroscience 104: 359–369

Catalán V, Gómez-Ambrosi J, Rodríguez A, Ramírez B, Rotellar F, Valentí V, Silva C, Gil MJ, Salvador J, Frühbeck G (2012) Increased tenascin C and toll-like receptor 4 levels in visceral adipose tissue as a link between inflammation and extracellular matrix remodeling in obesity. J Clin Endocrinol Metab 97: E1880–E1889

Celio MR, Blümcke I (1994) Perineuronal nets—a specialized form of extracellular matrix in the adult nervous system. Brain Res Brain Res Rev 19:128–145

Celio MR, Chicquet-Ehrismann R (1993) 'Perineuronal nets' around cortical interneurons expressing parvalbumin are rich in tenascin. Neurosci Lett 162:37–40

Chen J, Joon Lee H, Jakovcevski I, Shah R, Bhagat N, Loers G, Liu HY, Meiners S, Taschenberger G, Kügler S, Irintchev A, Schachner M (2010) The extracellular matrix glycoprotein tenascin-C is beneficial for spinal cord regeneration. Mol Ther 18:1769–1777

Chilosi M, Lestani M, Benedetti A, Montagna L, Pedron S, Scarpa A, Menestrina F, Hirohashi S, Pizzolo G, Semenzato G (1993) Constitutive expression of tenascin in T-dependent zones of human lymphoid tissues. Am J Pathol 143:1348–1355

Chiquet M, Fambrough DM (1984) Chick myotendinous antigen. II. A novel extracellular glycoprotein complex consisting of large disulfide-linked subunits. J Cell Biol 98:1937–1946

Chiquet-Ehrismann R (1991) Anti-adhesive molecules of the extracellular matrix. Curr Opin Cell Biol 3:800–804

Chung CY, Erickson HP (1994) Cell surface annexin II is a high affinity receptor for the alternatively spliced segment of tenascin-C. J Cell Biol 126:539–548

Chung CY, Zardi L, Erickson HP (1995) Binding of tenascin-C to soluble fibronectin and matrix fibrils. J Biol Chem 270: 29012–29017

Chung CY, Murphy-Ullrich JE, Erickson HP (1996) Mitogenesis, cell migration, and loss of focal adhesions induced by tenascin-C interacting with its cell surface receptor, annexin II. Mol Biol Cell 7:883–892

Clark RA, Erickson HP, Springer TA (1997) Tenascin supports lymphocyte rolling. J Cell Biol 137:755–765

Cleek RL, Rege AA, Denner LA, Eskin SG, Mikos AG (1997) Inhibition of smooth muscle cell growth in vitro by an antisense oligodeoxynucleotide released from poly(DL-lactic-co-glycolic acid) microparticles. J Biomed Mater Res 35:525–530

Conway JF, Parry DA (1991) Three-stranded alpha-fibrous proteins: the heptad repeat and its implications for structure. Int J Biol Macromol 13:14–16

Cowan KN, Jones PL, Rabinovitch M (2000) Elastase and matrix metalloproteinase inhibitors induce regression, and tenascin-C antisense prevents progression, of vascular disease. J Clin Invest 105:21–34

Crossin KL (1991) Cytotactin binding: inhibition of stimulated proliferation and intracellular alkalinization in fibroblasts. Proc Natl Acad Sci USA 88:11403–11407

Crossin KL, Hoffman S, Grumet M, Thiery JP, Edelman GM (1986) Site-restricted expression of cytotactin during development of the chicken embryo. J Cell Biol 102:1917–1930

Crossin KL, Hoffman S, Tan SS, Edelman GM (1989) Cytotactin and its proteoglycan ligand mark structural and functional boundaries in somatosensory cortex of the early postnatal mouse. Dev Biol 136:381–392

David S, Kroner A (2011) Repertoire of microglial and macrophage responses after spinal cord injury. Nat Rev Neurosci 12: 388–399

Deckner M, Lindholm T, Cullheim S, Risling M (2000) Differential expression of tenascin-C, tenascin-R, tenascin/J1, and tenascin-X in spinal cord scar tissue and in the olfactory system. Exp Neurol 166:350–362

Deller T, Haas CA, Naumann T, Joester A, Faissner A, Frotscher M (1997) Up-regulation of astrocyte-derived tenascin-C correlates with neurite outgrowth in the rat dentate gyrus after unilateral entorhinal cortex lesion. Neuroscience 81:829–846

