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Tenascin: A Multifunctional Extracellular Matrix Protein With a Restricted Distribution in Development and Disease

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Molecules of the extracellular matrix have long been known to promote cell attachment, affect cell morphology and cell migration, and affect neuronal attachment and neurite outgrowth during development [Hay, 1991]. It has been recognized only more recently that a variety of extracellular matrix proteins also exhibit counteradhesive properties that balance the adhesive forces mediated by traditional matrix proteins such as fibronectin [Crossin, 1996]. These counteradhesive forces include the ability to alter cell morphology to a more rounded state with the possible consequences of affecting intracellular physiology, decreasing cell migration on permissive substrates, and stimulating or reducing neurite sprouting and extension depending on the cellular circumstances. Surprisingly, both adhesive and counteradhesive domains are found in some extracellular matrix proteins, among them the unusual glycoprotein tenascin (TN). The ability of tenascin domains to affect adhesive or counteradhesive activities together with an attempt to understand the control of its gene expression will be considered in this review. Other reviews of the structure and functions of TN in development and disease are available [Crossin, 1996].

TN is a large glycoprotein of the extracellular matrix that exhibits a site-restricted distribution during development. It is expressed at very low levels in many adult tissues, but is reexpressed in many tumors, at sites of inflammation, and during regeneration of the peripheral nervous system [reviewed in Crossin, 1996]. The TN polypeptide is divided into four structural regions, each of which appears to have distinct biological functions. The amino-terminus is a cysteine-rich region that is responsible for linking the protein into hexamers forming a structure called a hexabrachion that is visible in rotary-shadowed electron micrographs. Adjacent to the cysteine-rich region are 13½ contiguous repeats homologous to the epidermal growth factor (EGF), and then a series of repeats homologous to the type III repeats of fibronectin (FN III). The smallest TN isoform contains eight FN III repeats, and between one and eight additional FN III repeats can be included as the result of alternative splicing of TN RNA to generate the known TN protein isoforms. The carboxyl-terminal segment is homologous to the β and *y* chains of fibrinogen, and contains a potential calcium binding site.

STRUCTURE–FUNCTION ANALYSIS OF TN AND TN RECOMBINANT DOMAINS

Early studies were equivocal as to whether TN could support cell attachment. This presumably was because TN can inhibit cell attachment to otherwise permissive substrates (e.g., fibronectin) through domains which have now been shown to be counteradhesive. It is now clear that multiple domains within the protein can support cell adhesion. Moreover, the adhesive and counteradhesive activity of TN can be mapped to distinct TN domains (see Fig. 1), each of which presumably has a specific set of receptors. Whether the adhesive or counteradhesive activities in TN predominate in any one situation appears to depend both on the assay used and on the receptor repertoire on a particular cell type.

Adhesion of a number of cell types to TN is now well established, and a number of cell surface receptors have been identified. Among the receptors identified to date are several integrins, a large family of heterodimeric cell surface recep-

