Review

Interaction between cell and extracellular matrix in heart disease: Multiple roles of tenascin-C in tissue remodeling

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Summary. The heart remodels myocardial tissue in physiological and pathological response. The cell-extracellular matrix (ECM) interaction provides not only structural and mechanical support but also important biological signaling during tissue remodeling. Among various ECM molecules, tenascin-C (TNC) is well known as a regulator of multiple cellular functions during embryogenesis, wound healing or cancer progression. In the heart, TNC appears in several important steps of embryonic development such as the initial differentiation of cardiomyocytes or coronary vasculo/angiogenesis, but it is not detected in a normal adult myocardium. However, TNC is found to re-express after myocardial injury and may regulate cellular behavior during tissue remodeling by modulating the attachment of cardiomyocytes to connective tissue, by enhancing migration and differentiation of myofibroblasts, and by inducing matrix metallo-proteinases. TNC also interacts with other ECM molecules and may modulate progression of fibrosis. Furthermore, transient and site specific expression of TNC closely associated with myocardial injury and inflammation suggests not only its key roles during tissue remodeling but also that TNC can be a marker for myocardial disease activity.

Key words: Tenascin-C, Extracellular matrix, Remodeling, Fibrosis, Myocarditis, Myocardial infarction

Introduction

Living tissue is composed of heterogeneous cells and extracellular matrix (ECM) which is synthesized by

those cells. Living tissues can dynamically remodel their structure by changing and rearranging their cellular and matrix components. Tissue remodeling is a widespread phenomenon which is essential for morphogenesis during embryonic development, physiological/pathological response to extrinsic stimuli, or tissue repair after injury. It is well recognized that, during this dynamic cellular activity, the extracellular matrix provides not only structural and mechanical support but also important biological signaling which influences cell motility, proliferation, differentiation, survival or apoptosis via cell-ECM interaction.

Among various ECM molecules, a category, matricellular proteins, has been introduced to emphasize their role as regulators of cellular functions (Bornstein, 1995; Bornstein and Sage, 2002). The group includes thrombospondin-1 and 2, SPARC (secreted proteins acid and rich in cysteine; osteonectin), tenascin-C, X, osteopontin, and CCN (cyr-62,CTGF). Matricellular proteins are generally expressed at high levels during embryonic development and in response to injury. They do not contribute directly to the formation of structural elements such as fibrils or basement membrane but serve to modulate cell-matrix interaction and function as bioactive molecules especially during tissue remodeling. In this review, we will discuss about the interaction between cardiomyocytes and ECM in the myocardium, while focusing on the role of tenascin-C during tissue remodeling.

Linkage between cardiomyocytes and ECM in the normal heart

In myocardium, the major ECM components are type I and type III collagen, which form a continuous hierarchial fibrillar collagen network extending from the epicardium to endomysium, surrounding individual cardiomyocytes (Katz, 1989). In the normal heart, cardiomyocytes are firmly anchored to this extracellular framework with 'costamere' adhesion complexes which

are composed of vinculin, talin, integrin α6ß1, laminin and possibly other cytoskeletal and extracellular molecules (Danowski et al., 1992; Imanaka-Yoshida, 1996, 1999, 2000) (Fig. 1). 'Costamere' is the rib-like striated distribution of vinculin between z-lines and sarcolemma originally described by Pardo (Pardo et al. , 1983). In culture, cardiomyocytes form a characteristic banded distribution of focal contacts corresponding to the costameric localization of vinculin (Imanaka-Yoshida et al., 1996, 1999). Costamere adhesion prevents cardiomyocytes from slippage during contraction and transmits the contraction force of myofibrils to interstitial collagen. Intercalated disks have been well known to join cardiomyocytes together to make the heart a functional syncytium. Equally, the costamere adhesion complex is another important mechanotrasducing system of the heart that integrates contraction forces generated by individual cardiomyocytes to allow the normal heart to function as a single effective pump. While cardiomyocytes generate internal contractile forces, they are constantly loaded by external mechanical stress which influences the growth and function of cells. Costamere adhesion is considered to transmit forces between the outside and inside of the cells in both directions and is a candidate for mechanical sensing (Ross and Borg, 2001; Sussman et al., 2002).

Cardiac remodeling

Cardiac remodeling consists physiologic and pathologic responses that may occur after myocardial infarction, inflammation, pressure overload (aortic stenosis, hypertension) and volume overload (Pfeffer and Braunwald, 1990; Braunwald and Bristow, 2000; Cohn et al., 2000). In cardiology, the term, cardiac remodeling is often manifested clinically as changes in left ventricular chamber volume associated with progressive heart failure after cardiac damage. Biologically, it involves structural alternation and rearrangement of cardiomyocytes, vascular cells, fibroblasts and interstitial connective tissue, followed by functional changes. Indeed, the cardiomyocyte is the major cell participating in the remodeling response (Cohn et al., 2000). Myocardial injury results in necrosis or apoptosis of cardiomyocytes, and surviving cardiomyocytes change connections among the cells and between the cells and the ECM, and become hypertrophied (Lorell and Carabello, 2000; Sutton and Sharpe, 2000). Necrosis of cardiomyocytes also elicits an inflammatory reaction, fibroblasts activation, and degradation and synthesis of ECM (Frangogiannis et al., 2002b). Consequently, the stroma in the lesions become fibrotic. The primary players in this fibroproliferative response are interstitial fibroblasts (reviewed in Manabe et al., 2002). Therefore, in ventricular remodeling, hypertrophy of cardiomyocytes and myocardial fibrosis occur usually simultaneously.