Devanathan V, Jakovcevski I, Santuccione A, Li S, Lee HJ, Peles E, Leshchyns'ka I, Sytnyk V, Schachner M (2010) Cellular form of prion protein inhibits Reelin-mediated shedding of Caspr from the neuronal cell surface to potentiate Caspr-mediated inhibition of neurite outgrowth. J Neurosci 30:9292–9305

DiProspero NA, Meiners S, Geller HM (1997) Inflammatory cytokines interact to modulate extracellular matrix and astrocytic support of neurite outgrowth. Exp Neurol 148:628–639

Dityatev A, Schachner M (2003) Extracellular matrix molecules and synaptic plasticity. Nat Rev Neurosci 4:456–468

Dityatev A, Schachner M, Sonderegger P (2010a) The dual role of the extracellular matrix in synaptic plasticity and homeostasis. Nat Rev Neurosci 11:735–746

Dityatev A, Seidenbecher CI, Schachner M (2010b) Compartmentalization from the outside: the extracellular matrix and functional microdomains in the brain. Trends Neurosci 33:503–512

Doerries U, Taylor J, Xiao Z, Lochter A, Montag D, Schachner M (1996) Distinct effects of recombinant tenascin-C domains on neuronal cell adhesion, growth cone guidance, and neuronal polarity. J Neurosci Res 43:420–438

Dörries U, Schachner M (1994) Tenascin mRNA isoforms in the developing mouse brain. J Neurosci Res 37:336–347

Faissner A (1997) The tenascin gene family in axon growth and guidance. Cell Tissue Res 290:331–341

Faissner A, Kruse J (1990) J1/tenascin is a repulsive substrate for central nervous system neurons. Neuron 5:627–637

Faissner A, Steindler D (1995) Boundaries and inhibitory molecules in developing neural tissues. Glia 13:233–254

Faissner A, Scholze A, Götz B (1994) Tenascin glycoproteins in developing neural tissues: only decoration? Perspect Dev Neurobiol 2:53–66

Fruttiger M, Schachner M, Martini R (1995) Tenascin-C expression during Wallerian degeneration in C57BL/Wld(S) mice: Possible implications for axonal regeneration. J Neurocytol 24:1–14

Fuss B, Pott U, Fischer P, Schwab ME, Schachner M (1991) Identification of a cDNA clone specific for the oligodendrocyte-derived repulsive extracellular matrix molecule J1–160/180. J Neurosci Res 29:299–307

Fuss B, Wintergerst ES, Bartsch U, Schachner M (1993) Molecular characterization and in situ mRNA localization of the neural recognition molecule J1–160/180: a modular structure similar to tenascin. J Cell Biol 120:1237–1249

Garcion E, Faissner A and ffrench-Constant C (2001) Knockout mice reveal a contribution of the extracellular matrix molecule tenascin-C to neural precursor proliferation and migration. Development 128:2485-2496

Goh FG, Piccinini AM, Krausgruber T, Udalova IA, Midwood KS (2010) Transcriptional regulation of the endogenous danger signal tenascin-C: a novel autocrine loop in inflammation. J Immunol 184:2655–2662

Götz B, Scholze A, Clement A, Joester A, Schütte K, Wigger F, Frank R, Spiess E, Ekblom P, Faissner A (1996) Tenascin-C contains distinct adhesive, anti-adhesive, and neurite outgrowth promoting sites for neurons. J Cell Biol 132:681–699

Götz M, Bolz J, Joester A, Faissner A (1997) Tenascin-C synthesis and influence on axonal growth during rat cortical development. Eur J Neurosci 9:496–506

Gratchev A, Kzhyshkowska J, Utikal J, Goerdt S (2005) Interleukin-4 and dexamethasone counterregulate extracellular matrix remodelling and phagocytosis in type-2 macrophages. Scand J Immunol 61:10–17

Grumet M, Hoffman S, Crossin KL, Edelman GM (1985) Cytotactin, an extracellular matrix protein of neural and non-neural tissues that mediates glia-neuron interaction. Proc Natl Acad Sci USA 82:8075–8079

Gueders MM, Hirst SJ, Quesada-Calvo F, Paulissen G, Hacha J, Gilles C, Gosset P, Louis R, Foidart JM, Lopez-Otin C, Noël A, Cataldo DD (2010) Matrix metalloproteinase-19 deficiency promotes tenascin-C accumulation and allergen-induced airway inflammation. Am J Respir Cell Mol Biol 43:286–295

