Tenascin-C in cardiovascular remodeling: potential impact for diagnosis, prognosis estimation and targeted therapy

Marcus Franz¹,*, Christian Jung¹, Alexander Lauten¹, Hans R Figulla¹, and Alexander Berndt²

¹Department of Internal Medicine I; Jena University Hospital; Jena, Germany; ²Institute of Pathology; Jena University Hospital; Jena, Germany

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Fetal variants of tenascin-C are not expressed in healthy adult myocardium. But, there is a relevant re-occurrence during pathologic cardiac tissue and vascular remodeling. Thus, these molecules, in particular B and C domain containing tenascin-C, might qualify as promising novel biomarkers for diagnosis and prognosis estimation. Since a stable extracellular deposition of fetal tenascin-C variants is present in diseased cardiac tissue, the molecules are excellent target structures for antibody-based delivery of diagnostic (e.g., radionuclides) or therapeutic (bioactive payloads) agents directly to the site of disease. Against the background that fetal tenascin-C variants are functionally involved in cardiovascular tissue remodeling, therapeutic functional blocking strategies could be experimentally tested in the future.

Introduction

Human cardiovascular diseases are the leading cause of death all over the world and therefore represent a relevant burden not only for the patients but also for health care systems.¹ The umbrella term cardiomyopathy comprises a variety of differently caused heart diseases. The most frequent cardiovascular disorders are arterial hypertension (AH) leading to hypertensive heart disease (HHD), coronary artery disease (CAD) resulting in ischemic cardiomyopathy (ICM), valvular heart diseases (VHD) with consecutive left ventricular hypertrophy as well as dilated cardiomyopathy (DCM) with primary ventricular dilatation and dysfunction. At advanced stages, patients suffering from any kind of cardiomyopathy might develop severe heart failure symptoms. Therapy strategies available today (e.g., medical therapy, implantable cardiac devices or artificial hearts) are capable to treat symptoms, prevent disease progression and, in some cases, also increase patients’ prognosis. Nevertheless, except of cardiac transplantation, there are no strategies to really cure the patients in terms of complete reversal of the underlying pathomechanisms.

Figure 1 gives a simplified overview of the most common cardiovascular diseases; diagnosis; prognosis; tenascin-C; therapy

Tenascin-C in Hypertensive Heart Disease

Arterial hypertension is known to cause left ventricular hypertrophy leading to diastolic dysfunction of the left ventricle exhibiting either concentric or eccentric geometry. The differentiation between these 2 forms of structural remodeling is of prognostic importance. It could be shown that serum levels of both B domain as well as C domain containing tenascin-C are significantly increased in patients with arterial hypertension and left ventricular hypertrophy compared to healthy subjects. Moreover, in particular B domain containing tenascin-C was capable to discriminate between concentric versus eccentric left ventricular hypertrophy with a cut-off value of 900 ng/ml.⁷ Also in patients suffering from pulmonary hypertension, a relevant expression of tenascin-C could be observed with a correlation to the extent of pulmonary
artery alterations. In addition, Celik and co-workers reported on significantly elevated tenascin-C serum levels in patients with acute pulmonary embolism and therefore suggested the molecule to be a promising indicator of the disease.

Tenascin-C in Ischemic Cardiomyopathy and Valvular Heart Diseases

Coronary artery disease leads to myocardial ischemia with first) myocardial infarction as an acute and critical clinical event and/or second) Ischemic Cardiomyopathy as a long-term consequence. Ischemia is a well-known trigger for ventricular remodeling possibly leading to systolic dysfunction.

An increased tissue expression of tenascin-C could be proven in coronary artery thrombi, coronary atherosclerotic plaques, coronary artery stenosis as well as bypass- grafts. Using human recombinant antibodies recognizing fetal variants of tenascin-C, e.g., the A1 or C domain containing variants, atherosclerotic plaques could be selectively detected in a mouse model and in human samples as well. This is of certain interest since such antibodies can be used for targeted imaging as well as treatment strategies also in humans. Interestingly, higher plasma levels of tenascin-C could be shown to be related with the complexity of coronary lesions after myocardial infarction, especially with total occlusion of the proximal left anterior descending artery and the extent of inflammation after myocardial infarction. A very recent study published by Sakamoto and co-workers could evidence that serum tenascin-C levels are associated with rupture of coronary plaques in patients with acute coronary syndrome.

