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Role of Tenascin-C in Systemic Lupus Erythematosus and Its Association with Disease Activity: Review Article

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ABSTRACT

Background: The cause and the mechanism for the development of systemic lupus erythematosus (SLE) are shrouded in mystery. The fact that tenascin-C (TN-C) is upregulated in response to trauma, inflammation, or cancer growth demonstrates that it is involved in cell signaling. Within the scope of this brief review, we discuss the significance of TN-C in the pathophysiology of SLE disease and the correlation between serum TN-C levels and disease activity.

Objective: Analyzing the Role of Tenascin-C and Its Relationship to Disease Activity in SLE

Methods: Tenascin-C, Systemic Lupus Erythematosus, and Disease Activity were all looked for in PubMed, Google Scholar, and Science Direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete study from January 2000 to May 2021 was included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

Conclusion: Important novel biomarker for active SLE, TN-C is also a crucial molecule in tissue remodeling and is linked to SLE. There has to be more high-quality research done on TN-C before it can be recommended as a helpful blood biomarker for tracking disease activity and anticipating flares in SLE patients.

Keywords: disease activity, systemic lupus erythematosus, Tenascin-C.

INTRODUCTION

Inflammatory and with far-reaching effects on multiple organs and tissues, systemic lupus erythematosus (SLE) is a devastating condition. Polyclonal activation of T and B cells, followed by the production of autoantibodies and immunological complexes, which then precipitate in various tissues and organs, causing their damage and ultimately leading to significant morbidity and mortality, characterizes this condition [1].

Individuals may experience a wide range of symptoms, such as joint pain, swelling, arthritis, a butterfly rash, hair loss, swollen lymph nodes, and more [2].

Symptoms of systemic lupus erythematosus (SLE) patients can vary widely, both serologically and clinically, and flares and remissions can be extremely unexpected, making it difficult to detect disease activity and provide appropriate treatment[3].

Anti-dsDNA antibodies and complement levels, two common traditional serological biomarkers, are unreliable predictors of disease recurrence and activity[4].

Variations in the extracellular matrix glycoprotein tenascin-C (TN-C) size (small & large variants). Such molecular structural variety demonstrates the existence of a rich variety of potential biological effects[5].

TN-C has been found to regulate both the innate and adaptive immune systems by affecting the production of several cytokines and the recruitment of immune cells to areas of inflammation or damage[6].

It was shown that many chronic inflammatory disorders share a common characteristic: elevated levels of tissue and plasma TN-C (myocarditis, inflammatory bowel disease, chronic hepatitis C)[7].

Structure of tenascin-C:

A total of 25 distinct molecules can be brought together by the four domains that make up tenascin-C. Some examples of these factors include pathogens, matrix proteins, soluble factors, and proteins found on the surface of cells. The EGF-like repeats operate as a low-affinity ligand for the EGF-receptor to stimulate mitogen-activated protein kinase and phospholipase-C signaling, while the tenascin assembly domain creates inter-molecular hydrophobic contacts and disulfide bridges, Fibronectin's type III-like repetitions bind a wide variety of proteins that interact with it, including integrins, aggrecan, perlecan, and members of the platelet-derived growth factor family. Oligomerization, stimulation of mitogenic responses, cell motility, adhesion, spreading, and more are all driven by tenascin-C because of this, functions such as protease and pro-inflammatory cytokine production, matrix assembly, neurite outgrowth and potentiation, and focal adhesion creation[8].

These protein building blocks are strung together like beads to form very lengthy molecules. Every Tenascin possesses an oligomerization domain at its N-terminus; this domain is responsible for hexamer

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formation in TN-C. Alternative splicing has been seen in TN-C and -R. Human TN-C contains eight consistent repetitions and nine additional repeats that can be spliced in various ways. Because of this, there are many different TN-C subunits, each with a unique amount and composition of fibronectin type III domain repeats[5].

The function of tenascin-C:

Even within a single cell type, TN-C can elicit a wide variety of effects. This wide variety of roles is achieved via alternative splicing of mRNA and the stage-specific activation of signal transduction pathways and/or target genes. Since TN-C has been shown to prevent cell adherence to fibronectin, it is considered an adhesion-modulating protein. Numerous knockout mouse models for TN-C are relied upon heavily for inferring functional research. Since TN-C is upregulated in response to a variety of stresses, including tissue damage, inflammation, and carcinogenesis, it is evident that it plays a function in cell signaling. Members of the FGF, PDGF, and TGFβ families, among others, can bind to tenascin-C through its FNIII5 receptor [9].