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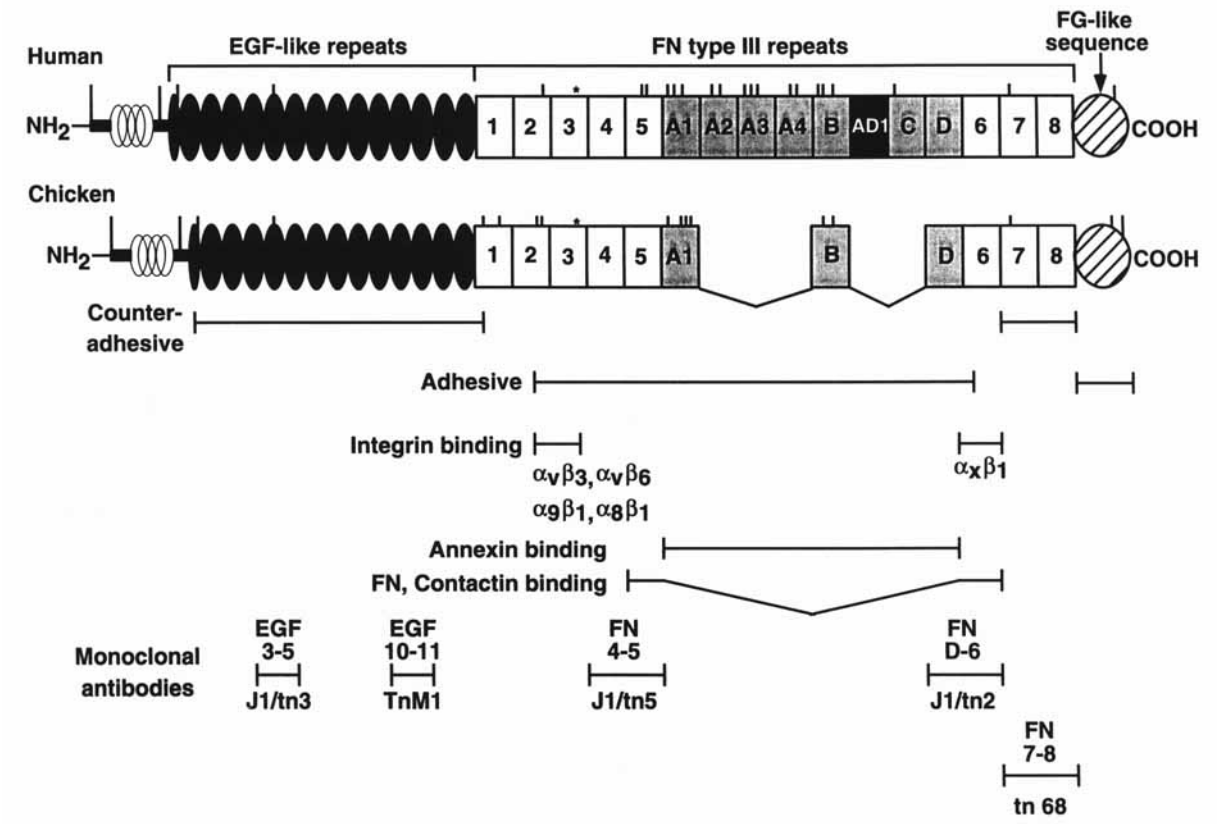

Fig. 1. Schematic model of the domain structure of tenascin. Schematic representations of the domains in human and chicken tenascin are shown. The shaded boxes represent fibronectin type III repeats that are alternatively spliced. Shown below are the regions where biological activities have been mapped using recombinant fragments or monoclonal antibodies.

tors that recognize a number of extracellular matrix proteins [Yamada, 1991; Hynes, 1992]. Integrins have been shown to bind to at least two different regions within TN [Bourdon and Ruoslahti, 1989; Prieto et al., 1993; Sriramarao et al., 1993; Joshi et al., 1993; Yokosaki et al., 1994; Phillips et al., 1995]. Integrin binding to extracellular matrix proteins often occurs via the recognition sequence RGD within the extracellular matrix proteins. In TN, RGD is present in chicken [Jones et al., 1988, 1989; Pearson et al., 1988] and human [Gulcher et al., 1989] homologs, but not in mouse [Weller et al., 1991], newt [Onda et al., 1991], or pig [Nishi et al., 1991] homologs in which the corresponding sequences are RVD, RGL, and RAD, respectively. All of these sequences are found at the same location within the third FN III repeat. The third FN III repeat has now been shown to bind to integrins αvβ3 and αvβ6 in addition to α9β1 and α8β1 integrins, but their binding is much less dependent on the RGD sequence than the binding of other integrins to their RGD-containing ligands. For example, when the RGD sequence in the chicken recombinant third FN III repeat was mutated to RAD, cell attachment was unaffected [Prieto et al., 1993]; when the sequence was mutated to RAA, cell attachment via αvβ3 integrin was almost completely abolished. In contrast, αvβ3 binding to vitronectin, a well established ligand for this integrin, was completely abolished when the RGD sequence was mutated to RAD [Cherny et al., 1993]. Cells expressing the α9β1 integrin bound equally well to the chicken TN fragments containing RGD, RAD, or RAA [Yokosaki et al., 1994]. This suggests that sites other than RGD within the third FN III repeat may be capable of supporting cell attachment.

