The role of tenascin C in cardiovascular disease

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Abstract

The extracellular matrix protein tenascin C (TnC) is expressed in a variety of embryonic tissues, but its expression in adult arteries is co-incident with sites of vascular disease. TnC expression has been linked to the development and complications of intimal hyperplasia, pulmonary artery hypertension, atherosclerosis, myocardial infarction, and heart failure. This review identifies the growing collection of evidence linking TnC with cardiovascular disease development. The transient upregulation of this extracellular matrix protein at sites of vascular disease could provide a means to target TnC in the development of diagnostics and new therapies. Studies in TnC-deficient mice have implicated this protein in the development of intimal hyperplasia. Further animal and human studies are required to thoroughly assess the role of TnC in some of the other pathologies it has been linked with, such as atherosclerosis and pulmonary hypertension. Large population studies are also warranted to clarify the diagnostic value of this extracellular matrix protein in cardiovascular disease, for example by targeting its expression using radiolabelled antibodies or measuring circulating concentrations of TnC.

Keywords
Cardiovascular disease • Extracellular matrix protein • Tenascin C

1. Introduction

Tenascin C (TnC) is a large extracellular matrix glycoprotein and was the first member identified of a family of four structurally similar proteins, including tenasin R, W and X.1 – 3 During early development, TnC is transiently expressed at a number of sites throughout the embryo, such as neural crest, central nervous system, lungs, and cardiovascular system.1 Despite this implied function during embryogenesis, knockout mice models of TnC grow to maturity without any overt signs of abnormalities.4 In normal adult tissue, only low levels of TnC are found. Higher levels of TnC expression have been reported in areas of wound healing, cancer development, and cardiovascular disease.1 Given this localization of TnC to sites of pathology, there has been increasing interest in assessing the role of this glycoprotein in disease development and targeting the protein in both diagnosis and therapy for a variety of pathologies.1 In this review, we summarize previous studies which have examined the expression and potential influence of TnC in cardiovascular disease.

2. Structure of TnC

The structure of TnC is relevant to its functions in health and disease and has been described in detail in previous reviews.1 – 3 TnC polypeptides are made up of a number of domains (Figure 1A) and include:

(a) An amino-terminal Tn assembly domain (TA) which is responsible for interactions between TnC polypeptides important in assembly of the multimeric protein;
(b) A contiguous group of repeats of epidermal growth factor-like domains;
(c) A series of fibronectin type III domains;
(d) A distal globular fibrinogen-homology domain.

While TnC is encoded by a single gene located at 9q33 in man, alternative splicing of mRNA can result in a large number of different isoforms with between 1 and 6 extra fibronectin type III domains (A1, A2, A4, B, C, and D) (Figure 1B). Ultimately, six TnC polypeptides can be assembled into a six armed structure referred to as a hexabrachion via interaction at the TA domains. This form of TnC has been identified within the extracellular matrix such as that present during embryonic development. The relative expression of different forms of TnC present in diseased adult tissue and circulating in the blood has been poorly described.

3. TnC interactions and signalling pathways

Associated with its complex structure, TnC has the capacity to interact with several different cell surface receptors. Different parts of the
Figure 1 Structure of Tenascin C. (A) This diagram has been adapted from previous work using predicted domain boundaries to determine the overall structure of the protein. A recent study suggested the earlier delineations derived from reverse transcription polymerase chain reaction and western blotting [(B) shown below the main structure] had several flaws and did not correlate to the natural domain boundaries particularly in the A1–4 region. The N-terminal domain is called the tenasin assembly domain (TA) and is involved in the formation of the quaternary hexabrachion structure. Within this region, there is a heat shock protein 33 motif probably responsible for TnC aggregation within the cell. The next region includes 14 epidermal growth factor (EGF) like repeats which are quite consistent. The EGF-like repeat domain modulates cell adhesion and cell motility. This region is considered to be counter adhesive for fibroblasts, neurons, and glia and may be involved in neuronal migration and axon path finding during development. The following region contains the fibronectin (FN) III like repeats. The FN-III repeats vary considerably in amino acid sequence and have a variety of ligands. The final C-terminal domain is the fibrinogen (FG)-like domain. This domain is the region of the protein that binds to toll-like receptor (TLR)-4 as an endogenous ligand. Due to alternative splicing of pre-mRNA of the FN III-like repeats, 6–12, TnC exists as a number of isoforms with varying functions and sizes. The smallest isoform has a predicted molecular weight of 171.3 kDa and is missing repeats 6–12. The largest isoform with a predicted molecular mass of 240.8 kDa has all the FN III-like repeats included. TnC is also glycosylated giving rise to the range of sizes reported for the various isoforms, e.g. the large isoform has a reported size range of 280–350 kDa.