Guntinas-Lichius O, Angelov DN, Morellini F, Lenzen M, Skouras E, Schachner M, Irintchev A (2005) Opposite impacts of tenascin-C and tenascin-R deficiency in mice on the functional outcome of facial nerve repair. Eur J Neurosci 22:2171–2179

Gurevicius K, Kuang F, Stoenica L, Irintchev A, Gureviciene I, Dityatev A, Schachner M, Tanila H (2009) Genetic ablation of tenascin-C expression leads to abnormal hippocampal CA1 structure and electrical activity in vivo. Hippocampus 19:1232–1246

Gutowski NJ, Newcombe J, Cuzner ML (1999) Tenascin-R and C in multiple sclerosis lesions: relevance to extracellular matrix remodelling. Neuropathol Appl Neurobiol 25:207–214

Hagihara K, Miura R, Kosaki R, Berglund E, Ranscht B, Yamaguchi Y (1999) Immunohistochemical evidence for the brevican-tenascin-R interaction: colocalization in perineuronal nets suggests a physiological role for the interaction in the adult rat brain. J Comp Neurol 410:256–264

Hagios C, Koch M, Spring J, Chiquet M, Chiquet-Ehrismann R (1996) Tenascin-Y: a protein of novel domain structure is secreted by differentiated fibroblasts of muscle connective tissue. J Cell Biol 134:1499–1512

Härkönen E, Virtanen I, Linnala A, Laitinen LL, Kinnula VL (1995) Modulation of fibronectin and tenascin production in human bronchial epithelial cells by inflammatory cytokines in vitro. Am J Respir Cell Mol Biol 13:109–115

Hasegawa M, Nakoshi Y, Muraki M, Sudo A, Kinoshita N, Yoshida T, Uchida A (2007) Expression of large tenascin-C splice variants in synovial fluid of patients with rheumatoid arthritis. J Orthop Res 25:563–568

Haunso A, Ibrahim M, Bartsch U, Letiembre M, Celio MR, Menoud P (2000) Morphology of perineuronal nets in tenascin-R and parvalbumin single and double knockout mice. Brain Res 864:142–145

Hauzenberger D, Olivier P, Gundersen D, Rüegg C (1999) Tenascin-C inhibits beta1 integrin-dependent T lymphocyte adhesion to fibronectin through the binding of its fnIII 1–5 repeats to fibronectin. Eur J Immunol 29:1435–1447

Hisatomi K, Sakamoto N, Mukae H, Hayashi T, Amenomori M, Ishimoto H, Fujita H, Ishii H, Nakayama S, Ishimatsu Y, Kohno S (2009) Elevated levels of tenascin-C in patients with cryptogenic organizing pneumonia. Intern Med 48:1501–1507

Hofstetter HH, Ibrahim SM, Koczan D, Kruse N, Weishaupt A, Toyka KV, Gold R (2005) Therapeutic efficacy of IL-17 neutralization in murine experimental autoimmune encephalomyelitis. Cell Immunol 237:123–130

Holley JE, Gveric D, Whatmore JL, Gutowski NJ (2005) Tenascin C induces a quiescent phenotype in cultured adult human astrocytes. Glia 52:53–58

Huang JY, Cheng YJ, Lin YP, Lin HC, Su CC, Juliano R, Yang BC (2010) Extracellular matrix of glioblastoma inhibits polarization

and transmigration of T cells: the role of tenascin-C in immune suppression. J Immunol 185:1450–1459

Husmann K, Faissner A, Schachner M (1992) Tenascin promotes cerebellar granule cell migration and neurite outgrowth by different domains in the fibronectin type III repeats. J Cell Biol 116:1475–1486

Ikeshima-Kataoka H, Saito S, Yuasa S (2007) Tenascin-C is required for proliferation of astrocytes in primary culture. In Vivo 21: 629–633

Ikeshima-Kataoka H, Shen JS, Eto Y, Saito S, Yuasa S (2008) Alteration of inflammatory cytokine production in the injured central nervous system of tenascin-deficient mice. In Vivo 22:409–413

Imanaka-Yoshida K, Hiroe M, Yasutomi Y, Toyozaki T, Tsuchiya T, Noda N, Maki T, Nishikawa T, Sakakura T, Yoshida T (2002) Tenascin-C is a useful marker for disease activity in myocarditis. J Pathol 197:388–394

