Weighting The Potential of Using Tenascin C in Diagnosis and Therapy of Atherosclerosis

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ABSTRACT

Tenascin is a protein family in the extra cellular matrix (ECM) that consists of four members: tenascin C, tenascin R, tenascin X, and tenascin W. Among the four tenascins, tenascin-C was the first identified and have been the most studied member of the family. In 2006, a patent was registered for a formula containing tenascin C, and the formula has been claimed to be beneficial in treating and preventing vascular diseases such as atherosclerosis. Therefore, this review discusses the structure of tenascin C molecule, its various functions, the possibility of imaging tenascin C expression for diagnosis, weighing the prospect of using tenascin C in the therapy of atherosclerosis, and future research suggestions.

Key words: extra cellular matrix, migration, proliferation, angiogenesis.

INTRODUCTION

Tenascin is a protein family in the extra cellular matrix (ECM) that consists of four members: tenascin C, tenascin R, tenascin X, and tenascin W. Among the four tenascins, tenascin-C was the first identified and have been the most studied member of the family. Tenascin C has been highly conserved among vertebrates and is mainly expressed during embryo development, especially during neural, skeletal, and vascular morphogenesis. In adult, normally the expression is greatly reduced and low expressions are only detected in tendons and their associated tissues. However, in processes involving remodeling and neovascularization such as in wound healing, or in pathological condition such as inflammation and malignancies the expression is increased.

In 2006, a patent was registered for a formula containing tenascin C, and the formula has been claimed to be beneficial in treating and preventing vascular diseases such as atherosclerosis, as “tenascin C can restore cardiac angiogenic function in a mammal that has diseased or senescent cardiac angiogenic function”.

Therefore, this review discusses the structure of tenascin C molecule, its various functions, the potential of imaging tenascin C expression for diagnosis, weighing the prospect of using tenascin C in the therapy of atherosclerosis, and future research suggestions.

THE STRUCTURE OF TENASCIN C MOLECULE

Tenascin C molecule consists of six individual subunits. The subunit consists of four domains. The first domain is the amino-terminal that contains a highly conserved heptad repeats, and cysteine residues allowing the six individual subunits to assemble to form a hexamer molecule. The second domain consists of 14.5 repeats of epidermal growth factor (EGF)-like molecule.
The third domain consists of five and three fibronectin type III (FN III) repeats flanking additional distinctive repeats. The numbers of the additional repeats depend on alternative splicing, and the maximal is nine repeats. Alternative splicing produces many combinations of the additional repeat and thus many tenascin C isoforms. The fourth domain is the carboxyl-terminal fibronectin-like globular domain (Figure 1).

**The Function in Apoptosis**

In a study, the fragment containing the EGF like domain promoted apoptosis of cultured smooth muscle cells (SMCs), while intact tenasin C did not. The apoptosis promoting active site may be cryptic in the intact protein. The apoptosis leading mechanism of EGF like domain is not well understood, and it is not related to loss of adhesion that is previously provided by the fibrinogen like domain.

**The Function in Cardiac Remodeling**

Tenascin C appears at areas of extensive remodeling after myocardial infarction, i.e. at the borders of the infarcted area. In addition, in myocardial infarction, tenasin C serum level is increased 12 hours after the symptoms, peaks at day-5, then gradually decreases, but is still rather high at day 28. Therefore, it is claimed as a novel predictor of left ventricular remodeling and may be used to predict the prognosis of acute myocardial infarction.

Its effect as anti-adhesive agent may loosen the cardiomyocytes from ECM and facilitate migration of endothelial cells to form new capillaries. Tenascin C also causes recruitment of myofibroblasts that produce collagen fibers, while tenasin C itself as ECM has elastic properties, that is beneficial to resist mechanical loading. However, it may increase MMP production that promotes ECM degradation and thus increases the risk of cardiac dilatation and rupture. Therefore, in cardiac remodeling, tenasin C has dual action, and what causes it to be beneficial or detrimental remains unclear.

