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Review Article

What is the importance of tenascins in the pathophysiology of various diseases?

Qual a importância das tenascinas na fisiopatologia de diversas doenças?

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ABSTRACT: Tenascins are a group of proteins that make up the extracellular matrix of different tissues. They are involved with signaling and structural functions in different organs, which justifies the development of studies on their relationship with diseases in different systems. Our objective was to shed light, through an in-depth review, of the way in which tenascins are involved in triggering various organic disorders. Each type of Tenascin is related to specific disorders. Tenascin X is involved in triggering collagen diseases, while types C and W stand out in situations of trauma, inflammation and tumors. Tenascin R is involved exclusively in the central nervous system and in neuronal migration and differentiation processes. Understanding the real role of these proteins is a valuable resource for understanding the pathophysiology of various diseases, in addition to providing research into new diagnostic methods and prospecting therapeutic targets for drug development.

KEY WORDS: Tenascins; Pathophysiology; Diseases.

RESUMO: As tenascinas são um grupo de proteínas que compõem a matriz extracelular de diferentes tecidos. Estão envolvidas com a sinalização e função estrutural de diferentes órgãos, o que justifica o desenvolvimento de estudos devido sua relação com doenças em diferentes sistemas. Nosso objetivo foi lançar luz, através de uma revisão, mostrando as vias de envolvimento que as tenascinas têm em diferentes distúrbios orgânicos. Cada tipo de tenascina está relacionada com uma desordem específica. A tenascina X está envolvida no desencadeamento de doenças do colágeno, enquanto a tenascina C e W destacam-se em situações de trauma, inflamação e tumores. A tenascina R está envolvida exclusivamente no sistema nervoso central e na migração neuronal e no processo de diferenciação. Compreender o real papel dessas proteínas é um recurso valioso para a compreensão da fisiopatologia de diversas doenças, além de possibilitar a pesquisa de novos métodos diagnósticos e a prospecção de alvos terapêuticos para o desenvolvimento de fármacos.

PALAVRAS-CHAVE: Tenascinas; Fisiopatologia; Doenças.

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INTRODUCTION

Tenascins are a family of extracellular membrane (ECM) glycoproteins that act in migration, differentiation, cell movement, in addition to contributing to molecular adhesion. They can also bind to and therefore influence the function of growth factor peptides and other molecules produced by ECM cells[1]. Tenascins are made up of six identical subunits expressed in mesenchymal tissues[1,2,3,4,5,6]. Each polypeptide chain of a molecule of Tenascin has different domains. Repeated domains similar to epidermal growth factor (EGF), those similar to fibronectin type III, and sequences homologous to fibrinogen at its C-terminus.

The Tenascin family is composed of five members: Tenascin-C (TN-C), Tenascin-R (TN-R), Tenascin-X (TN-X), Tenascin-Y (TN-Y) and Tenascin-W (TN-W) (Figure 1). It is known, until then, that they are related to the pathophysiology of arterial diseases such as aortic aneurysms, peripheral venous disease, cardiomyopathies and cardiac remodeling, ocular changes, nasal polyposis, respiratory diseases, neuropsychiatric disorders, gastrointestinal diseases and uterine changes. Furthermore, they are involved with wound healing, regeneration and osteoarticular remodeling. Therefore, this article aimed to do a bibliographical survey of various diseases that have in their pathophysiology a relationship with some component of the tenascin family.