4. In vitro studies assessing the determinants of TnC production and the interaction of TnC with vascular cells

The determinants of TnC expression have been examined in vitro in a variety of cells relevant to vascular disease, including vascular smooth muscle cells (VSMCs), endothelial cells, and monocyte-macrophages (Table 1). Overall, a range of factors implicated in cardiovascular disease, including cytokines, angiostensin II, and haemodynamic forces appear to be able to upregulate TnC expression in vitro. A number of medications have been reported to reduce TnC expression, including steroids, cilostazol, and non-steroidal anti-inflammatory drugs. Identified intra-cellular regulators of TnC expression in vascular cells include homeobox transcription factor Prx1, Rho, and extra-cellular signal-regulated kinases. TnC expression has been shown to be under post-transcription control in non-vascular sites, such as within breast cancer metastases, where micro RNAs, including miR-355, have been shown to control TnC expression.

The actions of TnC have also been examined in vitro employing a range of cell types and TnC fragments (Table 2). TnC has been reported to promote angiogenesis and release of pro-inflammatory cytokines and MMPs. TnC has also been reported to inhibit T cell proliferation and activation in vitro. The effects of TnC within in vitro studies seem to vary according to the fragment of TnC employed and the cell type studied. The region of TnC which contains the fibronectin type III repeats, and which varies by isoform type (Figure 1), appears to control the ability of TnC to influence cell adhesion. The epidermal growth factor-like domains of TnC have been suggested to control cell survival, while the distal globular fibrinogen-homology domain has been associated with stimulating cytokine production.

5. Animal studies examining the expression and role of TnC in cardiovascular disease

The association of TnC with a range of cardiovascular pathologies has been examined in murine, porcine, bovine, and canine models of human cardiovascular diseases (Tables 3–5). The most common pathology studied has been intimal hyperplasia (Table 3). TnC has been implicated in the development of intimal hyperplasia following angioplasty, stenting, arteriotomy, and bypass grafting in animal species as diverse as mice and pigs. TnC is expressed very rapidly following arterial injury in these models and its expression is reduced in situations where intimal hyperplasia is inhibited, such as prostaglandin E2 deficiency or treatment with a nitric oxide donor. Importantly, intimal hyperplasia has been reported to be reduced in two distinct mouse models of TnC deficiency, suggesting that this protein plays...
an active role in this pathology.\textsuperscript{52,53} Indeed in one study that employed arterial grafts placed in the carotid artery, a reduced proliferation of neointimal cells was demonstrated in TnC deficient by comparison to wild-type mice.\textsuperscript{52} This same research group reported a similar finding of reduced number and proliferation of neointimal cells after aortotomy in TnC-deficient mice.\textsuperscript{53}

Studies in rodent, pig, and dog models of myocardial infarction have demonstrated that TnC is highly expressed from approximately day 1 to day 14 within the peri-infarct area. This has promoted interest in developing diagnostic aids that incorporate antibodies targeting this protein (Table 4).\textsuperscript{34,59–64} The TnC expression has been linked to an exaggerated repair process after myocardial infarction with reduced interstitial fibrosis reported in TnC-deficient mice following coronary artery ligation.\textsuperscript{59} TnC-deficient mice also have reduced myocardial stiffness on echocardiography after myocardial infarction.\textsuperscript{59} TnC expression has also been positively linked to a range of other cardiovascular pathologies, including atherosclerosis, pulmonary artery hypertension, neovascularization, the peri-infarct repair process following stroke, angiotensin II-induced cardiac fibrosis, vasospasm following subarachnoid haemorrhage, and vascular calcification (Table 5).\textsuperscript{10,17,21,23,59,65–71} In keeping with in vitro findings noted earlier, neovascularization has been reported to be reduced in TnC-deficient mice, suggesting TnC promotes angiogenesis.\textsuperscript{10}

To summarize, studies in animal models most clearly support a role of TnC in intimal hyperplasia, although the exact mechanisms for this are unclear. Although TnC is associated with many other cardiovascular pathologies in animal models, clear evidence that links TnC with their development and outcomes is currently lacking.