Imanaka-Yoshida K, Hiroe M, Yoshida T (2004) Interaction between cell and extracellular matrix in heart disease: multiple roles of tenascin-C in tissue remodeling. Histol Histopathol 19:517–525

Irintchev A, Salvini TF, Faissner A, Wernig A (1993) Differential expression of tenascin after denervation, damage or paralysis of mouse soleus muscle. J Neurocytol 22:955–965

Jadidi-Niaragh F, Mirshafiey A (2011) Th17 cell, the new player of neuroinflammatory process in multiple sclerosis. Scand J Immunol 74:1–13

Jakovcevski I, Wu J, Karl N, Leshchyns'ka I, Sytnyk V, Chen J, Irintchev A, Schachner M (2007) Glial scar expression of CHL1, the close homolog of the adhesion molecule L1, limits recovery after spinal cord injury. J Neurosci 27:7222–7233

Jankovski A, Sotelo C (1996) Subventricular zone-olfactory bulb migratory pathway in the adult mouse: cellular composition and specificity as determined by heterochronic and heterotopic transplantation. J Comp Neurol 371:376–396

Joester A, Faissner A (1999) Evidence for combinatorial variability of tenascin-C isoforms and developmental regulation in the mouse central nervous system. J Biol Chem 274:17144–17151

Joester A, Faissner A (2001) The structure and function of tenascins in the nervous system. Matrix Biol 20:13–22

Jones FS, Jones PL (2000) The tenascin family of ECM glycoproteins: structure, function, and regulation during embryonic development and tissue remodeling. Dev Dyn 218:235–259

Jones FS, Burgoon MP, Hoffman S, Crossin KL, Cunningham BA, Edelman GM (1988) A cDNA clone for cytotactin contains sequences similar to epidermal growth factor-like repeats and segments of fibronectin and fibrinogen. Proc Natl Acad Sci USA 85:2186–2190

Kaarteenaho-Wiik R, Lakari E, Soini Y, Pöllänen R, Kinnula VL, Pääkkö P (2000) Tenascin expression and distribution in pleural inflammatory and fibrotic diseases. J Histochem Cytochem 48:1257–1268

Kanayama M, Morimoto J, Matsui Y, Ikesue M, Danzaki K, Kurotaki D, Ito K, Yoshida T, Uede T (2011) $\alpha 9\beta 1$ integrin-mediated signaling serves as an intrinsic regulator of pathogenic Th17 cell generation. J Immunol 187:5851–5864

Knaggs HE, Layton AM, Morris C, Wood EJ, Holland DB, Cunliffe WJ (1994) Investigation of the expression of the extracellular matrix glycoproteins tenascin and fibronectin during acne vulgaris. Br J Dermatol 130:576–582

Koukoulis GK, Koso-Thomas AK, Zardi L, Gabbiani G, Gould VE (1999) Enhanced tenascin expression correlates with inflammation in primary sclerosing cholangitis. Pathol Res Pract 195: 727–731

Koyama Y, Kusubata M, Yoshiki A, Hiraiwa N, Ohashi T, Irie S, Kusakabe M (1998) Effect of tenascin-C deficiency on chemically induced dermatitis in the mouse. J Invest Dermatol 111:930–935

Krishnamoorthy G, Wekerle H (2009) EAE: an immunologist's magic eye. Eur J Immunol 39:2031–2035

Laitinen LA, Laitinen A, Altraja A, Virtanen I, Kämpe M, Simonsson BG, Karlsson SE, Håkansson L, Venge P, Sillastu H (1996) Bronchial biopsy findings in intermittent or "early" asthma. J Allergy Clin Immunol 98(5 Pt 2):S3-6; discussion S33-40

Laywell ED, Dörries U, Bartsch U, Faissner A, Schachner M, Steindler DA (1992) Enhanced expression of the developmentally regulated extracellular matrix molecule tenascin following adult brain injury. Proc Natl Acad Sci USA 89:2634–2638

Lee HJ, Jakovcevski I, Radonjic N, Hoelters L, Schachner M, Irintchev A (2009) Better functional outcome of compression spinal cord injury in mice is associated with enhanced H-reflex responses. Exp Neurol 216:365–374

Lee HJ, Bian S, Jakovcevski I, Wu B, Irintchev A, Schachner M (2012) Delayed applications of L1 and chondroitinase ABC promote recovery after spinal cord injury. J Neurotrauma 29:1850–1863