A number of studies [Prieto et al., 1993; Sriramarao et al., 1993; Phillips et al., 1995] suggest that other β1 integrins may bind to sites in TN other than the RGD-containing third FN type III repeat. For example, the sixth FN type III repeat in chicken TN supports the attachment of both central (CNS) and peripheral nervous

system (PNS) neurons. This repeat is also capable of enhancing neurite sprouting from CNS and PNS neurons. In contrast, the third FN type III repeat supports the attachment of PNS but not CNS neurons. In PNS neurons, this repeat is capable of enhancing neurite elongation in cells that attach to it, although the percentage of cells exhibiting neurites is not increased. These findings suggest two conclusions: CNS and PNS neurons express different subsets of integrins that are capable of recognizing different domains of TN, and neurite sprouting and neurite elongation mediated by TN are separable events that are mediated by distinct TN domains [Phillips et al., 1995].

A number of other types of cell surface receptor for TN have been demonstrated in cell attachment assays and suggested by biochemical assays [reviewed in Crossin et al., 1996]. For example, annexin II binds TN specifically through the TN alternatively spliced FN III repeats A through D [Chung and Erickson, 1994]. In contrast, the neural cell adhesion molecule contactin/F11 [Zisch et al., 1992] as well as fibronectin [Chiquet-Ehrismann et al., 1991] both appear to bind better to the smallest isoform of TN, indicating that alternative splicing may be a means for selecting for a particular cell surface and extracellular matrix ligands for TN. Heparin and heparan sulfate proteoglycans as well as chondroitin sulfate proteoglycans, including syndecan, have also been shown to be receptors for TN. The heparin binding activity appears to be mediated by the C-terminal fibrinogen domain since this domain is able to bind to heparin–agarose, and heparatinase treatment of cells abolishes their ability to attach to the fibrinogen domain in cell attachment assays.

EFFECTS OF TN ON CELLULAR PHYSIOLOGY AND CELL SIGNALING

The binding of TN to integrins may activate signal transduction pathways which are known to be affected by this receptor family [Schwartz, 1992]. A number of early studies indicated that when cells attached to TN or to mixed substrates of TN and other extracellular matrix proteins they remained round and did not flatten. Flattening of cells on the substratum and growth factor stimulation are both accompanied by increases in intracellular pH (pH_i). In the presence of TN, cells maintained a lower pH_i [Crossin, 1991] and the different domains within TN were subsequently shown to affect pH_i differently [Krushel et al., 1994]. For example, the adhesive fragments, comprising the second through sixth fibronectin type III repeats and the fibrinogen domain, induced an increase in pH_i in fibroblast and glioma cell lines similar to that observed in cells plated on fibronectin. These two fragments had different effects, however, on cell morphology [Prieto et al., 1992; Krushel et al., 1994]. The FN III repeats supported cell attachment and spreading, whereas on the fibrinogen domain cells remained round. The increased pH_i in cells plated on FN III repeats could be reversed by preincubation of the cells with RGD-containing peptides to inhibit integrin function. Similarly, the increase in pH_i mediated by the fibrinogen domain was prevented when cells were pretreated with heparatinase, suggesting that a heparan sulfate proteoglycan at the cell surface mediates the response to this domain. The counteradhesive repeats of TN (the EGF domains and FN type III repeats 7 and 8) kept cells at a lower pH_i, thus resembling the activity of intact TN. The ability of TN to mediate these effects on pH_i was sensitive to the activity of protein kinase C, inasmuch as drugs that effect protein kinase C activity were able to reverse the effects of the different TN domains on pH_i. Recent studies have shown that TN is subject to degradation by matrix metalloproteinases in vitro [Imai et al., 1994; Siri et al., 1995]. This suggests that proteolytic fragments generated in vivo may be able to exert different effects on pH_i during development, wounding, and disease. The types of effects that may be mediated by pH_i changes of this magnitude include the activity of cytoplasmic enzymes, intracellular trafficking, cytoskeletal integrity, and effects on neural physiology [discussed in Crossin, 1996].