6. Human studies examining the expression of TnC in relation to cardiovascular disease

A large number of studies have examined the expression of TnC in biopsies removed from patients with a variety of cardiac and other cardiovascular diseases (Tables 6 and 7).\textsuperscript{9,10,20,31,34,38,72–84} TnC expression within athero-thrombosis has been associated with acute coronary syndrome.\textsuperscript{10,38,72} TnC staining was localized in areas of plaque rupture and macrophage infiltration. Similar to animal studies, TnC expression has also been localized within areas of intimal hyperplasia (at sites of coronary restenosis or in saphenous vein coronary artery bypass grafts), myocardial infarction, cardiomyopathy, and coronary valve calcification.\textsuperscript{34,38,73–76} High tissue levels of TnC have also been reported within a range of other cardiovascular pathologies, including carotid atherosclerosis, pulmonary artery

\begin{table}[h]
\centering
\caption{Determinants of TnC expression in vitro in a variety of cells relevant to cardiovascular disease}
\begin{tabular}{|l|l|l|}
\hline
\textbf{Upregulators of TnC} & \textbf{Cell type studied} & \textbf{TnC form induced} \\
\hline
Prostaglandin E2 & Mouse VSMCs\textsuperscript{5} & mRNA \\
LPS and other TLR ligands & Monocyte-derived cells such as macrophages\textsuperscript{6} & mRNA and protein \\
Wnt pathway & Mouse pulmonary artery VSMCs\textsuperscript{7} & mRNA and protein \\
CD137 ligation & RAW264.7 (murine myeloid cell line)\textsuperscript{8} & mRNA \\
ERK 1/2 mitogen-activated protein kinases & Human pulmonary artery VSMCs\textsuperscript{9} & mRNA and protein \\
RhoA and Rho kinase ROCK & Rat pulmonary artery endothelial cells\textsuperscript{10,11} & mRNA \\
Interleukin-4 & Human peripheral blood-derived macrophages\textsuperscript{12} & mRNA \\
Cyclic stretch & Human aortic VSMCs & mRNA and protein \\
Platelet-derived growth factor & Rat aortic VSMCs\textsuperscript{15–17} & mRNA and protein including three isoforms (210, 220, and 250 kDa) \\
Prx1 (homeobox transcription factor) & VSMC cell line\textsuperscript{18} & mRNA \\
Denatured collagen (via β3 integrin and ERK 1/2) & VSMC cell line\textsuperscript{19,20} & mRNA and protein \\
Angiotensin II & Human aortic VSMC & mRNA and protein \\
 & Rat aortic VSMC & mRNA and protein \\
 & Human aortic endothelial cells\textsuperscript{16,17,21,22} & mRNA and protein \\
Transforming growth factor beta & Human aortic VSMC & mRNA \\
 & Rat aortic VSMC & mRNA \\
 & Human aortic endothelial cells\textsuperscript{17,21} & mRNA and protein \\
\hline
\textbf{Downregulators of TnC} & \textbf{Cell type studied} & \textbf{TnC form downregulated} \\
\hline
Shear stress mimicking atheroprone flow & Human iliac vein endothelial and VSMC co-culture\textsuperscript{23} & mRNA \\
Dexamethasone & Human peripheral blood-derived macrophages\textsuperscript{12} & mRNA \\
Cilostazol & Rat aortic VSMC\textsuperscript{15} & mRNA \\
Glafenine hydrochloride (NSAID) & Human aortic VSMCs\textsuperscript{24} & Protein \\
9-cis retinoid acid & Human aortic VSMCs\textsuperscript{25} & Protein \\
Polymerized (compared to monomer) type 1 collagen & Human umbilical artery VSMCs\textsuperscript{26} & mRNA \\
\hline
\end{tabular}
\end{table}
hypertension, abdominal aortic aneurysm, renal access graft intimal hyperplasia, renal transplant vasculopathy, and varicose veins.\textsuperscript{1,10,15,17,18} In contrast to the large number of studies examining the expression of TnC in tissue biopsies, there have been fewer investigations of the association of circulating concentrations of TnC with cardiovascular disease.\textsuperscript{70,85–91} The serum or plasma concentration of TnC has been reported to be increased in patients with a range of cardiac problems, including acute myocardial infarction, pulmonary thromboembolism, pulmonary artery hypertension, left ventricular hypertrophy, and dilated cardiomyopathy compared with controls in cross-sectional studies (Table 8).\textsuperscript{85–91} Overall, the number of subjects included in these studies has been small, however, with a total of only 408 cases and 136 controls included in the independent cross-sectional studies identified in this systematic review (Table 8). The TnC isoform measured in these studies has varied but in most instances appears to have been the high molecular weight isoform containing the fibronectin type III repeat domain. Assays have been performed using commercial enzyme-linked immunoassays from two different companies.\textsuperscript{87–89} The circulating TnC concentration has not only been reported to be increased in patients with cardiac