Tenascin-C in the heart

Tenascin-C (TNC) is a prototype member of a matricellular protein. It is specifically expressed during
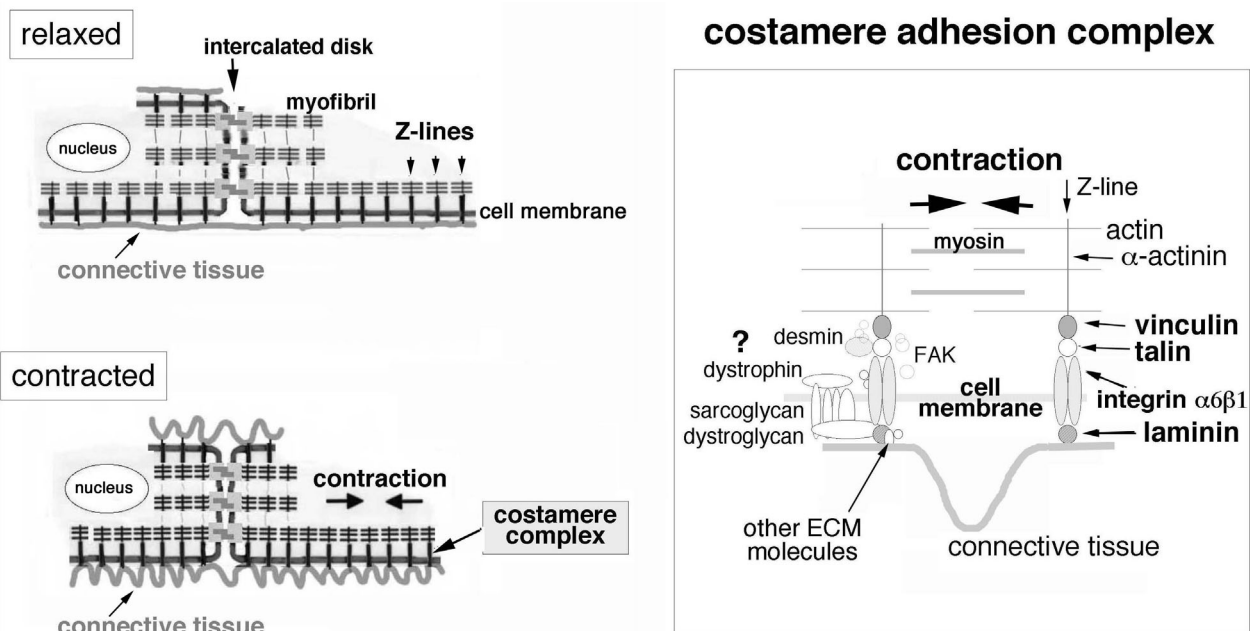

Fig. 1. Diagram of adhesion linkage between cardiomyocytes and ECM in the normal heart. Individual Z-lines of myofibrils are anchored to connective tissue by costamere adhesion complexes which include vinculin, talin, integrin a6b1 and laminin. When the myofibrils contract, the forces are transmitted to extracellular connective tissue through these adhesion complexes. Other molecules such as dystrophin, dystroglycan, and desmin might be also involved in forming the costamere adhesion complex.

embryonic development or early stages of tissue remodeling during inflammation, wound healing or cancer progression (for review, see Jones and Jones, 2000a,b; Chiquet-Ehrismann and Chiquet, 2003). TNC is a hexameric glycoprotein, each subunit consisting of an assembly domain; epidermal growth factor (EGF)-like repeats, a variable number of fibronectin type III (FN III) repeats containing alternative spliced domains, and a C-terminal fibrinogen-related domain. Alternative spliced domains of FN III repeats are known to have the ability to promote cell proliferation, migration or regulate cells attachment (Chung and Erickson, 1994; Chung et al.,1996; Fischer et al., 1997; Tsunoda et al., 2003). TNC is barely detected in the normal adult heart but transiently expressed at distinct sites closely associated with active tissue remodeling during embryonic development and a heart affected by a pathologic condition.

Possible roles during cardiac development

TNC appears in several important steps during the very early stage of cardiogenesis. At first, TNC is expressed by precardiac mesodermal cells when they differentiate into cardiomyocytes. Once the cells become differentiated and express sarcomeric proteins, they stop expressing TNC (Imanaka-Yoshida et al., 2003). It is also worth noting that TNC can be involved in coronary vasculo/angionenesis and recruitment of fibroblasts. In adult tissues, several lines of evidence have suggested its important role in neovascularization in wound healing or cancer stroma (Zagzag et al., 2002). The origin of coronary vascular cells and interstitial fibroblasts differs from that of cardiomyocytes. While the primitive heart tube is formed from the lateral plate mesoderm, mesenchymal cells of the transverse septum form a cauliflower-like structure called the proepicardial organ (PEO) between the primitive heart and the liver bud (Fig. 2). When the primitive heart tube starts looping, aggregate cells detach from the PEO, transfer and spread over the heart, and give rise to coronary vessels and fibroblasts (Mikawa et al., 1992; Poelmann et al., 1993; Mikawa and Gourdie, 1996). When the cells start to migrate from the PEO toward the heart, they express TNC. Interestingly, once the cells are transferred onto the heart, the expression of TNC quickly diminishes (Imanaka-Yoshida et al., 2003). It appears there may exist a mechanism which inhibits TNC expression in the normal myocardium. The restricted expression of TNC strongly suggests its significant roles in cell differentiation or coronary vasculogenesis, however, hearts develop normally in TNC knockout mice (Saga et al., 1992; Forsberg et al., 1996; Imanaka-Yoshida et al., 2003). Obviously, there should exist a compensatory mechanism, although the evidence of upregulation of other genes to substitute the loss of TNC has not been identified yet (Mackie and Tucker, 1999). Alternatively, quick clearance of TNC at appropriate time points might be more critical for heart development.

TNC is re-expressed in pathological conditions

In the normal adult heart, TNC is not detected in the myocardium except at the chorda tendinae of papillary muscles (Sato and Shimada, 2001) and base of valve leaflets (unpublished data). However, TNC reappears under various pathologic conditions such as myocardial infarction (Willems et al., 1996; Imanaka-Yoshida et al., 2001a), myocarditis (Imanaka-Yoshida et al., 2002; Sato et al., 2002), hibernating myocardium (Frangogiannis et al., 2002a) and some cases of dilated cardiomyopathy (Tamura et al., 1996). A prominent feature is its expression is inevitably associated with cell injury and active inflammation. In the mouse autoimmune myocarditis model, immunoreactivity of TNC appears at the initial stage of myocytolysis, persists during the active stage, and disappears in the healed stage. TNC is always observed in the vicinity of damaged cardiomyocytes in foci of inflammation, and the level of expression reflects the extent of inflammation (Imanaka-Yoshida et al., 2002).