Li X, Yuan FL, Lu WG, Zhao YQ, Li CW, Li JP, Xu RS (2010) The role of interleukin-17 in mediating joint destruction in rheumatoid arthritis. Biochem Biophys Res Commun 397:131–135

Liao H, Bu WY, Wang TH, Ahmed S, Xiao ZC (2005) Tenascin-R plays a role in neuroprotection via its distinct domains that coordinate to modulate the microglia function. J Biol Chem 280:8316–8323

Liao H, Huang W, Niu R, Sun L, Zhang L (2008) Cross-talk between the epidermal growth factor-like repeats/fibronectin 6–8 repeats domains of tenascin-R and microglia modulates neural stem/progenitor cell proliferation and differentiation. J Neurosci Res 86:27–34

Lochter A, Schachner M (1993) Tenascin and extracellular matrix glycoproteins: from promotion to polarization of neurite growth in vitro. J Neurosci 13:3986–4000

Lochter A, Taylor J, Braunewell KH, Holm J, Schachner M (1995) Control of neuronal morphology in vitro: interplay between adhesive substrate forces and molecular instruction. J Neurosci Res 42:145–158

Martini R (1994) Expression and functional roles of neural cell surface molecules and extracellular matrix components during development and regeneration of peripheral nerves. J Neurocytol 23:1–28

Maseruka H, Bonshek RE, Tullo AB (1997) Tenascin-C expression in normal, inflamed, and scarred human corneas. Br J Ophthalmol 81:677–682

Meiners S, Nur-e-Kamal MS, Mercado ML (2001) Identification of a neurite outgrowth-promoting motif within the alternatively spliced region of human tenascin-C. J Neurosci 21:7215–7225

Metzger M, Bartsch S, Bartsch U, Bock J, Schachner M, Braun K (2006) Regional and cellular distribution of the extracellular matrix protein tenascin-C in the chick forebrain and its role in neonatal learning. Neuroscience 141:1709–1719

Meuronen A, Karisola P, Leino M, Savinko T, Sirola K, Majuri ML, Piirilä P, Virtanen I, Mäkelä M, Laitinen A, Laitinen LA, Alenius H (2011) Attenuated expression of tenascin-C in ovalbumin-challenged STAT4−/− mice. Respir Res 12:2

Midwood K, Sacre S, Piccinini AM, Inglis J, Trebaul A, Chan E, Drexler S, Sofat N, Kashiwagi M, Orend G, Brennan F, Foxwell B (2009) Tenascin-C is an endogenous activator of Toll-like receptor 4 that is essential for maintaining inflammation in arthritic joint disease. Nat Med 15:774–780

Milev P, Fischer D, Haring M, Schulthess T, Margolis RK, Chiquet-Ehrismann R, Margolis RU (1997) The fibrinogen-like globe of tenascin-C mediates its interactions with neurocan and