### Table 2: Reports of the effects of TnC on cells relevant to cardiovascular disease in vitro

<table>
<thead>
<tr>
<th>TnC form or intervention</th>
<th>Cell type</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>TnC fragment (A2 isoform)</td>
<td>Human dermal microvascular endothelial cells</td>
<td>Proliferation inhibited\textsuperscript{10}</td>
</tr>
<tr>
<td>TnC from commercial company (Chemicon)</td>
<td>Rat cardiac microvascular endothelial cells</td>
<td>Promotes response to angiogenic signals, such as PDGF and VEGF\textsuperscript{10}</td>
</tr>
<tr>
<td>TnC from commercial company (Chemicon)</td>
<td>Bovine and human retinal endothelial cells</td>
<td>Promotes endothelial cell tube formation and branching\textsuperscript{12}</td>
</tr>
<tr>
<td>Recombinant chick TnC</td>
<td>Bovine aortic endothelial cells</td>
<td>Stimulates actin cytoskeletal reorganization typical of sprouting endothelial cells\textsuperscript{39}</td>
</tr>
<tr>
<td>Large and small splice variants of TnC</td>
<td>Bovine aortic endothelial cells</td>
<td>TnC fragment containing Fn A-D induces loss of focal adhesion by binding annexin II\textsuperscript{66,67}</td>
</tr>
<tr>
<td>TnC blocking antibody</td>
<td>Bovine aortic endothelial cells</td>
<td>Inhibits signs of angiogenesis such as sprouting cells\textsuperscript{48}</td>
</tr>
<tr>
<td>TnC from a cell line</td>
<td>Human umbilical endothelial cells</td>
<td>Binds to α5β1 and αvβ3 integrins\textsuperscript{49}</td>
</tr>
<tr>
<td>Large isoform of TnC</td>
<td>Rat and human VSMC</td>
<td>Upregulates MMP-2 which cleaves TnC\textsuperscript{31}</td>
</tr>
<tr>
<td>EGF-like TnC domain</td>
<td>Rat and human VSMC</td>
<td>Induces apoptosis\textsuperscript{21}</td>
</tr>
<tr>
<td>Recombinant A1A2 isoform</td>
<td>Rat VSMC</td>
<td>Promotes VSMC chemotaxis (unlike other TnC isoforms)\textsuperscript{33}</td>
</tr>
<tr>
<td>TnC isolated from a glial cell line</td>
<td>Adult rat cardiomyocytes</td>
<td>Promotes cardiomyocyte attachment to laminin\textsuperscript{34}</td>
</tr>
<tr>
<td>TnC antisense oligonucleotide</td>
<td>Rat pulmonary arteries in organ culture</td>
<td>Promotes VSMC apoptosis and upregulates osteopontin expression\textsuperscript{37}</td>
</tr>
<tr>
<td>Human TnC from commercial company (Chemicon)</td>
<td>Rat pulmonary artery VSMCs</td>
<td>Stimulates proliferation and survival via αvβ3 integrin\textsuperscript{20,44}</td>
</tr>
<tr>
<td>TnC fragment containing Fn A–D</td>
<td>Human aortic VSMC</td>
<td>Reduces focal adhesion VSMC&gt; endothelial cells\textsuperscript{21}</td>
</tr>
<tr>
<td>TnC-deficient mouse</td>
<td>Mouse macrophages</td>
<td>Behaved as wild-type macrophages in response to TGF\textsuperscript{28}</td>
</tr>
<tr>
<td>Human recombinant TnC (fibrinogen-like globe)</td>
<td>Human macrophages</td>
<td>Stimulated TNFα, IL-6, and IL-8 production\textsuperscript{51}</td>