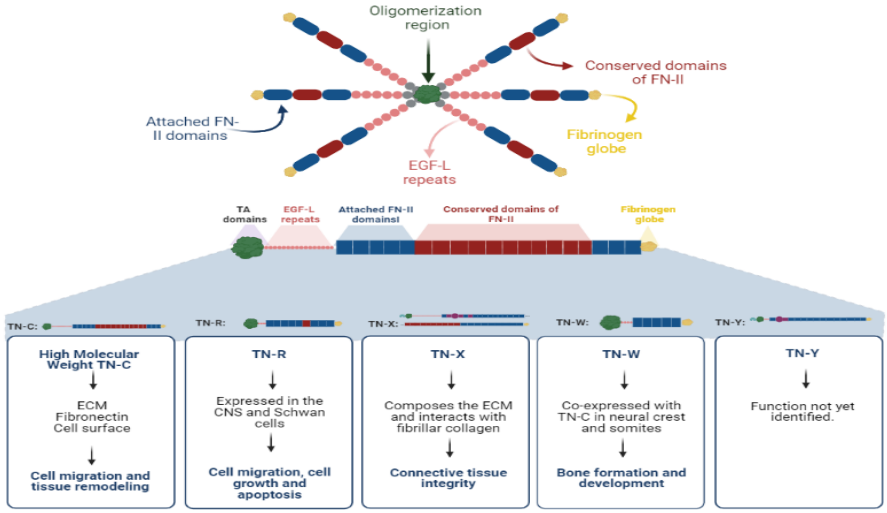

Figure 1 - Below shows, in a systematic way, the types of tenascins identified so far, relating them to their respective functions. In addition, the main places where they are found were highlighted. TN-C (tenascin-C); TN-R (tenascin-R); TN-X (tenascin-X); TN-W(tenascin-W); TN-Y (tenascin-Y); ECM: extracellular matrix; EGF-L: epidermal growth factor

METHODS

A literature review was carried in the year 2022 in the databases of the platforms: Cochrane Central Register of Controlled Trials, MEDLINE/Pubmed, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), SciELO, Lilacs/Bvsalud /bireme/bvs and Google Scholar. The following descriptors were used: "Tenascin" and "physiopathology", in Portuguese, French and English. All articles published in Portuguese, French and English that dealt with the pathophysiological processes in which tenascins were involved were used as inclusion criteria.

RESULTS

Of the 45 articles found, 35 were included in the search for meeting the established criteria. Articles that did not mention Tenascins and their relationship with organic disorders were excluded.

DISCUSSION

Tenascin family

TN-C is structured into four distinct domains that are able to interact with ECM constituents[3]. It has two more common isoforms that are differentiated by size and suggest different functions. The higher molecular weight isoform, called large TN-C, is related to cell migration and tissue remodeling processes[3]. As for the isoform of lower molecular weight, so far there are no studies that clarify its function.

TN-R is a glycoprotein composed of four domains and is involved in modulating functions such as migration, growth and apoptosis in the central nervous system (CNS)[7]. It has the lowest molecular weight among the members of the Tenascin family and is almost exclusively expressed in the CNS and Schwann cells during the development of peripheral nerves[7].

TN-X is often associated with connective tissues and composes the ECM through interactions with fibrillar collagen[8].

In apparent contrast to other tenascins, it has a major influence on the role of connective tissue integrity[8]. This glycoprotein binds to collagen fibrils and regulates their tissue deposition. Similar to TN-C, it is also induced by inflammatory stimuli and during the healing process.[8]

TN-W is co-expressed along with TN-C in neural crest cells and somites[9]. Both, during human development, show partially overlapping expression patterns in the embryonic and adult skeleton. TN-C is more expressed in the adult period and TN-W in the embryo[9]. Most research based on the regulation of physiological TN-W expression indicates its significant role in osteogenesis, having the function of accelerating formation and development of bones, being predominantly expressed in the periosteum of adult individuals[10].

The influence of tenascins on the pathophysiology of different organs and systems

Epithelium

Chawla and Ghosh[11] emphasized the importance of understanding the epithelial healing process and the influence of TN-C. At first, there is a transition from fibroblasts to myofibroblasts, due to signaling through the smooth muscle alpha-Actin protein (α-SMA) which is produced by injured cells[11]. A posteriori, there is contraction followed by excessive collagen secretion type I and fibronectin. In the penultimate stage, there is expression of fibrotic proteins: acid secreted protein rich in cysteine (SPARC) and TN-C. Finally, there is insufficient secretion of metalloproteinases (MMPs), especially MMPs 1 and 13[11]. The authors concluded that TN-C is a fibrotic marker and that its production, by myofibroblasts, involves the formation of scars.

Eyes

Wallace et al.[12] investigated the pathophysiology of glaucoma, with regard to the deposition of extracellular matrix (ECM) components in the lamina cribrosa (LC) of the optic nerve. Among the proteins analyzed were Tenascins C and X. The authors recognized that these proteins play a role in glaucoma induction throughout the fibrotic process and contribute to more deposition and renewal of ECM components, both in LC and in the trabecular meshwork, being, therefore, maleficent[12].

Also regarding to glaucoma, Wallace, Pokrovskaya and O'Brien[13] reiterated the contributions of Tenascins-C and X to the fibrotic process and the consequent increase in intraocular pressure[13]. However, they did not specify the exact mechanisms. Regarding the TN-C and other components of the ECM, the authors highlighted the importance of the integrity of the matrix in order to maintain the proper organization of the connective tissues[13]. If the structure of this tissue does not withstand the tension forces, what happens when there is an increase in TN-C and TN-X, open-angle glaucoma may develop.