phosphacan/protein-tyrosine phosphatase-zeta/beta. J Biol Chem 272:15501–15509
Miljkovic D, Stosic-Grujicic S, Markovic M, Momcilovic M, Ramic Z, Maksimovic-Ivanic D, Mijatovic S, Popadic D, Cvetkovic I, Mostarica-Stojkovic M (2006) Strain difference in susceptibility to experimental autoimmune encephalomyelitis between Albino Oxford and Dark Agouti rats correlates with disparity in production of IL-17, but not nitric oxide. J Neurosci Res 84:379–388
Miljković D, Timotijević G, Mostarica Stojković M (2011) Astrocytes in the tempest of multiple sclerosis. FEBS Lett 585: 3781–3788
Miller E (2012) Multiple sclerosis. Adv Exp Med Biol 724:222–238
Mitrovic N, Doerries U, Schachner M (1994) Expression of the extracellular matrix glycoprotein tenascin in the somatosensory cortex of the mouse during postnatal development: an immunocytochemical and in situ hybridization analysis. J Neurocytol 23:364–378
Moore CS, Abdullah SL, Brown A, Arulpragasam A, Crocker SJ (2011) How factors secreted from astrocytes impact myelin repair. J Neurosci Res 89:13–21
Morellini F, Sivukhina E, Stoenica L, Oulianova E, Bukalo O, Jakovcevski I, Dityatev A, Irintchev A, Schachner M (2010) Improved reversal learning and working memory and enhanced reactivity to novelty in mice with enhanced GABAergic innervation in the dentate gyrus. Cereb Cortex 20:2712–2727
Morganti MC, Taylor J, Pesheva P, Schachner M (1990) Oligodendrocyte-derived J1–160/180 extracellular matrix glycoproteins are adhesive or repulsive depending on the partner cell type and time of interaction. Exp Neurol 109:98–110
Nakic M, Mitrovic N, Sperk G, Schachner M (1996) Kainic acid activates transient expression of tenascin-C in the adult rat hippocampus. J Neurosci Res 44:355–362
Nash B, Thomson CE, Linington C, Arthur AT, McClure JD, McBride MW, Barnett SC (2011) Functional duality of astrocytes in myelination. J Neurosci 31:13028–13038
Neidhardt J, Fehr S, Kutsche M, Lohler J, Schachner M (2003) Tenascin-N: characterization of a novel member of the tenascin family that mediates neurite repulsion from hippocampal explants. Mol Cell Neurosci 23:193–209
Nies DE, Hemesath TJ, Kim JH, Gulcher JR, Stefansson K (1991) The complete cDNA sequence of human hexabrachion (Tenascin). A multidomain protein containing unique epidermal growth factor repeats. J Biol Chem 266:2818–2823
Paron I, Berchtold S, Vörös J, Shamarla M, Erkan M, Höfler H, Esposito I (2011) Tenascin-C enhances pancreatic cancer cell growth and motility and affects cell adhesion through activation of the integrin pathway. PLoS ONE 6:e21684
Patel L, Sun W, Glasson SS, Morris EA, Flannery CR, Chockalingam PS (2011) Tenascin-C induces inflammatory mediators and matrix degradation in osteoarthritic cartilage. BMC Musculoskelet Disord 12:164
Pesheva P, Probstmeier R (2000) The yin and yang of tenascin-R in CNS development and pathology. Prog Neurobiol 61:465–493
Pesheva P, Spiess E, Schachner M (1989) J1–160 and J1–180 are oligodendrocyte secreted nonpermissive substrates for cell adhesion. J Cell Biol 109:1765–1778
Pesheva P, Gennarini G, Goridis C, Schachner M (1993) The F3/11 cell adhesion molecule mediates the repulsion of neurons by the extracellular matrix glycoprotein J1–160/180. Neuron 10:69–82
Pesheva P, Probstmeier R, Skubitz AP, McCarthy JB, Furcht LT, Schachner M (1994) Tenascin-R (J1 160/180 inhibits fibronectin-mediated cell adhesion—functional relatedness to tenascin-C. J Cell Sci 107:2323–2333
Pesheva P, Gloor S, Schachner M, Probstmeier R (1997) Tenascin-R is an intrinsic autocrine factor for oligodendrocyte differentiation and promotes cell adhesion by a sulfatide-mediated mechanism. J Neurosci 17:4642–4651
Peter NR, Shah RT, Chen J, Irintchev A, Schachner M (2012) Adhesion molecules close homolog of L1 and tenascin-C affect blood-spinal cord barrier repair. NeuroReport 23:479–482
Prieto AL, Jones FS, Cunningham BA, Crossin KL, Edelman GM (1990) Localization during development of alternatively spliced forms of cytotactin mRNA by in situ hybridization. J Cell Biol 111:685–698
Ransohoff RM, Brown MA (2012) Innate immunity in the central nervous system. J Clin Invest 122:1164–1171
Rathjen FG, Wolff JM, Chiquet-Ehrismann R (1991) Restrictin: a chick neural extracellular matrix protein involved in cell attachment co-purifies with the cell recognition molecule F11. Development 113:151–164
Rhodes KE, Fawcett JW (2004) Chondroitin sulphate proteoglycans: preventing plasticity or protecting the CNS? J Anat 204: 33–48
Riedl S, Tandara A, Reinshagen M, Hinz U, Faissner A, Bodenmüller H, Buhr HJ, Herfarth C, Möller P (2011) Serum tenascin-C is an indicator of inflammatory bowel disease activity. Int J Colorectal Dis 16:285–291
Rolls A, Shechter R, Schwartz M (2009) The bright side of the glial scar in CNS repair. Nat Rev Neurosci 10:235–241
Rüegg CR, Chiquet-Ehrismann R, Alkan SS (1989) Tenascin, an extracellular matrix protein, exerts immunomodulatory activities. Proc Natl Acad Sci U S A 86:7437–7441
Ruhmann M, Piccinini AM, Kong PL, Midwood KS (2012) Endogenous activation of adaptive immunity: tenascin-C drives interleukin-17 synthesis in murine arthritic joint disease. Arthritis Rheum 64:2179–2190
Saghatelyan AK, Gorissen S, Albert M, Hertlein B, Schachner M, Dityatev A (2000) The extracellular matrix molecule tenascin-R and its HNK-1 carbohydrate modulate perisomatic inhibition and long-term potentiation in the CA1 region of the hippocampus. Eur J Neurosci 12:3331–3342
Saghatelyan AK, Dityatev A, Schmidt S, Schuster T, Bartsch U, Schachner M (2001) Reduced perisomatic inhibition, increased excitatory transmission, and impaired long-term potentiation in mice deficient for the extracellular matrix glycoprotein tenascin-R. Mol Cell Neurosci 17:226–240
Salas A, Fernández-Bañares F, Casalots J, González C, Tarroch X, Forcada P, González G (2003) Subepithelial myofibroblasts and tenascin expression in microscopic colitis. Histopathology 43:48–54
Sandvig A, Berry M, Barrett LB, Butt A, Logan A (2004) Myelin-, reactive glia-, and scar-derived CNS axon growth inhibitors: expression, receptor signaling, and correlation with axon regeneration. Glia 46:225–251
Satta J, Soini Y, Pöllänen R, Pääkkö P, Juvonen T (1997) Tenascin expression is associated with a chronic inflammatory process in abdominal aortic aneurysms. J Vasc Surg 26:670–675
Schachner M (1994) Neural recognition molecules in disease and regeneration. Curr Opin Neurobiol 4:726–734
Schachner M, Taylor J, Bartsch U, Pesheva P (1994) The perplexing multifunctionality of janusin, a tenascin-related molecule. Perspect Dev Neurobiol 2:33–41
Schenk S, Muser J, Vollmer G, Chiquet-Ehrismann R (1995) Tenascin-C in serum: a questionable tumor marker. Int J Cancer 61:443–449
Šekeljić V, Andjus PR (2012) Tenascin-C and its functions in neuronal plasticity. Int J Biochem Cell Biol 44:825–829
Siri A, Carnemolla B, Saginati M, Leprini A, Casari G, Baralle F, Zardi L (1991) Human tenascin: primary structure, pre-mRNA splicing patterns and localization of the epitopes recognized by two monoclonal antibodies. Nucleic Acids Res 19:525–531