</tr>
<tr>
<td>TnC extracted from chick embryo brains</td>
<td>Human polymorphonuclear leucocytes and monocytes</td>
<td>Inhibited chemotaxis via α5β1 integrin\textsuperscript{36}</td>
</tr>
<tr>
<td>TnC from commercial company (Chemicon)</td>
<td>Human monocyte-macrophages</td>
<td>Stimulates MMP-9 secretion\textsuperscript{28}</td>
</tr>
<tr>
<td>TnC from commercial company (Life Technologies)</td>
<td>Mouse macrophage cell line (RAW264.7)</td>
<td>Stimulates MMP-9 expression\textsuperscript{45}</td>
</tr>
<tr>
<td>TnC from chick embryo fibroblast cultures</td>
<td>Human monocytes and T lymphocytes</td>
<td>Inhibited monocyte adhesion to fibronectin and T cell activation by alloantigens not anti-CD3 antibody\textsuperscript{50}</td>
</tr>
<tr>
<td>TnC isolated from U251 glioma cell line and recombinant fragments</td>
<td>Human T lymphocytes</td>
<td>TnFnIII A1A2 inhibits T cell activation\textsuperscript{15}</td>
</tr>
<tr>
<td>Recombinant TnC fragments</td>
<td>Human T lymphocytes</td>
<td>TnFnIII 1–5 inhibits αvβ1 and αvβ3 mediated adhesion to fibronectin\textsuperscript{40}</td>
</tr>
<tr>
<td>TnC isolated from U251 glioma cell line (Chemicon)</td>
<td>Human T lymphocytes</td>
<td>Inhibited anti-CD3-induced cell proliferation\textsuperscript{51}</td>
</tr>
<tr>
<td>Recombinant TnC fragments</td>
<td>Human T lymphocytes</td>
<td>Supports tethering and rolling via binding to the terminal fibrinogen like domain of TnC in a parallel-plate flow chamber\textsuperscript{52}</td>
</tr>
<tr>
<td>Plasmin cleaved TnC</td>
<td>Human T lymphocytes</td>
<td>Plasmin cleavage of TnC converts it from a non-adhesive to an adhesive substrate for T cells\textsuperscript{43}</td>
</tr>
<tr>
<td>TnC isolated from U251 glioma cell line</td>
<td>Human platelets</td>
<td>Platelets adhere to and are activated by TnC\textsuperscript{29}</td>
</tr>
</tbody>
</table>
disease but also related to specific clinical findings, imaging results, and subsequent outcomes in these patients. Serum TnC concentration has, for example, been correlated with New York Heart Association functional class and left ventricular ejection fraction in patients with heart failure. Serum TnC has also been reported to predict the prospective incidence of cardiovascular events in patients who have recently had a myocardial infarction, have heart failure or chronic kidney disease. The reported area under the curves of receiver operator characteristic curves in these studies were between 0.77 and 0.79. These findings suggest that most likely serum TnC would need to be combined with other clinical and biomarker predictors to be of clinical value. In summary, data from human association studies fit with animal data linking TnC with a range of cardiovascular diseases, although the therapeutic and diagnostic value has been little examined.