Vicente et al.[14] analyzed the deposition of TN-C in the corneas of patients with aniridia. According to the authors, TN-C would act as a signal from macrophages and mesenchymal cells towards the corneal healing process, through the regulation of the inflammatory process, fibrosis and revascularization, but they did not point out whether TN-C would act in a beneficial way or malefic. Through the analysis of histological sections, the authors identified that TN-C was abundantly present in the anterior stroma of patients with aniridia. Meanwhile, in normal corneas, it has not been identified[14].

Respiratory system

Liu et al.[15] identified that an abnormal ECM – with altered values for Tenascin and fibronectin – could be related to the proliferation of the epithelium, accumulation of eosinophils and the formation of edema. And that, ultimately, would cause the formation of nasal polyps[15].

Another contribution on the pathophysiology of nasal polyps was that of Payne et al.[16]. They explored the etiology of rhinosinusitis with nasal polyps. Through the use of Polymerase Chain Reaction - Reverse Transcriptase (RT-PCR), the authors indicated an increase of approximately ten times in the amount of TN-C in patients with rhinosinusitis with nasal polyps[16].

In the case of asthma, Holloway and Koppelman[17] discovered new genes involved in the production of TN-C, thus contributing to its pathophysiology. The Simple Nucleotide Polymorphism (SNP) 44513 A/T in exon 17 was analyzed from a collection carried out in 446 patients diagnosed with asthma and 658 without, with a strong association between the SNP and the disease. The authors concluded that TN-C is not only a biomarker glycoprotein for the disease, but also appears to promote airway remodeling[17].

Also in the field of asthma, Amin[18] identified that the expression of TN-C in patients with allergic asthma was much higher than in the other two groups (control and patients with non-allergic asthma)[18]. Furthermore, in individuals with allergic asthma, an association was found between the expression of TN-C and laminin with lymphocytes CD3, CD4, CD8 and CD25[18]. The hypothesis formulated by the author is that lymphocytes, together with eosinophils, cooperate in the process of bronchial fibrosis by interfering with the growth process of fibroblasts and MMP-9, which contributes to the deposition of TN-C in the bronchiolar basement membrane[18].

Cardiovascular system

Minear et al.[19] aimed to investigate whether genetic variations, in the context of single nucleotide polymorphisms (SNPs) for the production of TN-C, were associated with atherosclerosis and coronary artery disease (CAD), and pointed out that the SNP rs12347433 may be biologically relevant, as TN-C is usually increased in these diseases.

In Acute Myocardial Infarction (AMI), according to Frangogiannis[20], TN-C is present at the borders of remodeling areas, between the infarcted area and the viable area of the myocardium[20]. In contrast, in cardiac hypertrophy due to overload of pressure, the TN-C is increased intensely but transiently. However, its role in the development of hypertrophy or fibrosis has not yet been investigated[20]. In myocarditis,

cardiomyopathies and cardiac allografts, TN-C seems to induce autoimmune myocarditis. At the same time, this glycoprotein appears to be essential for the revascularization process around the cardiac allograft[20].

Guo et al.[21] investigated the role of TN-C in acute aortic dissection (AAD). The research was aimed at patients admitted to hospital due to AAD. The study demonstrated that patients who progressed to death had significantly higher levels of TN-C than those who survived AAD. This finding reverberated in the correlation that the increase in serum TN-C concentration is directly proportional to the severity of the process, and may be a useful biomarker in AAD[21].

As for TN-X, according to Frangogiannis[20], it is still not well known about its role in heart disease. Some cases have been reported regarding the deficiency of this glycoprotein in patients who had valvular diseases, particularly mitral valve prolapse. However, due to its low prevalence, a relationship between TN-X and valve morphology cannot yet be established[20].

Digestive Tract

Islam et al.[22] analyzed how TN-C modulates the inflammatory cascade in myofibroblasts of the subepithelial layer of the intestine and in intestinal epithelial cells in colitis. They used wild and knockout mice. The latter lacked the genes for the production of TN-C and increased intestinal inflammation and mucosal abrasion were observed. The authors concluded that TN-C, in the case of wild mice, contributed to cell migration, remodeling and intestinal protection[22].