Smith GM, Hale JH (1997) Macrophage/Microglia regulation of astrocytic tenascin: synergistic action of transforming growth factor-beta and basic fibroblast growth factor. J Neurosci 17:9624–9633

Soini Y, Pöllänen R, Autio-Harmainen H, Lehto VP (1997) Tenascin expression in lichen sclerosus. Int J Gynecol Pathol 16:313–318

Sorokin L (2010) The impact of the extracellular matrix on inflammation. Nat Rev Immunol 10:712–723

Spring J, Beck K, Chiquet-Erishmann R (1989) Two contrary functions of tenascin: dissection of the active sites by recombinant tenascin fragments. Cell 59:325–334

Srinivasan J, Schachner M, Catterall WA (1998) Interaction of voltage-gated sodium channels with the extracellular matrix molecules tenascin-C and tenascin-R. Proc Natl Acad Sci U S A 95:15753–15757

Taylor HC, Lightner VA, Beyer WF Jr, McCaslin D, Briscoe G, Erickson HP (1989) Biochemical and structural studies of tenascin/hexabrachion proteins. J Cell Biochem 41:71–90

Taylor J, Pesheva P, Schachner M (1993) Influence of janusin and tenascin on growth cone behavior in vitro. J Neurosci Res 35:347–362

Tiitta O, Sipponen P, Gould V, Virtanen I (1994) Tenascin expression in inflammatory, dysplastic and neoplastic lesions of the human stomach. Virchows Arch 425:369–374

Tiitta O, Luomanen M, Hietanen J, Virtanen I (1995) Tenascin expression in mucocutaneous diseases and related lesions of human oral mucosa. Arch Oral Biol 40:1039–1045

Tojyo I, Yamaguchi A, Nitta T, Yoshida H, Fujita S, Yoshida T (2008) Effect of hypoxia and interleukin-1beta on expression of tenascin-C in temporomandibular joint. Oral Dis 14:45–50