The specific expression suggests that TNC can be a marker for myocardial disease activity. Recently, we evaluated the diagnostic value of TNC expression in biopsy specimens from patients with myocarditis, and confirmed that immunoreactivity reflects clinical disease
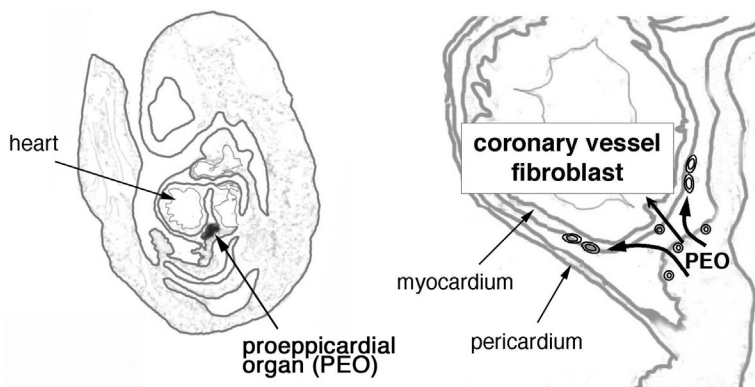

Fig. 2. Diagram of a saggital section of E 9.5 mouse embryo. A proepicardial organ (PEO) transiently forms between the primitive heart and the liver bud. Cells transfer from the PEO to the heart, spread over the surface, then migrate into the myocardium and become coronary vascular cells and interstitial fibroblasts.

activity as observed in animal models, which suggests its practical usefulness. Furthermore, using anti-TNC antibody labeled with [111]Indium, we succeeded imaging the inflammatory lesion in a rat autoimmune myocarditis model *in vivo* (Sato et al., 2002). Immunoscintigraphic imaging or measuring serum TNC level by ELISA may provide a new noninvasive and accurate approach for the diagnosis of myocardial disease activity including myocarditis or rejection of the transplanted heart.

TNC inducing factors

During myocardial tissue remodeling under pathological conditions, cardiomyocytes never express TNC, but interstitial fibroblasts are the major source of TNC (Imanaka-Yoshida et al., 2001a, 2002). Various factors upregulate TNC expression. In general, inflammatory cytokines or growth factors such as TNF-α, IFN-γ, TGF-ß, CTGF, ßFGF, IL-1, IL-4 can upregulate the expression of TNC (Rettig et al., 1994; Harkonen et al., 1995; Sakai et al., 1995; Makhluf et al., 1996; Latijnhouwers et al., 1998; Noda et al., 2000; Gore-Hyer et al., 2002). Angiotensin II, a key regulator in cardiovascular tissue remodeling, is also known to stimulate TNC synthesis (Mackie et al., 1992; Sharifi et al., 1992). Furthermore, oxidative stress (Aziz et al., 1997; Yamamoto et al., 1999) and hypoxia (Lal et al., 2001) induce TNC expression. Recently, we found that extracellular acidosis upregulates the expression of TNC in cardiac fibroblasts (Fig. 3). These *in vitro* data suggest that ischemia and reperfusion could induce TNC expression in the heart.

Another important TNC inducing factor is mechanical stress. TNC has been known to be present in musculoskeletal regions in which high mechanical forces are transmitted (Jarvinen et al., 2000). Several lines of evidence demonstrate that mechanical stress upregulates TNC expression *in vitro*. (Chiquet-Ehrismann et al., 1994; Chiquet, 1999, 2003; Yamamoto et al., 1999, 2001) In fact, the TNC gene promotor contains a mechano-responsive element which contains a GAGACC sequence motif like 'shear stress response element' in the PDGF-B gene (Chiquet, 1999).

Roles of TNC during tissue remodeling after myocardial infarction

The most well-known function of TNC would be anti-adhesion (for review, see Orend and Chiquet-Ehrismann, 2000). Earlier work demonstrated that TNC disrupts the interaction of cells with fibronectin (Chiquet-Ehrismann et al., 1986) and causes down-regulation of focal adhesion (Murphy-Ullrich et al., 1991). Recently, the effects of TNC on cell adhesion is understood to be rather more complex than simple disruption or inhibition of adhesion, and the term, "de-adhesion", is preferentially used.

Murphy-Ullrich and co-workers classified strength of cell-ECM adhesion into three levels: (1) weak adherence (attached but not spread), (2) intermediate adherence (spreading cells without focal adhesion and stress fibers) and (3) strong adherence (with stress fibers and focal adhesion). De-adhesion was defined as the transition from strong adherence to intermediate adherence, and it was characterized by the disassembly of focal adhesion plaques and stress fibers (Greenwood and Murphy-Ullrich, 1998; Murphy-Ullrich, 2001).

Tissue remodeling after myocardial infarction is a good example to discuss the role of TNC in myocardium. During tissue repair after infarction, the most intriguing point is its exclusive localization at the border zone between the infarcted lesion and intact myocardium (Fig.4). Since the edge of the residual myocardium is the most active site of tissue remodeling, this characteristic localization suggests its particular
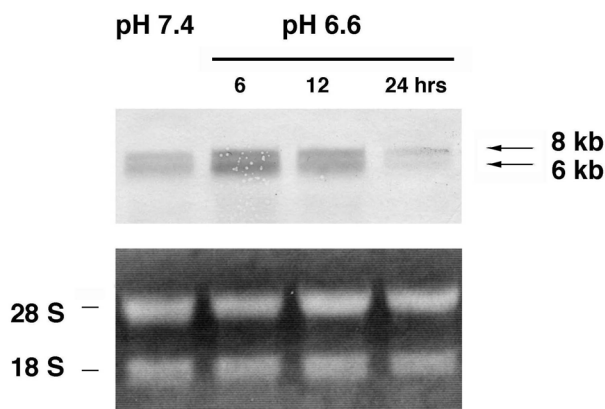
Fig. 3. Effect of acidosis on expression of tenascin-C in rat cardiac fibroblasts. RNA was isolated from cells cultured in control (pH7.4) and at 6, 12, and 24 hors after medium replacement at pH 6.6. The membrane was subjected to nothernblottig using a digoxigenin labeled cRNA probe. As a loading control, 28 S and 18 S rRNA were used.
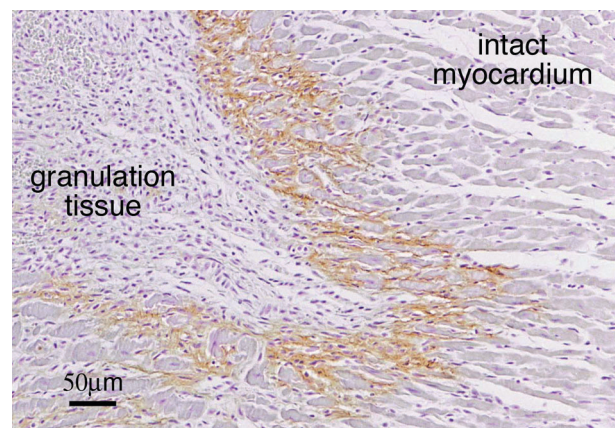
Fig. 4. Immunostaining for tenascin-C in a rat myocardial section obtained 5 days after coronary ligation. Tenascin-C molecule depositts in the border zone between infarcted and intact areas.