7. Association of genetic polymorphisms in the gene encoding TnC and cardiovascular disease

TnC is encoded by a large gene composed of 28 exons spanning nearly 100 kb on Chromosome 9 (NCBI Nucleotide database Ref Seq NC_000009). Its transcription is directed by a single promoter and regulated by both positive and negative elements located in the first untranslated exon, which is separated from the translation initiation site in exon 2 by a large intron of approximately 18 kb. The reported area under the curves of receiver operator characteristic curves in these studies were between 0.77 and 0.79. These findings suggest that most likely serum TnC would need to be combined with other clinical and biomarker predictors to be of clinical value. In summary, data from human association studies fit with animal data linking TnC with a range of cardiovascular diseases, although the therapeutic and diagnostic value has been little examined.
not been thoroughly investigated. It is tempting to speculate that inheritance of particular polymorphic variants could influence expression levels of TnC and account for some of the individual variation in risk of cardiovascular disease. A genome-wide association study of genes for biomarkers of cardiovascular disease identified rs17819305, located in intron 15 of the TnC gene, as being associated...
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with gammaglutamyl transferase levels in 1955 hypertensive subjects.96 Otherwise, there has only been a single published study specifically examining the association of genetic polymorphisms in TNC and cardiovascular disease, and this did not include rs17819305.97 Minear et al.97 genotyped a total of 35 single nucleotide polymorphisms (SNPs), including 21 haplotype tagging SNPs, in a range of subjects that had been assessed for different measures of atherosclerosis. The subjects examined included 205 heart transplant donors who had provided ascending aortic samples; 1325 patients who had undergone coronary angiography to assess severity of coronary atherosclerosis; and 879 families with a history of coronary artery disease. Three SNPs, rs12347433, rs4552883, and rs17819305, representing a block of linkage disequilibrium were significantly associated with aortic atherosclerosis plaque presence in the heart transplant donors and coronary heart disease in the two large subject groups. One of these SNPs, rs12347433, is a synonymous polymorphism causing a change in the mRNA without affecting the amino acid sequence of the TnC protein. This type of synonymous polymorphism has been suggested to alter mRNA function or stability which could alter translation and thus TnC expression. However, none of these SNPs was associated with TnC expression measured by microarrays within the 104 patients in which aortic RNA was available, suggesting these polymorphisms may be acting via mechanisms unrelated to aortic concentration of TnC mRNA.

8. Summary and future directions

A large number of studies suggest that TnC is transiently expressed in association with a range of cardiovascular diseases in both animal models and patients. Whether this association is part of the repair process or pathological is not completely resolved in most instances. Studies from TnC-deficient mice suggest that in the case of intimal hyperplasia at the site of cell proliferation based on proliferating cell nuclear antigen expression31 and particularly macrophage rich areas77 the role of TnC in atherosclerosis is less clear. The role of TnC in atherosclerosis is less clear cut, although a number of findings (such as its expression at sites of plaque rupture, its involvement in neovascularization, and its ability to influence VSMC phenotype and pro-inflammatory cytokine/MMP production) would suggest that it may play a role in promoting the development and complications of this pathology.10,36,38,45,51,72 We identified no studies examining TnC deficiency, overexpression, or inhibition on atherosclerosis progression in animal models. Studies of this type are required to provide further insight on the role of this extracellular matrix protein in cardiovascular disease. The rapid