A study conducted by Chiovaro et al.[6] found a greater expression of TN-W, as well as TN-C, in the stroma of most solid nodules located in the colon. The authors highlighted the possible role of TN-W and TN-C as malignancy biomarkers in colon cancer[6].

The role of TN-X was investigated by Aktar et al.[23]. They found that the patients in the sample, deficient in the expression of TN-X, had increased sensory and motor symptoms linked to the gastrointestinal tract (GIT), including abdominal pain and constipation, when compared to control cases with normal levels of TN-X[23]. The patients in the sample had cancer and a portion from a distant region of the tumor was used. The authors supported the hypothesis that the ECM is not just a support structure of the TGI, but an integral part for its functioning, especially with regard to the microenvironment of colonic motor neurons[23].

Genitourinary System

Farrell et al.[24] investigated the distribution of Tenascin, fibrinogen and fibronectin in Vulvar Schlorus Lichen (LEV). There was a greater expression of Tenascin in the epidermis, corresponding to the sclerotic zone and a low amount present in the inflamed regions[24]. Although the authors found a greater presence of Tenascin in histological sections affected by LEV, they still reported not knowing how this increase occurs[24]. They mentioned the likely role of IL-4 in stimulating fibroblasts to produce Tenascin. As for the function of Tenascin, they stated that it seems to play a role in intercellular union, at the same time that it may have an anti-adhesive function and produce a motility effect. Finally, the article was inconclusive as to its role in the pathophysiology of LEV.

Deffieux and Fernandez[25] in an attempt to understand the pathophysiology of adenomyosis, they emphasize that it is produced by fibroblasts of the endometrial stroma and that tenascin acts as an inhibitor of bronectin and favors the migration of epithelial cells and epithelial glands to the connective tissue, thus participating in part of the process. of myometrial hyperplasia. In addition, the Epithelial Growth Factor (EGF) was pointed out by the authors as a possible stimulator of the production of Tenascin[25].

Leimgruber et al.[26] studied the normal response of smooth muscle cells (CMLs) in the prostate when exposed to bacterial lipopolysaccharides (LPS). The research was carried out in mice and it was found that LPS triggered an increase in TN-C expression.

Osteoarticular system

Alford and Hankenson[27] found that TN-C knockout mice showed uncontrolled bone regeneration, in which osteoblasts even occluded the bone marrow. The implications of these findings lie in the recognition of the fundamental role of TN-C in the regulation of osteogenesis and osteoclast maturation[27].

Tojyo et al.[28] investigated the presence of TN-C in the synovial membrane in temporomandibular joint (TMJ) dysfunction. They found that, under conditions of hypoxia, there is increased expression of TN-C in fibroblast cells, which is not seen in articular discs[28]. Hypoxia, together with the release of IL-1 β, stimulate an increase in TN-C production. The research identified that there was an increase in TN-C in the inflammatory phase of the synovial membrane of TMJ dysfunction.

Ribistch et al.[29] carried out a study focusing on genes that regulate the production of collagen types I, III, V, as well as those that determine the expression of TN-C. Based on an experiment carried out in horses, the authors concluded that the increase in decorin and the reduction in TN-C represent the initial stage in tendon diseases arising from aging, which is attributed to the decrease in the thickness of the collagen fibrils[29].

Nervous system

Bot et al.[30] focused their efforts on evaluating whether TN-C could act as a biomarker for Major Depression Disorder (MDD). Through regression analysis, the authors identified that the levels of TN-C in the blood serum of the bgroup of patients with MDD were higher than in healthy people.

Also in the context of MDD, Krivosova et al.[31] verified the serum predictive value of TN-C in patients diagnosed with MDD. They emphasized that although several studies have revealed that TN-C can be used as a biomarker, they have not identified a correlation[31].

Chen et al.[32] carried out a study in mice with the aim of investigating epileptic seizures, and demonstrated that the increase in TN-R decreases the convulsive period, the severity of the convulsion and increases the latency period. The authors conclude that the alteration of the perineural network is related

to epilepsy and that preventing this destruction is important to control the occurrence and severity of seizures. TN-R would have a possible antiepileptic effect in conjunction with other components of the MEC[32].

Another collaboration, with regard to ischemic and hemorrhagic strokes, was given by Kawakita et al.[33] they recognized that the role of TN-C is not yet fully understood in the context of these diseases, the authors pointed out that TN-C accentuates the post-stroke inflammatory process. They highlighted that TN-C together with other inflammatory markers potentiates the post-stroke response[33-34].