role. In the normal heart, as we discussed above, cardiomyocytes join each other by intercalated disks, and are also linked laterally to the ECM with costamere adhesion. After myocardial infarction, borderline cardiomyocytes which lose neighboring cells must extensively rearrange cytoskeletons, cell shape, and form new cell-ECM attachments (Matsushita et al., 1999). For this active structural change, the residual cardiomyocytes must not be stably fixed. Therefore, it is fascinating to think that the de-adhesion molecule TNC deposited in the lesion may unfasten cardiomyocytes from their linkage to connective tissue. Our recent in vitro data suggest the mechanism to modulate adhesion of cardiomyocytes by TNC can be complex (Imanaka-Yoshida et al., 2001a). When cardiomyocytes isolated from an adult rat are plated on laminin coated glasses, the presence of TNC in the substratum increases the number of attached cells. Under interference reflection microscopy (IRM), these cell attachment sites mostly appear as gray contacts but do not show the striated distribution of dark contact corresponding to costameric adhesion. Under IRM, dark areas of the images indicate the distance between the ventral surface and the substratum is very close, about 10 to 15 nm, while gray areas indicate a separation of about 30 nm (Izzard and Lochner, 1980). This finding means that TNC shifts strong costameric adhesion to loose gray contacts. However, addition of exogenous TNC does not cause disruption of the stable costameric adhesion. Instead, TNC can upregulate transcription and activity of metalloproteinases (MMPs) in some types of cells (Tremble et al., 1994; Jian et al., 2001b; Kalembeyi et al., 2003). Cardiac fibroblasts are stimulated to upregulate MMPs (unpublished data).

Taken together, it seems likely that, during myocardial tissue repair, TNC at the border zone induces MMPs which degrade the linkage between residual cardiomyocytes and the surrounding matrix, leaving cardiomyocytes free to move. Simultaneously, TNC itself weakly adheres to cardiomyocytes. Adhering to the matrix is essential for most cells, because various important outside-in / inside-out signals, including survival signals, are transduced through the cell adhesion sites. Thus, even during tissue remodeling, cardiomyocytes need to somehow keep themselves attached under continuous mechanical stress during the contraction/relaxation cycle. TNC may tentatively attach the cells just like a 'Post-it' tape until they adapt to a new environment.

Furthermore, the TNC molecule possesses an elastic property (Oberhauser et al., 1998) and is suggested to act as a 'shock absorber' for mechanical stress (Chiquet et al., 2003; Jarvinen et al., 2003). This is another attractive possibility because borderzone myocardium is subjected to most heavy mechanical loading.

TNC may regulate recruitment of myofibroblasts

During wound repair of various tissues, residential fibroblasts at the edge of the injured tissue transform to myofibroblasts which migrate into the damaged area and produce procollagen and other ECM proteins as well as ECM-degrading enzymes (Gabbiani, 1998, 2003; Serini and Gabbiani, 1999; Powell, 2000). Myofibroblasts share characteristics with both fibroblasts and smooth muscle cells. They express smooth muscle specific proteins such as α-smooth muscle actin, have a well-developed contractile apparatus and exert mechanical forces on the matrix that minimize the wound area (Clark, 1996).

A close relationship between TNC and myofibroblasts in cancer stroma or repertories of myofibroblasts in normal tissue have been reported (Hanamura et al., 1997; Kalembey et al., 1997; Yoshida et al., 1997). Recently, we carefully compared the spatiotemporal distribution of myofibroblasts and TNC molecules during myocardial tissue remodeling, and found that TNC deposition precedes the appearance of myofibroblasts, and that myofibroblasts appear in the area where TNC molecules are deposited (Imanaka-Yoshida et al., 2001a). This observation indicates that TNC may regulate the recruitment of myofibroblasts. Previous reports have shown that TNC stimulates the migration and proliferation of cancer cells (Yoshida et al., 1999; Tsunoda et al., 2003). In culture, TNC enhances migration and expression of α-smooth muscle actin of cardiac fibroblasts (unpublished data). TNC could be a major modulator of recruitment of myofibroblasts at an early stage of myocardial tissue repair.

Interactions between TNC and other remodeling-related proteins during progression of fibrosis

Myocardial fibrosis as well as hypertrophy of cardiomyocytes is often observed in ventricular remodeling. Fibrosis is defined as the increase of fibrillar collagen in intermyocardial spaces. Myocardial fibrosis has been classified into two groups: replacement fibrosis and reactive fibrosis (Weber et al., 1989). In replacement fibrosis, myocytes necrosis elicits an inflammatory reaction and myocardial dropout is filled by collagen fibers. In contrast, in case of reactive fibrosis, fibrillar collagen surrounds individual cardiomyocytes increases without the loss of cardiomyocytes. Histologically, it seems that collagen fibrils start to increase in the perivascular region in the myocardium and eventually extend among individual myocytes. This type of fibrosis is often observed in the pressure-overloaded hypertrophied heart. Recently, low grade inflammation of small arteries, in part, initiated by local activation of the renin-angiotensin-aldosteron system, has received much attention as a trigger of reactive fibrosis (Stier et al., 2002; Virdis and Schiffrin, 2003)