In cardiac tissue of patients suffering from coronary artery disease who underwent cardiac surgery for revascularization, a distinct re-occurrence of fetal variants of tenascin-C could be evidenced on the mRNA as well as on the protein level. By comparative analysis of tissue samples taken from different regions within the human heart, in particular the right atrial auricle, which is localized near the right atrium and the left side of the interventricular septum, it could be demonstrated that this re-expression phenomenon occurs in the whole organ. This observation speaks well for the fact that cardiac tissue remodeling is an all-encompassing ischemia induced effect, which is not exclusively restricted to the ischemic area. Among the different fetal splicing variants of Tenascin-C, especially the A1 domain containing molecule seems to be overexpressed in remodelled human cardiac tissue from patients with coronary artery disease. Detailed analysis of the protein deposition patterns of A1 domain containing tenascin-C in human cardiac tissue revealed a spatial association to areas of cardiac interstitial fibrosis as well as vessel structures. The vascular deposition is clearly perivascular on the extra-luminal side of the endothelial basement membrane. The extensive re-expression of fetal tenascin-C variants described for ischemic cardiomyopathy is also present in valvular heart diseases, in particular left ventricular hypertrophy due to severe aortic valve stenosis which is the most frequent acquired heart valve disease in humans. Besides surgical aortic valve replacement, transcatheter aortic valve implantation (TAVI) is a novel, less-invasive, strategy to treat patients with aortic stenosis. Reverse
left ventricular remodeling after TAVI, due to decreased afterload, could be shown to be associated with transient changes in serum levels of B as well as C domain containing tenasin-C. In particular, there was a peak in tenasin-C serum concentration one week after TAVI procedure. The findings underline the suggested important role of the molecule in the process of active myocardial tissue remodeling.

Moreover, cardiac tissue remodeling after myocardial infarction could be demonstrated to be associated with an overexpression of tenasin-C variants. In patients with an acute myocardial infarction, serum levels of tenasin-C were significantly increased compared to healthy control subjects with a prognostic value in terms of the prediction of an increase in left ventricular dimensions as well as major adverse cardiac events (MACE). Also with respect to long-term outcome after acute myocardial infarction, tenasin-C serum levels could be proven to be of prognostic value.

These findings qualify the molecule not only as an interesting novel biomarker of ischemia-associated myocardial remodeling but also as an interesting target molecule for antibody based targeted delivery of contrast agents for molecular imaging or bioactive payloads or drugs directly to the side of disease.

Another interesting and potentially important aspect that should be discussed in this chapter is the association of polymorphic tenasin-C variants with coronary artery disease or atherosclerosis in general. Minear and colleagues conducted an excellent study focusing on this question. By genotyping of 35 single nucleotide polymorphisms (SNPs) in different patient groups, the authors could identify 3 SNPs that showed a significant association with the occurrence of 1) atherosclerotic aortic plaques in heart transplant donors and 2) coronary artery disease. One of these 3 SNPs, rs12347433, is a so-called synonymous coding SNP that has been suggested to be of functional impact within the process of atherosclerosis and coronary artery disease development by altering mRNA stability or function potentially influencing tenasin-C expression. The latter hypothesis of an association between the identified SNPs and tenasin-C mRNA expression has not been proven yet.

**Tenasin-C in Dilated Cardiomyopathy**

Dilated cardiomyopathy (DCM) is characterized by systolic left ventricular dysfunction of the heart in combination with a dilatation of heart chambers. Patients suffer from heart failure symptoms and have an impaired prognosis. DCM associated cardiac tissue remodeling entails the re-occurrence of fetal variants of cell-adhesion modulating molecules. Even in 1996, Gabler and co-workers reported on a re-expression of fetal fibronectin variants in DCM tissue being virtually absent in healthy adult hearts. At the same time, a re-expression of tenasin in cardiac biopsies of DCM patients with a distribution pattern along the margins of fibrotic areas could be observed. Some years later, the first reports occurred on significantly elevated tenasin-C serum levels in patients suffering from DCM. Aso and co-workers could demonstrate higher circulating tenasin-C levels in patients with DCM compared to controls. Additionally, higher serum levels of the molecule have been shown to be associated with heart failure severity, left ventricular dysfunction and remodeling in DCM. In particular, tenasin-C in combination with B-type natriuretic peptide estimation in patients serum, has an incremental prognostic value in patients with DCM and decompensated heart failure.

A great and hitherto unsolved clinical problem in DCM patients is the lack of sufficient prognosis predicting markers. Typically, patients with DCM initially present for the first time with dyspnoea and other heart failure symptoms. Even at this early stage, left ventricular function might be severely impaired. Although there are a variety of diagnostic tools available including endomyocardial biopsy, we do not have sufficient parameters predicting clinical outcome and long-term prognosis of such patients. In that context, a preliminary study investigating some key molecules of cardiac ECM remodeling in serum and tissue of DCM patients could identify especially B domain containing tenasin-C variants to serve as promising biomarkers predicting long-term survival even at the time point of initial clinical presentation. The follow-up period in this study was up to 8 y. Taking these findings into account, tenasin-C variants should be further evaluated as prognosis predicting biomarkers in DCM patients because of the great need to improve the clinical management of the described patients’ collective. These findings go in line with a study performed by Sarli and colleagues who could identify tenasin-C as a predictor of left ventricular remodeling and also mortality in DCM patients.

**Tenasin-C in Myocarditis**

Human myocarditis is a complex disease with a variable clinical presentation. On the one hand, patients might be free of any symptoms, on the other hand, patients can present with severe heart failure or even cardiogenic shock. Also in myocarditis, an increased expression of tenasin-C, in diseased cardiac tissue as well as in patients’ serum, has been shown (reviewed in 11). Imamura-Yoshida et al. firstly suggested tenasin-C as a useful marker for disease activity in myocarditis in 2002. In 2005, Morimoto and co-workers reported on the diagnostic value of tenasin-C for the evaluation of human acute myocarditis. Also for rheumatic carditis, tenasin-C has been shown to be a promising novel biomarker for diagnosis and prognosis prediction.