Several studies have suggested that changes in gene expression result when cells interact with each other or with a variety of substrata. Based on the signaling results discussed above, it is possible that cellular interaction with TN may induce changes in gene expression. Cell shape changes such as those affected by the presence of TN have also been shown to be important in regulating the expression of several genes associated with the synthesis and degradation of the ECM itself. One recent study compared fibroblasts plated on FN or mixtures of FN and TN. When compared with cells plated on FN, those plated on the mixture of FN and TN showed an increase in the synthesis of four

gene products: collagenase, stromelysin, a 92 kDa gelatinase, and c-*fos* [Tremble et al., 1994]. The effect on metalloproteinase expression was reversed in the presence of a monoclonal antibody that reacts with the seventh and eighth FN type III repeats, suggesting that these changes in gene expression may be related to the counteradhesive activity of TN.

We recently used a subtractive hybridization strategy [Mauro et al., 1994] to explore directly whether the presence of TN could change gene expression in early embryonic neuronal cells. Like the previous study on gene expression changes following N-CAM-mediated neuronal aggregation, these studies with TN revealed a number of cDNA clones encoding cell adhesion molecules, ECM molecules, and ribosomal proteins, the expression of which differed between TN-treated and untreated neurons [Crossin, 1996]. The cDNA clones enriched in the cDNA libraries prepared from TN-treated cells include neurofascin [Rathjen et al., 1987] and the chicken homolog of the opioid binding CAM, OB-CAM, both cell adhesion molecules of the Ig superfamily. Claustrin, an ECM keratan sulfate proteoglycan with counteradhesive properties [McCabe and Cole, 1992], was found to be enriched in the library prepared from untreated cells, suggesting that its synthesis was downregulated by the presence of TN. This proteoglycan also has been shown to inhibit neurite outgrowth and cell attachment on permissive substrates [Cole and McCabe, 1991], and thus it shares with TN several biological activities. In addition, several transcription factors were enriched in the TN-treated cDNA library. These gene expression studies indicate that the expression of TN at particular locales during development and in disease may result in subsequent changes in gene expression that may in turn affect tissue differentiation or cellular migration.

THE TN NULL MUTANT MOUSE

The combination of these biological properties and the dramatic site-restricted distribution of TN during embryogenesis suggested that the molecule may dramatically affect developing morphology when and where it is expressed. It was therefore surprising that mice with targeted deletions of the TN gene [Saga et al., 1992] were initially reported to be essentially normal and reproductively competent. However, a detailed analysis of the developing nervous system and behavioral analyses were not carried out in this initial study, and recent developmental and behavioral studies indicate that these tenascin null mice are not normal. For example, in the TN null mutant mouse, although the development of the barrel cortex is normal, the response of glial cells after wounding was not normal [Steindler et al., 1995]. Moreover, other studies have indicated that motor coordination in these animals is abnormal and that there may be possible malfunctions in the peripheral nervous system innervating the gut. These findings would be consistent with a role for TN in neural crest development and in the development of the cerebellar and cerebral cortices, as suggested by the distribution pattern of TN and by perturbation studies.

The evaluation of this and other transgenic mice raises question about earlier notions that the importance or function of a molecule could be discerned from the phenotype of a null mutant animal. Normal phenotypes have been observed after the knockout of other developmentally significant gene products [reviewed in Crossin, 1994; Routtenberg, 1995], and it has been suggested that related gene products may compensate for the function of the deleted gene product. It is also possible that evolution has selected for particular combinations of molecules, no one of which is uniquely necessary for the development of a particular phenotype. That is to say that backup strategies have been evolved for particularly important morphogenetic functions.

CONTROL OF TENASCIN GENE EXPRESSION BY PATTERN-FORMING GENES

Tenascin exhibits a dramatic site-restricted expression in the anterior–posterior axis during gastrulation, neurulation, and somite formation [Crossin et al., 1986]. The presence of TN during somite formation has been postulated to play a role in the movement of neural crest cells through the somites, and possibly their condensation and differentiation, to form the peripheral ganglia [discussed in Crossin, 1994; Crossin et al., 1996]. Supporting this hypothesis is the observation that neural crest cell migration can be perturbed by introduction of TN antibodies both in vivo and in vitro. During development of both central and peripheral nervous systems, TN has been shown to be important in such critical processes as neuronal migration, axon guidance, synaptogenesis, and border forma-

tion, for example, in the barrel cortex. The expression of TN in nervous tissue sharply decreases during development and the protein is not expressed at high levels in the adult [reviewed in Faissner, 1996]. It is reexpressed, however, in a variety of glial tumors, and antibodies to TN have recently been used as probes for the localization and possible treatment of such tumors [reviewed in Carnemolla et al., 1996].