Fibrotic lesions do not form by abrupt deposition of collagen molecules, but through multiple steps of synthesis and degradation of various matrix proteins

which are the consequence of numerous cell-ECM and ECM-ECM interactions. TNC is one of the acute stage proteins of the cascade of progression of fibrosis and has been supposed to work as a scaffold for collagen deposition (Yamada et al., 1992; Imanaka-Yoshida et al., 2001a,b; 2002). TNC not only controls cellular activity but also interacts with other ECM molecules directly or indirectly. TNC is often co-localized with FN in cancer stroma (Hanamura et al., 1997; Yoshida et al., 1997), and binds to soluble FN, FN fibrils *in vitro* (Chiquet-Ehrismann et al., 1991; Chung et al., 1995). TNC also binds to several proteoglycans (Chiquet and Fambrough, 1984; Vaughan et al., 1987, 1994; Salmivirta et al., 1991; Barnea et al., 1994; Grumet et al., 1994; Milev et al., 1994). Binding to a heparansulphate proteoglycan, perlecan, mediates the incorporation of TNC into FN fibrils (Chung and Erickson, 1997). Furthermore, TNC causes a reduction in the assembly of an FN matrix by fibroblasts through regulation of Rho GTPase activity or FAK phosphorylation (Wenk et al., 2000; Midwood and Schwarzbauer, 2002). TNC also inhibits FN-induced integrin signaling by interfering with the binding of FN to syndecan-4 (Huang et al., 2001). Therefore, some functions of TNC such as down-regulation of focal adhesion may be due to attenuation of cellular signaling from FN.

TNC often co-expresses with MMPs in areas of active tissue remodeling in pathological conditions (Cowan et al., 1999; Streuli, 1999; Jian et al., 2001a). In addition to its potential to induce MMPs, TNC can enhance the effect of TGF-ß on MMP-9 induction in breast cancer cells (Kalembeyi et al., 2003). Conversely, denaturation of native collagen type I by MMP upregulates TNC expression in smooth muscle cells (Jones et al., 1997). These findings indicate reciprocal regulation between TNC and MMPs which degrade ECM molecules.

Conclusion and future directions

Traditionally, "cardiac remodeling" has been considered as changes associated with progressive heart failure and is often regarded as a detrimental process almost equal to ventricular dilatation. However, the term itself is neutral and should describe both favorable and unfavorable changes. Recently, imbalance of MMPs and inhibitors of MMPs (TIMPs) have received much attention in progression of unfavorable cardiac remodeling (Mann and Spinale, 1998; Mann, 2002; Spinale, 2002; Heeneman et al., 2003). Conceptually, excessive activation of MMPs might cause progressive degradation of ECMs and slippage of myocytes within the LV wall, and resulting the LV wall thinning and dilatation.

Overall, is TNC harmful or beneficial for myocardial remodeling? Induction of MMPs and de-adhesion by TNC might cause LV dilatation. On the other hand, TNC enhances the recruitment of myofibroblasts and possibly supports collagen fibers deposition. Logically, an increase of myofibroblasts and acceleration of fibrosis generate traction forces that prevent ventricular dilatation. However, excessive fibrosis would lead to a stiffer and less compliant ventricle. Therefore understanding the function of TNC in myocardial remodeling may not be straightforward. Nevertheless, TNC can be a key molecule to explore and diagnose cardiac remodeling and might be a potential therapeutic target to control the balance of beneficial and undesirable cellular responses.

References

Aziz S.M., Toborek M., Hennig B., Mattson M.P., Guo H., Lipke D.W. (1997). Oxidative stress mediates monocrotaline-induced alterations in tenascin expression in pulmonary artery endothelial cells. Int. J. Biochem. Cell Biol. 29, 775-787.

Barnea G., Grumet M., Milev P., Silvennoinen O., Levy J.B., Sap J. and Schlessinger J. (1994). Receptor tyrosine phosphatase beta is expressed in the form of proteoglycan and binds to the extracellular matrix protein tenascin. J. Biol. Chem. 269, 14349-14352.

Bornstein P. (1995). Diversity of function is inherent in matricellular proteins: an appraisal of thrombospondin 1. J. Cell Biol. 130, 503-506.

Bornstein P. and Sage E.H. (2002). Matricellular proteins: extracellular modulators of cell function. Curr. Opin. Cell Biol. 14, 608-616.

Braunwald E. and Bristow M.R. (2000). Congestive heart failure: Fifty years of progress. Circulation 102, IV14-23

Chiquet M. (1999). Regulation of extracellular matrix gene expression by mechanical stress. Matrix Biol. 18, 417-426.

Chiquet M. and Fambrough D.M. (1984). Chick myotendinous antigen. II. A novel extracellular glycoprotein complex consisting of large disulfide-linked subunits. J. Cell Biol. 98, 1937-1946.

Chiquet M., Renedo A.S., Huber F. and Fluck M. (2003). How do fibroblasts translate mechanical signals into changes in extracellular matrix production? Matrix Biol. 22, 73-80.

Chiquet-Ehrismann R. and Chiquet M. (2003). Tenascins: regulation and putative functions during pathological stress. J. Pathol. 200, 488-499.

Chiquet-Ehrismann R., Mackie E.J., Pearson C.A. and Sakakura T. (1986). Tenascin: an extracellular matrix protein involved in tissue interactions during fetal development and oncogenesis. Cell 47, 131-139.

Chiquet-Ehrismann R., Matsuoka Y., Hofer U., Spring J., Bernasconi C. and Chiquet M. (1991). Tenascin variants: differential binding to fibronectin and distinct distribution in cell cultures and tissues. Cell Regul. 2, 927-938.

Chiquet-Ehrismann R., Tannheimer M., Koch M., Brunner A., Spring J., Martin D., Baumgartner S. and Chiquet M. (1994). Tenascin-C expression by fibroblasts is elevated in stressed collagen gels. J. Cell Biol. 127, 2093-2101.

Chung C.Y. and Erickson H.P. (1994). Cell surface annexin II is a high affinity receptor for the alternatively spliced segment of tenascin-C. J. Cell Biol. 126, 539-548.