**Tenasin-C and Rare Cardiac Disorders**

Recently, some interesting studies came up investigating the impact of tenasin-C tissue expression as well as serum levels in rarely occurring cardiac diseases. Thus, in non-compaction cardiomyopathy (ventricular noncompaction / hypertrabeculation), in a cross-sectional study high serum tenasin-C levels could be observed compared to normal controls even when systolic left ventricular function was still unimpaired. Basing on these data, the molecule has been suggested as a possible biomarker for
Diagnosis of non-compaction cardiomyopathy. Also in hypertrophic cardiomyopathy, serum tenascin-C levels could be proven to be of prognostic value. Moreover, there is growing evidence that tenascin-C might play an important role in pathogenesis and progression of degenerative diseases of the aorta. Trescher and colleagues reported on an increased tissue deposition of tenascin-C in chronic aortic dilatation compared to normal controls with a homogenous distribution within the tunica media. In acute dissection, there was a further increased staining with a heterogeneous distribution pattern. Tenascin-C assessment in peripheral blood revealed significantly increased levels in Type-A dissection compared to chronic dilatation. These very interesting findings speak well for a functional role of tenascin-C in the process of aortic wall destabilization and are therefore of great clinical impact. Moreover, in a sophisticated mouse model of acute dissection of the aorta, Kimura and co-workers could nicely prove that the induction tenascin-C is a protective mechanisms contributing to the maintenance of aortic integrity under conditions of hemodynamic stress.

**Discriminative Value of Serum Tenascin-C Analysis in Cardiomyopathies of Different Etiology**

It could be demonstrated that in different cardiac diseases associated with myocardial tissue remodeling, a distinct re-expression of fetal tenascin-C variants is present not occurring in healthy hearts. Thus, the question arises, if there are differences in tenascin-C expression and liberation into body fluids in differentially caused heart diseases, e.g., hypertensive, ischemic, valvular or dilated cardiomyopathy. In a study investigating serum levels of B domain and C domain containing tenascin-C in patients with left ventricular dysfunction due to these 4 different aetiologies revealed no differences. Within the groups, there were some interesting correlations to clinical parameters. In conclusion, the elevated serum levels of fetal tenascin-C variants should be considered as a common reaction pattern of diseased cardiac tissue, irrespective of the underlying pathological stimulus.

**Tenascin-C and Cardiac Allograft Rejection**

Heart transplantation is the only curative treatment option in patients suffering from end-stage heart failure. Due to limited availability of organs, it is of great interest to optimize survival and reduce morbidity of heart transplanted patients. Besides acute rejection in the early post-transplantation period, chronic rejection with vasculopathy and fibrosis is a major prognosis-limiting problem in heart transplant recipients especially in the later stages after. In a rat model of chronic cardiac rejection it could be recently demonstrated that rejection associated tissue remodeling, in particular CAV and CIF development is accompanied by the re-expression of B domain containing tenascin-C. The protein is deposited in areas of luminal obstruction in CAV vessels as well as in areas of CIF in association to the grade of chronic rejection. Thus, the molecule is of great interest also for chronic rejection after heart transplantation not only as a diagnostic biomarker but also as a promising target molecule for antibody-based delivery of bioactive payloads or diagnostic agents.

The rejection-associated re-expression could also be proven for the human system. These findings are of certain interest since human recombinant antibodies recognizing fetal tenascin-C variants are available. These antibodies might serve as vehicles for drugs or diagnostics directly to the side of disease while sparing healthy tissue.

For fetal variants of fibronectin, e.g., the ED-A domain containing variants (ED-A\(^+\) Fn), similar antibodies are available. ED-A\(^+\) Fn is also expressed in chronically rejected hearts and, in the heart transplantation animal model mentioned above, a selective targeting of CAV and CIF in heart rejection could be evidenced by near-infrared fluorescence imaging. Thus, it is of great scientific and also clinical interest to test the value of anti-tenascin-C antibodies as vehicles for targeted imaging or even treatment strategies in cardiac rejection. To elucidate these open questions is the object of current studies.

**Summary and Conclusions**

Fetal variants of tenascin-C are not expressed in healthy adult (human) myocardium. But, there is a relevant re-occurrence during pathologic cardiac tissue and vascular remodeling. Thus, these molecules, in particular B and C domain containing tenascin-C, might qualify as promising novel biomarkers for diagnosis and prognosis estimation. This has to be evaluated in more detail in future clinical studies including larger patient numbers. Since a stable extracellular deposition of fetal tenascin-C variants is present in diseased cardiac tissue, the molecules are excellent target structures for antibody-based delivery of diagnostic (e.g., radionuclides) or therapeutic (bioactive payloads) agents directly to the site of disease. Against the background that fetal tenascin-C variants are functionally involved in cardiovascular tissue remodeling, therapeutic functional blocking strategies could be experimentally tested in the future. Additionally, their exact functional role should be elucidated to enhance our understanding of the biological impact of tenascin-C in heart diseases.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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