In the context of traumatic brain injury (TBI), Minta et al.[34] assessed whether there were changes in serum and cerebrospinal fluid (CSF) levels of TN-C, TN-R, brevican and neurocan over time. They also compared these levels with people who had not been traumatized. They concluded that increased levels of TN-C, TN-R represent poor prognosis and have greater predictive value than possible changes in brevican and neurocan values[34].

Minta et al.[34] also reported that TN-R is a more specific CNS protein than TN-C, as the latter is present in other tissues, such as muscle. This statement is consistent with the work by Morawski et al.[7] who identified the influence of TN-R on CNS synapses, which contribute to the stabilization of interneuronal communications[34].

Still dealing with TBI, Griffiths et al.[35] carried out an experiment in mice in which they identified a decrease in fibronectin in the cortex at different times: 15 minutes, 1 hour and 2 hours, after injury. There was an increase in TN-C in 15 minutes and in 7 days after injury in the hippocampus region. This same glycoprotein showed a significant decrease on the 7th and 14th days after the trauma, in the cerebral cortex[35]. The alteration in its expression, in the first moments after the trauma, was interpreted by the authors as responsible for the disarrangement of neuronal circuits. In the chronic phase, a new change in TNC expression was observed, which would be a reflection of a change in circuits[35].

Blood vessels

Demirkıran et al.[36] carried out a research with the objective of determining if there would be variations in the expression of TN-C, through immunohistochemistry in the ECM, of veins in the saphenofemoral junction of the thigh, according to the stage of chronic venous insufficiency of lower member. From the histological analysis, they identified that in the early stages of the disease C2 and C3, based on the Clinical Classification of Venous Disease (CEAP), the tunica intima of the veins showed increased expression of TN-C.[36] In the more advanced clinical stages, of C4 to C6, this increased expression of TN-C was not restricted only to the tunica intima, but advanced to the media, enabling fibrosis in both layers of the varicose veins. From that, it was observed a stiffening of the media layer of the vessel wall and an increase in the deposition of fibronectin[36].

In order to systematize what is known so far about the role of Tenascins in the pathophysiology of different clinical conditions, Figure 2 is presented below.

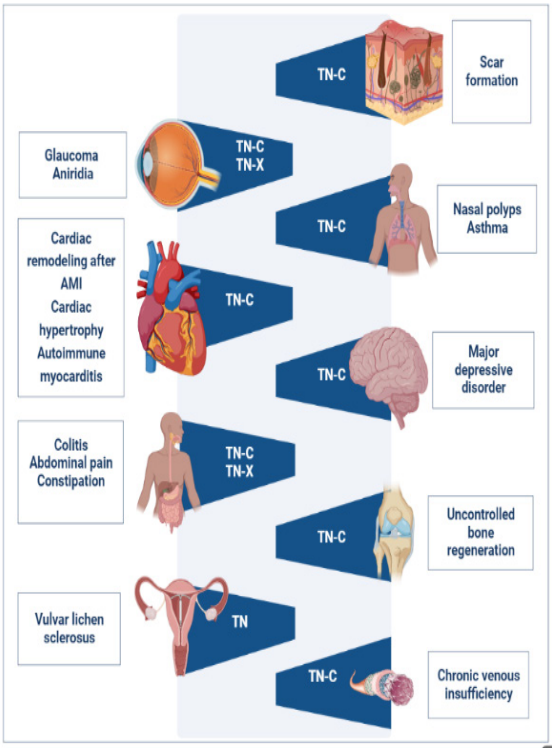

Figure 2 - It associates the specific type of Tenascin with the respective system involved. TN-C (tenascin-C); TN-R (tenascin-R); TN-X (tenascin-X); TN-W(tenascin-W); TN-Y (tenascin-Y). AIM: Atache miocardic isquemic

CONCLUSION

The Tenascin family is involved in several pathological events, some being present only in certain organs and others in more than one, such as TN-X, which is related to collagen diseases. While types C and W stand out in situations of trauma, inflammation and tumors. TN-R is involved exclusively in the CNS and in processes of migration and neuronal differentiation. However, there are still no studies that demonstrate the real involvement of TN-Z in the pathophysiology of diseases.

Understanding the real role of these proteins is a valuable resource for understanding the pathophysiology of various diseases, which can provide insight into new diagnostic tools and the investigation of new therapeutic targets for drug development.

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