Chung C.Y., Zardi L. and Erickson H.P. (1995). Binding of tenascin-C to soluble fibronectin and matrix fibrils. J. Biol. Chem. 270, 29012-29017.

Chung C.Y., Murphy-Ullrich J.E. and Erickson H.P. (1996). Mitogenesis, cell migration, and loss of focal adhesions induced by tenascin-C interacting with its cell surface receptor, annexin II. Mol. Biol. Cell 7, 883-892.

Chung C.Y. and Erickson H.P. (1997). Glycosaminoglycans modulate fibronectin matrix assembly and are essential for matrix incorporation of tenascin-C. J. Cell Sci. 110, 1413-1419.

Clark R.A.F (1996) Wound Repair: Overview and general consideration. In: The molecular mechanism of wound repair. 2nd ed. Clark R.A.F (eds). Plenum Press . New York. pp 3-50.

Cohn J.N., Ferrari R. and Sharpe N.U. (2000). Cardiac remodeling-concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. J. Am. Coll. Cardiol. 35, 569-582

Cowan K.N., Jones P.L. and Rabinovitch M. (1999). Regression of hypertrophied rat pulmonary arteries in organ culture is associated with suppression of proteolytic activity, inhibition of tenascin-C, and smooth muscle cell apoptosis. Circ Res. 84, 1223-1233.

Danowski B.A., Imanaka-Yoshida K., Sanger J.M. and Sanger J.W. (1992). Costameres are sites of force transmission to the substratum in adult rat cardiomyocytes. J. Cell Biol. 118, 1411-1420.

Fischer D., Brown-Ludi M., Schulthess T. and Chiquet-Ehrismann R. (1997). Concerted action of tenascin-C domains in cell adhesion, anti-adhesion and promotion of neurite outgrowth. J. Cell Sci. 110, 1513-1522.

Forsberg E., Hirsch E., Frohlich L., Meyer M., Ekblom P., Aszodi A., Werner S. and Fassler R. (1996). Skin wounds and severed nerves heal normally in mice lacking tenascin-C. Proc. Natl. Acad. Sci. USA 93, 6594-6599.

Frangogiannis N.G., Shimoni S., Chang S., Ren G., Dewald O., Gersch C., Shan K., Aggeli C., Reardon M. and Letsou G.V.U. (2002a). Active interstitial remodeling: an important process in the hibernating human myocardium. J. Am. Coll. Cardiol. 39, 1468-1474

Frangogiannis N.G., Smith C.W. and Entman M.L. (2002b). The inflammatory response in myocardial infarction. Cardiovasc. Res. 53, 31-47.

Gabbiani G. (1998). Evolution and clinical implications of the myofibroblast concept. Cardiovasc. Res. 38, 545-548.

Gabbiani G. (2003). The myofibroblast in wound healing and fibrocontractive diseases. J. Pathol. 200, 500-503.

Gore-Hyer E., Shegogue D., Markiewicz M., Lo S., Hazen-Martin D., Greene E.L., Grotendorst G. and Trojanowska M. (2002). TGF-beta and CTGF have overlapping and distinct fibrogenic effects on human renal cells. Am. J. Physiol. Renal Physiol. 283, F707-716.

Greenwood J.A. and Murphy-Ullrich J.E. (1998). Signaling of de-adhesion in cellular regulation and motility. Microsc. Res. Techniq.. 43, 420-432

Grumet M., Milev P., Sakurai T., Karthikeyan L., Bourdon M., Margolis R.K. and Margolis R.U. (1994). Interactions with tenascin and differential effects on cell adhesion of neurocan and phosphacan, two major chondroitin sulfate proteoglycans of nervous tissue. J .Biol. Chem. 269, 12142-12146.

Hanamura N., Yoshida T., Matsumoto E., Kawarada Y. and Sakakura T.

(1997). Expression of fibronectin and tenascin-C mRNA by myofibroblasts, vasucular cells and epithelial cells in human colon adenomas and carcinomas. Int .J.Cancer. 73, 10-15

Harkonen E., Virtanen I., Linnala A., Laitinen L.L. and Kinnula V.L. (1995). Modulation of fibronectin and tenascin production in human bronchial epithelial cells by inflammatory cytokines in vitro. Am. J. Respir. Cell Mol. Biol. 13, 109-115.

Heeneman S., Cleutjens J.P., Faber B.C., Creemers E.E., van Suylen R.J., Lutgens E., Cleutjens K.B. and Daemen M.J. (2003). The dynamic extracellular matrix: intervention strategies during heart failure and atherosclerosis. J. Pathol. 200, 516-525.

Huang W., Chiquet-Ehrismann R., Moyano J.V., Garcia-Pardo A. and Orend G. (2001). Interference of tenascin-C with syndecan-4 binding to fibronectin blocks cell adhesion and stimulates tumor cell proliferation. Cancer Res. 61, 8586-8594.

Imanaka-Yoshida K. (2000). The transmission of contractility through cell adhesion. Prog. Mol. Subcell. Biol. 25, 21-35.

Imanaka-Yoshida K., Danowski B.A., Sanger J.M. and Sanger J.W. (1996). Living adult rat cardiomyocytes in culture: Evidence for dissociation of costameric distribution of vinculin from costameric distributions of attachments. Cell Motil. Cytoskel. 33, 263-275.

Imanaka-Yoshida K., Enomoto-Iwamoto K., Yoshida T. and Sakakura T. (1999). Contraction force of cardiomyocytes is transmitted to the extracellular matrix through an attachment complex composed of vinculin, talin, integrin $\alpha6\beta1$ and laminin. Cell Motil. Cytoskel. 42, 1-11.

Imanaka-Yoshida K., Hiroe M., Nishikawa T., Ishiyama S., Shimojo T., Ohta Y., Sakakura T. and Yoshida T. (2001a). Tenascin-C modulates adhesion of cardiomyocytes to extracellular matrix during tissue remodeling after myocardial infarction. Lab. Invest. 81, 1015-1024.

Imanaka-Yoshida K., Matsura R., Isaka N., Nakano T., Sakakura T-and Yoshida T. (2001b). Serial extracellular matrix changes in neointimal lesions of human coronary artery after percuatneous tansluminal coronary angioplasty: clinical significance of early tenascin-C expression. Virchows Archiv. 439, 185-190.