Based on these unusual spatiotemporal expression patterns, it was hypothesized that the products of homeodomain proteins might control the *spatiotemporal* expression of TN. Homeobox-containing gene products are expressed in distinctive anterior–posterior and dorsal–ventral patterns in *Drosophila* [McGinnis and Krumlauf, 1992]; mutations in these genes result in a variety of homeotic transformations, for example, the development of legs in the places where antennae should be. All of these genes are transcription factors containing a helix-loop-helix DNA binding motif called the homeodomain, and they have distinct homologs in vertebrates.

Recent studies have indicated that the products of homeodomain-containing genes could participate in the regulation of TN expression. For example, co-transfection of TN promoter/reporter constructs and constructs driving the synthesis of the *Evx-1* homeodomain protein resulted in the dramatic enhancement of TN promoter activity [Jones et al., 1992]. The region responsible for the activation was an 89 base pair region which contained a TRE-AP1 site known to be involved in the response of many genes to growth factors by binding of transcription factors of the *fos* and *jun* families [Curran and Franza, 1988]. The site within this 89 base pair segment of the TN promoter was also found to bind to the *Fushi tarazu* homeodomain protein, suggesting that direct binding of homeodomain proteins also plays a role in the expression of TN [Jones et al., 1992]. In cotransfection experiments, other homeobox-containing genes were also shown to activate the TN promoter including *hoxA1, hoxB9, hoxD9, pax-3,* and *pax-6,* all of which encode different classes of homeodomain proteins [Jones and Copertino, 1996].

Recent comparisons of the chicken [Jones et al., 1990], mouse [Copertino et al., 1995], and human TN [Gherzi et al., 1995] promoters emphasize the potential importance of homeobox control of TN gene expression. The proximal regions of these promoters exhibit a remarkable structural similarity. In particular, TAAT motifs that resemble binding sites for homeodomain proteins are conserved between the human, mouse, and chicken promoters. In addition, the mammalian promoters also contained the TRE-AP1 sequence, which was shown to be required for activation by *Evx-1* although this sequence is located in a different region from that in the chicken promoter. A number of other potential regulatory elements have been identified in the chicken, mouse, and human promoters. How these different regulatory regions act to result in the place-dependent expression of TN is a critical area of ongoing research, the results of which may help to explain how TN expression is regulated during development and in disease.

PERSPECTIVES

Further studies on the control of TN gene expression, cellular signaling initiated by TN binding, and subsequent changes in gene expression provide a challenging arena for future studies on this unusual counteradhesive ECM protein. Preliminary studies have established that a variety of transcription factors from the *hox* and *pax* gene families may be important in controlling tenascin gene expression. Whether these sequences function *in vivo* to control the exquisite spatiotemporal expression patterns of tenascin is of particular interest for understanding morphogenesis since many *hox* and *pax* mutants have aberrant morphological phenotypes. Further studies on the cell surface receptors for tenascin and the signaling pathways activated by tenascin binding are also an important avenue for further study, especially with regard to the elucidation of how TN and its various fragments mediate its counteradhesive properties. Related to this issue is whether binding of a particular ECM protein or cell surface receptor to TN affects the subsequent binding of any of these molecules to other ligands. It appears that the activity of intact TN represents a summation of its adhesive and counteradhesive domains together with the repertoire of particular cell surface receptors and ECM proteins made by particular types of cells. An understanding of changes in the gene expression programs that result from TN-mediated cell signaling would significantly advance our understanding of the role of TN and other counteradhesive proteins

in development and disease. The accumulation of such studies on TN should yield a better understanding of the role of this protein in affecting cellular processes, including cell proliferation, cell migration, cell differentiation, neurite sprouting and outgrowth, and differential gene expression, that are important in development, regeneration, and disease.

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