**Imaging of Tenascin C Expression for Diagnosis**

A study developed an antibody (G11) that is specific to an alternative-splicing generated extra domain C of tenascin C.
tenascin-C (the C domain). The C domain is not detected in normal adult tissues, but is abundant in macrophage-rich plaques. The antibody could be used to visualize angiogenesis in gliomas and lung tumors, and murine advanced atherosclerotic plaques ex vivo. In the future, radio-labeling of the antibody combined with PET may be used to visualize advanced atherosclerotic plaque containing macrophage infiltration. Further, different antibodies to different domains of tenascin C that plays a role in plaque formation and stabilization can be developed. Compared to other methods available such as angiography, ultrasound, computed tomography, optical coherence tomography, and magnetic resonance imaging, this emerging method is advantageous in the potential of gaining molecular insight in the advance of plaque formation and stabilization.

**WEIGHTING THE PROSPECT OF USING TENASCIN C IN THE THERAPY OF ATHEROSCLEROSIS**

A study showed for the first time that tenascin C was expressed in normal adult heart by endothelial cells. In addition, it was also expressed in bone marrow and cardiac tissue at the borders of myocardial infarction. Tenascin C expression is supposed to activate local endothelial cells and to recruit endothelial progenitor cells (EPCs) to migrate to the site, and to promote angiogenic pathways. Further, tenascin-C immunostaining of coronary thrombi showed that it was expressed in the endothelial cells of intrathrombi channels. Therefore it is supposed that tenascin C plays a role in neo-vascularization and re-canalization of fibrin clots.

According to the patent inventor, after administration, tenascin C transportation to the site of atherosclerosis will be effected by the presence of a carrier system, and additional expression of tenascin C in the diseased cardiac endothelial cells will be induced by PDGF that is included in the formula.

The use of the patented tenascin C containing formula seems promising. However, the claim that it will re-canalized fibrin clot based on the fact that tenascin C is found in intrathrombi channels tends to be exaggerated, as the so called intra thrombi channels might represent the micro vessels in the granuloma that is present in a certain stage of atherosclerosis. Therefore, whether the formula will work in atherosclerotic individuals still needs to be proven.

Furthermore, in advanced human atherosclerotic plaques, tenascin C is upregulated, especially around the lipid core and plaque shoulders, and additional tenascin C from the formula may not give significant effect. Finally, a serious side effect may be predicted from the administration of tenascin C, i.e. it will cause rupture of the plaque, thus thrombosis and clinical manifestation of myocardial infarction. In addition, there may be off target effect in the form of the spread of existing malignancy. This prediction is based on the fact that advanced plaques contain macrophages, T cells, mast cells, and SMCs, all of which are capable of secreting MMPs upon induction by the administered tenascin C, and MMPs may destabilize the fibrous cap of the atherosclerotic plaque that ends up in rupture. Further, MMPs may induce apoptosis of SMCs through fragmentation of tenasin-C, and cause the thinning of the vascular wall. In case of existing malignancy, administration of tenasin C and induction of MMCs may promote cancer cell migration and proliferation, and also tumor angiogenesis.

**FUTURE RESEARCH SUGGESTIONS**

Tenascin C has various functions conferred by individual or several active sites that work and cooperate in harmony. Therefore, identification of the various active sites, their function and cooperation in the four domains of tenasin C, is very crucial to design a recombinant tenasin C, with a certain desirable function, by deleting the non desired active site.

**CONCLUSION**

Imaging of tenascin C expression can be developed and used to get molecular information about the advance of plaque formation and stabilization. However, the use of intact tenasin C for the therapy of atherosclerosis needs to be proven and may result in serious side effects, while recombinant tenasin C may be potential in the future.

**REFERENCES**

5. Wallner k, Li C, Shah PK, Wu KJ, Schwartz SM, Sharifi BG. EGF-like domain of tenasin-C is proapoptotic for cultured