Imanaka-Yoshida K., Hiroe M., Yasutomi Y., Toyozaki T., Tsuchiya T., Noda N., Maki S., Nishikawa T., Sakakura T. and Yoshida T. (2002). Tenascin-C is a useful marker for disease activity in myocarditis. J. Pathol. 197, 387-394.

Imanaka-Yoshida K., Matsumoto K., Hara M., Sakakura T., Yoshida T. (2003). The dinamic expression of tenascin-C and tenascin-X during early heart development. Differentiation 71, 291-298.

Izzard C.S. and Lochner L.R. (1980). Formation of cell-to-substrate contacts during fibroblast motility: an interference-reflexion study. J. Cell Sci. 42, 81-116.

Jarvinen T.A., Kannus P., Jarvinen T.L., Jozsa L., Kalimo H. and Jarvinen M. (2000). Tenascin-C in the pathobiology and healing process of musculoskeletal tissue injury. Scand. J. Med. Sci. Sports 10, 376-382.

Jarvinen T.A.H., Jozsa L., Kannus P., Jarvinen T.L.N., Hurme T., Kvist M., Pelto-Huikko M., Kalimo H. and Jarvinen M. (2003). Mechanical loading regulates the expression of tenascin-C in the myotendinous junction and tendon but does not induce de novo synthesis in the skeletal muscle. J Cell Sci. 116, 857-866.

Jian B., Jones P.L., Li Q., Mohler E.R., III, Schoen F.J. and Levy R.J. (2001a). Matrix metalloproteinase-2 is Associated with tenascin-C in calcific aortic stenosis. Am. J. Pathol. 159, 321-327.

Jian B., Jones P.L., Li Q., Mohler E.R., 3rd, Schoen F.J. and Levy R.J.

(2001b). Matrix metalloproteinase-2 is associated with tenascin-C in calcific aortic stenosis. Am. J . Pathol. 159, 321-327.

Jones P.L., Crack J. and Rabinovitch M. (1997). Regulation of Tenascin-C, a vascular smooth muscle cell survival factor that interacts with the alpha v beta 3 Integrin to promote epidermal growth factor receptor phosphorylation and growth. J. Cell Biol. 139, 279-293.

Jones F.S. and Jones P.L. (2000a). The tenascin family of ECM glycoproteins: structure, function, and regulation during embryonic development and tissue remodeling. Dev. Dyn. 218, 235-259.

Jones P.L. and Jones F.S. (2000b). Tenascin-C in development and disease: gene regulation and cell function. Matrix Biol. 19, 581-596.

Kalembey I., Yoshida T., Iriyama K. and Sakakura T. (1997). Analysis of tenascin mRNA expression in the murine mammary gland from embryogenesis to carcinogenesis: an in situ hybridization study. Int. J. Dev. Biol. 41, 569-573.

Kalembeyi I., Inada H., Nishiura R., Imanaka-Yoshida K., Sakakura T. and Yoshida T. (2003). Tenascin-C upregulates matrix metalloproteinase-9 in breast cancer cells: Direct and synergistic effects with transforming growth factor. Int. J. Cancer 105, 53-60.

Katz A.M. (1989). Cardiac interstitium in health and disease: the fibrillar collagne network. J. Am. Coll. Cardiol. 13, 1657-1662.

Lal A., Peters H., St Croix B., Haroon Z.A., Dewhirst M.W., Strausberg R.L., Kaanders J.H., van der Kogel A.J. and Riggins G.J. (2001). Transcriptional response to hypoxia in human tumors. J. Natl. Cancer Inst. 93, 1337-1343.

Latijnhouwers M.A., Pfundt R., de Jongh G.J. and Schalkwijk J. (1998). Tenascin-C expression in human epidermal keratinocytes is regulated by inflammatory cytokines and a stress response pathway. Matrix Biol. 17, 305-316.

Lorell B.H. and Carabello B.A. (2000). Left ventricular hypertrophy: pathogenesis, detection, and prognosis. Circulation 102, 470-479.

Mackie E.J., Scott-Burden T., Hahn A.W., Kern F., Bernhardt J., Regenass S., Weller A. and Buhler F.R. (1992). Expression of tenascin by vascular smooth muscle cells. Alterations in hypertensive rats and stimulation by angiotensin II. Am. J.Pathol. 141, 377-388.

Mackie E.J. and Tucker R.P. (1999). The tenascin-C knockout revisited. J. Cell Sci. 112, 3847-3853.

Makhluf H.A., Stepniakowska J., Hoffman S., Smith E., LeRoy E.C., Trojanowska M. (1996). IL-4 upregulates tenascin synthesis in scleroderma and healthy skin fibroblasts. J. Invest. Dermatol. 107, 856-859.

Manabe I., Shindo T. and Nagai R. (2002). Gene expression in fibroblasts and fibrosis: involvement in cardiac hypertrophy. Circ. .Res. 91, 1103-1113.

Mann D.L. (2002). Inflammatory mediators and the failing heart: past, present, and the foreseeable future. Circ Res. 91, 988-998.

Mann D.L. and Spinale F.G. (1998). Activation of matrix metalloproteinases in the failing human heart: breaking the tie that binds. Circulation. 98, 1699-1702.

Matsushita T., Oyamada M., Fujimoto K., Yasuda Y., Masuda S., Wada Y., Oka T. and Takamatsu T. (1999). Remodeling of cell-cell and cell-extracellular matrix interactions at the border zone of rat myocardial infarcts. Circ. Res. 85, 1046-1055.

Midwood K.S and Schwarzbauer J.E. (2002). Tenascin-C modulates matrix contraction via focal adhesion kinase- and Rho-mediated signaling pathways. Mol. Biol.Cell. 13, 3601-3613.

Mikawa T., Cohen-Gould L. and Fischman D.A. (1992). Clonal analysis of cardiac morphogenesis in the chicken embryo using a replication-defective retrovirus. III: Polyclonal origin of adjacent ventricular myocytes. Dev. Dyn.. 195, 133-141.

Mikawa T. and Gourdie R.G. (1996). Pericardial mesoderm generates a population of coronary smooth muscle cells migrating into the heart along with ingrowth of the epicardial organ. Dev. Biol. 174, 221-232.