<table>
<thead>
<tr>
<th>Number of cases and controls</th>
<th>Biopsies</th>
<th>Cases</th>
<th>Controls</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Carotid atheroma and control 'normal' iliac artery</td>
<td>Patients undergoing carotid endarterectomy</td>
<td>Patients having AAA repair</td>
<td>Staining for TnC mRNA in atherosclerotic plaques and particularly macrophage rich areas77</td>
</tr>
<tr>
<td>16</td>
<td>Carotid atheroma</td>
<td>Patients undergoing carotid endarterectomy</td>
<td>None</td>
<td>Large (280 kDa) and small (220 kDa) TnC isoforms and 85 and 65 kDa EGF-like domain fragments detected11</td>
</tr>
<tr>
<td>10</td>
<td>Long saphenous vein</td>
<td>Patients undergoing varicose veins surgery</td>
<td>Patients undergoing coronary bypass surgery</td>
<td>Upregulation of TnC78</td>
</tr>
<tr>
<td>NS</td>
<td>Long saphenous vein</td>
<td>Patients undergoing varicose veins surgery</td>
<td>Patients undergoing coronary bypass surgery</td>
<td>Increased intimal TnC expression79</td>
</tr>
<tr>
<td>18</td>
<td>Pulmonary artery</td>
<td>Familial pulmonary artery hypertension</td>
<td>None</td>
<td>TnC highly expressed in all biopsies9</td>
</tr>
<tr>
<td>7</td>
<td>Pulmonary artery</td>
<td>Pulmonary artery hypertension</td>
<td>None</td>
<td>TnC staining correlates with grade of pulmonary artery pathology (Heath-Edwards grading)20</td>
</tr>
<tr>
<td>17</td>
<td>Infra-renal aorta</td>
<td>Patients undergoing AAA repair</td>
<td>Organ donors</td>
<td>TnC upregulated in AAA60</td>
</tr>
<tr>
<td>23</td>
<td>Infra-renal aorta</td>
<td>Patients undergoing AAA repair</td>
<td>Patients undergoing aortic bypass for occlusive disease</td>
<td>Increased staining for TnC in AAA samples association with adventitial inflammation and neovascularization81</td>
</tr>
<tr>
<td>15</td>
<td>Thoracic aortic biopsies</td>
<td>Marfan syndrome and bicuspid aortic valve undergoing thoracic aortic aneurysm repair</td>
<td>NS</td>
<td>Reduced TnC expression by VSMCs from aneurysm biopsies82</td>
</tr>
<tr>
<td>12</td>
<td>Graft stenoses</td>
<td>Failed PTFE loop arterio-venous grafts</td>
<td>None</td>
<td>TnC staining marked in luminal layer of intimal hyperplasia at the site of cell proliferation based on proliferating cell nuclear antigen expression83</td>
</tr>
<tr>
<td>10</td>
<td>Renal arteries</td>
<td>Failed kidney transplants</td>
<td>None</td>
<td>Increased TnC expression observed in media early in rejection process54</td>
</tr>
</tbody>
</table>

EGF: epidermal growth factor; TnC: tenascin C; AAA: abdominal aortic aneurysm; VSMC: vascular smooth muscle cells; PTFE: polytetrafluoroethylene; NS: not stated.

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upregulation of TnC following ischaemia events, such as myocardial infarction, suggests the possibility of targeting TnC as a diagnostic or prognostic aid in patients with cardiovascular disease, e.g. as a circulating or tissue biomarker. Further studies in larger populations are, however, required to assess the feasibility and clinical value of such an approach.

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### References


**Table 8 Case–control studies examining the association of circulating TnC concentrations with cardiac disease**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cases</th>
<th>Controls</th>
<th>Sample</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary thromboembolism</td>
<td>34</td>
<td>120 ± 38*</td>
<td>Healthy volunteers</td>
<td>20</td>
</tr>
<tr>
<td>Pulmonary artery hypertension</td>
<td>36</td>
<td>111 ± 13*</td>
<td>Age- and gender-matched healthy volunteers</td>
<td>44</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>95</td>
<td>1000 (700–1200)*</td>
<td>Healthy volunteers</td>
<td>12</td>
</tr>
<tr>
<td>Dilated cardiomyopathy (day 5)</td>
<td>107</td>
<td>73 ± 35*</td>
<td>Healthy volunteers</td>
<td>20</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>105</td>
<td>83 ± 43*</td>
<td>Healthy volunteers</td>
<td>20</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>31</td>
<td>69 ± 33*</td>
<td>Age- and gender-matched healthy volunteers</td>
<td>20</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>64</td>
<td>60 ± 40</td>
<td>Patients responding to CRT</td>
<td>46</td>
</tr>
</tbody>
</table>

Comparisons of TnC between cases and controls: *P < 0.01; **P < 0.05. Shown are mean and standard deviation except superscript ‘a’ where median and inter-quartile range are shown.

In this study, the lower molecular weight FNIIIB domain containing TnC isoform was measured while in other studies the higher molecular weight FNIIIIC domain containing TnC isoform appears to have been measured. TnC, tenasin C; AUC, area under the curve; ROC, receiver operator characteristic; LV, left ventricular; NYHA, New York Heart Association; MACE, major adverse cardiovascular events; CRT, cardiac resynchronization therapy.

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