It has been found that tenascin-C immunoprecipitates with the signaling protein Wnt3a. There is a decrease in β-catenin-mediated Wnt3a signaling when tenascin-C and Wnt3a are introduced to the medium of cells harboring a reporter construct. Wnt3a signaling is upregulated when it is combined with tenascin-C on the surface of tissue culture plastic. These results suggest that tenascin-C, depending on whether it is soluble or attached to a substrate, can either inhibit or boost the characteristics of growth and signaling factors upon binding[10].

As a stress protein, TN-C plays a key role in controlling cell adhesion, migration, and proliferation. To better combat chronic inflammation, tumor growth, and metastasis, deeper comprehension of its functions could pave the way for novel uses in tissue healing. The establishment of immune-competent animal models in which TN-C and several of its frequent variations are expressed as highly controlled, tissue-specific proteins presents a significant challenge[11].

Protein tenascin-C acts on adhesions in a modulatory fashion. Tenascin-ability C's to inhibit fibronectin/syndecan-4 interactions is one mechanism of action (a). This affects integrin signaling via fibronectin, resulting in the lessening of stress fibers, focal adhesions, and matrix contraction. Direct integrin ligand signaling is another mechanism through which tenascin-C can affect cell fate (b). Increased tenascin-C expression in response to mechanical strain is mediated through SRF-independent and SAP-dependent MKL-1 signaling [12].

Clinical significance of **tenascin-C:**

Myocarditis and various types of cancer are just two of the many diseases for which TN-C is being studied as a possible biomarker. TN-C is a highly investigated protein for its potential in therapy and detection due to its extensive participation in cellular signaling and function. By attaching to a chemokine coreceptor location on the HIV-1 envelope protein, recent research has demonstrated that TN-C can prevent HIV infection in immune cells[13].

Role of tenascin-C in SLE:

Anti-dsDNA antibodies and complement levels, two common traditional serological biomarkers for lupus, are unreliable indicators of SLE activity and predictors of future illness exacerbations[14].

A lack of accurate biomarkers for SLE has slowed both assessments of disease activity and medication response. This is driving a greater push to identify novel biomarkers that can be utilized as surrogate markers for SLE activity and/or to forecast illness flares. Despite TN-lack C's of specificity for any disease, it was discovered that its levels in the blood were useful in distinguishing patients with SLE who were actively ill from those who had a minimal disease. Having to begin or increase glucocorticoid treatment was also linked to higher TN-C levels[15].

Because TN-C was discovered to be a more accurate predictor of disease worsening than more traditional biomarkers, it may be easier to determine whether it's time to increase immunosuppressive treatment in SLE, highlighting the disease's therapeutic relevance[16].

Catalán *et al.* [17] evaluated the predictive value of TNC in SLE by conducting a case-control study with 50 SLE patients (25 patients with inactive SLE and 25 patients with active SLE) and 25 healthy controls. The findings revealed that TNC levels were significantly greater in patients with active SLE compared to those of inactive patients and healthy volunteers. There was also a favorable connection between TNC and SLE Disease Activity Index score in this study. White blood cell count, platelet count, complement components 3, 4, and hemoglobin level were all adversely linked with TNC.

In addition, **Závada *et al.*** [14] monitored 59 patients with SLE for an average of 11 months and compared them to 65 controls to assess the prognostic value of TNC in SLE. Patients with active SLE had a considerably higher level of TNC after the study compared to healthy controls; furthermore, higher baseline levels of serum TNC were associated with a significantly higher risk of flare. Researchers concluded that TNC was associated with SLE activity and might be used to predict the requirement for more aggressive immunosuppressive treatment.

CONCLUSION

TN-C is a major new biomarker for active SLE and a crucial molecule in tissue remodeling. TN-C has shown promise as a serum biomarker for monitoring disease activity and predicting flares in lupus erythematosus (SLE) patients, but more rigorous research is required to confirm this.

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