Tongiorgi E, Bernhardt RR, Zinn K, Schachner M (1995) Tenascin-C mRNA is expressed in cranial neural crest cells, in some placodal derivatives, and in discrete domains of the embryonic zebrafish brain. J Neurobiol 28:391–407

Trebaul A, Chan EK, Midwood KS (2007) Regulation of fibroblast migration by tenascin-C. Biochem Soc Trans 35:695–697

Treloar HB, Ray A, Dinglasan LA, Schachner M, Greer CA (2009) Tenascin-C is an inhibitory boundary molecule in the developing olfactory bulb. J Neurosci 29:9405–9416

Truong LD, Foster SV, Barrios R, D'Agati V, Verani RR, Gonzalez JM, Suki WN (1996) Tenascin is an ubiquitous extracellular matrix protein of human renal interstitium in normal and pathologic conditions. Nephron 72:579–586

Tucker RP, Brunso-Bechtold JK, Jenrath DA, Khan NA, Poss PM, Sweatt AJ, Xu Y (1994) Cellular origins of tenascin in the developing nervous system. Perspect Dev Neurobiol 2:89–99

Uede T (2011) Osteopontin, intrinsic tissue regulator of intractable inflammatory diseases. Pathol Int 61:265–280

Vaughan L, Huber S, Chiquet M, Winterhalter KH (1987) A major, six-armed glycoprotein from embryonic cartilage. EMBO J 6:349–353

Veje K, Hyllested-Winge JL, Ostergaard K (2003) Topographic and zonal distribution of tenascin in human articular cartilage from femoral heads: normal versus mild and severe osteoarthritis. Osteoarthritis Cartilage 11:217–227

Wallner K, Li C, Shah PK, Fishbein MC, Forrester JS, Kaul S, Sharifi BG (1999) Tenascin-C is expressed in macrophage-rich human coronary atherosclerotic plaque. Circulation 99:1284–1289

Weber P, Montag D, Schachner M, Bernhardt RR (1998) Zebrafish tenascin-W, a new member of the tenascin family. J Neurobiol 35:1–16

Weber P, Bartsch U, Rasband MN, Czaniera R, Lang Y, Bluethmann H, Margolis RU, Levinson SR, Shrager P, Montag D, Schachner M (1999) Mice deficient for tenascin-R display alterations of the extracellular matrix and decreased axonal conduction velocities in the CNS. J Neurosci 19:4245–4262

Wiese S, Karus M, Faissner A (2012) Astrocytes as a source for extracellular matrix molecules and cytokines. Front Pharmacol 3:120

Wintergerst ES, Fuss B, Bartsch U (1993) Localization of janusin mRNA in the central nervous system of the developing and adult mouse. Eur J Neurosci 5:299–310

Wu B, Matic D, Djogo N, Szpotowicz E, Schachner M, Jakovcevski I (2012) Improved regeneration after spinal cord injury in mice lacking functional T- and B-lymphocytes. Exp Neurol 237: 274–285

Xiao ZC, Ragsdale DS, Malhotra JD, Mattei LN, Braun PE, Schachner M, Isom LL (1999) Tenascin-R is a functional modulator of sodium channel beta subunits. J Biol Chem 274: 26511–26517

Yoshida H, Yoshida T, Iizuka T, Sakakura T, Fujita S (1996) An immunohistochemical and in situ hybridization study of the expression of tenascin in synovial membranes from human temporomandibular joints with internal derangement. Arch Oral Biol 41:1081–1085

Yuasa S (1996) Bergmann glial development in the mouse cerebellum as revealed by tenascin expression. Anat Embryol (Berl) 194:223–230

Zhang Y, Winterbottom JK, Schachner M, Lieberman AR, Anderson PN (1997) Tenascin-C expression and axonal sprouting following injury to the spinal dorsal columns in the adult rat. J Neurosci Res 49:433–450

Zhao Y, Young SL, McIntosh JC (1998) Induction of tenascin in rat lungs undergoing bleomycin-induced tenascin inflammation - pulmonary fibrosis. Am J Physiol 274:L1049–L1057

Zhao C, Fancy SP, Franklin RJ, ffrench-Constant C (2009) Up-regulation of oligodendrocyte precursor cell alphaV integrin and its extracellular ligands during central nervous system remyelination. J Neurosci Res 87:3447-345