Milev P., Friedlander D.R., Sakurai T., Karthikeyan L., Flad M., Margolis R.K., Grumet M. and Margolis R.U. (1994). Interactions of the chondroitin sulfate proteoglycan phosphacan, the extracellular domain of a receptor-type protein tyrosine phosphatase, with neurons, glia, and neural cell adhesion molecules. J. Cell Biol. 127, 1703-1715.

Murphy-Ullrich, J.E. (2001). The de-adhesive activity of matricellular proteins: is intermediate cell adhesion an adaptive state? J. Clin. Invest. 107, 785-790.

Murphy-Ullrich J.E., Lightner V.A., Aukhil I., Yan Y.Z., Erickson H.P. and Hook M. (1991). Focal adhesion integrity is downregulated by the alternatively spliced domain of human tenascin. J. Cell Biol. 115, 1127-1136.

Noda N., Minoura H., Nishiura R., Toyoda N., Imanaka-Yoshida K., Sakakura T. and Yoshida T. (2000). Expression of tenascin-C in stromal cells ot the murine uterus during early pregnancy: Induction by interleukin-1 alpha, prostaglandin E2 and prostaglandin F2 alpha. Biol. Reprod. 63, 1723-1730

Oberhauser A.F., Marszalek P.E., Erickson H.P. and Fernandez J.M. (1998). The molecular elasticity of the extracellular matrix protein tenascin. Nature 393, 181-185.

Orend G. and Chiquet-Ehrismann R. (2000). Adhesion modulation by antiadhesive molecules of the extracellular matrix. Exp. Cell Res. 261, 104-110.

Pardo J.V., Siliciano J.D. and Craig S.W. (1983). Vinculin is a component of an extensive network of myofibril-sarcolemma attachment regions in cardiac muscle fibers. J. Cell Biol. 97, 1081-1088.

Pfeffer M .and Braunwald E. (1990). Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation 81, 1161-1172.

Poelmann R., Gittenberger-de Groot A., Mentink M., Bokenkamp R. and Hogers B. (1993). Development of the cardiac coronary vascular endothelium, studied with antiendothelial antibodies, in chicken-quail chimeras. Circ. Res. 73, 559-568.

Powell D.W. (2000). Myofibroblasts: paracrine cells important in health and disease. Trans. Am. Clin. Climatol Assoc. 111, 271-292.

Rettig W.J., Erickson H.P., Albino A.P. and Garin-Chesa P. (1994). Induction of human tenascin (neuronectin) by growth factors and cytokines: cell type-specific signals and signalling pathways. J. Cell Sci. 107, 487-497.

Ross R.S.and Borg T.K. (2001). Integrins and the myocardium. Circ Res. 88, 1112-1119.

Saga Y., Yagi T., Ikawa Y. and Sakakura T. and Aizawa S. (1992). Mice develop normally without tenascin. Genes Dev. 6, 1821-1831

Sakai T., Ohta M., Furukawa Y., Saga Y., Aizawa S., Kawakatsu H. and Saito M. (1995). Tenascin-C induction by the diffusible factor epidermal growth factor in stromal-epithelial interactions. J. Cell. Physiol. 165, 18-29.

Salmivirta M., Elenius K., Vainio S., Hofer U., Chiquet-Ehrismann R., Thesleff I. and Jalkanen M. (1991). Syndecan from embryonic tooth mesenchyme binds tenascin. J. Biol. Chem. 266, 7733-7739.

Sato I. and Shimada K. (2001). Quantitative analysis of tenascin in

chordae tendineae of human left ventricular papillary muscle with aging. Ann Anat. 183, 443-448.

Sato M., Toyozaki T., Odaka K., Uehara T., Arano Y., Hasegawa H., Yoshida K., Imanaka-Yoshida K., Yoshida T., Hiroe M., Tadokoro H., Irie T., Tanada S. and Komuro I. (2002). Detection of experimental autoimmune myocarditis in rats by ^{111}In monoclonal antibody specific for tenascin-C. Circulation. 106, 1397-1402.

Serini G. and Gabbiani G. (1999). Mechanisms of myofibroblast activity and phenotypic modulation. Exp. Cell Res. 250, 273-283.

Sharifi B.G., LaFleur D.W., Pirola C.J., Forrester J.S. and Fagin J.A. (1992). Angiotensin II regulates tenascin gene expression in vascular smooth muscle cells. J. Biol. Chem. 267, 23910-23915.

Spinale F.G. (2002). Matrix metalloproteinases: regulation and dysregulation in the failing heart. Circ. Res. 90, 520-530.

Stier C.T., Jr., Chander P.N. and Rocha R. (2002). Aldosterone as a mediator in cardiovascular injury. Cardiol. Rev. 10, 97-107.

Streuli C. (1999). Extracellular matrix remodelling and cellular differentiation. Curr. Opin. Cell Biol. 11, 634-640.

Sussman M.A., McCulloch A. and Borg T.K. (2002). Dance Band on the Titanic: Biomechanical Signaling in Cardiac Hypertrophy. Circ. Res. 91, 888-898

Sutton M.G. and Sharpe N. (2000). Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation 101, 2981-2988.

Tamura A., Kusachi S., Nogami K., Yamanishi A., Kajikawa Y., Hirohata S and Tsuji T. (1996). Tenascin expression in endomyocardial biopsy specimens in patients with dilated cardiomyopathy: distribution along margins of fibrotic lesions. Heart 75, 291-294.

Tremble P., Chiquet-Ehrismann R. and Werb Z. (1994). The extracellular matrix ligands fibronectin and tenascin collaborate in regulating collagenase gene expression in fibroblasts. Mol.. Biol. Cell 5, 439-453.

Tsunoda T., Inada H., Kalembeyi I., Imanaka-Yoshida K., Sakakibara M., Okada R., Katsuta K., Sakakura T., Majima Y. and Yoshida T. (2003). Involvement of large tenascin-C splice variants in breast cancer progression. Am. J. Pathol. 162, 1857-1867.

Vaughan L., Huber S., Chiquet M. and Winterhalter K.H. (1987). A major, six-armed glycoprotein from embryonic cartilage. EMBO. J. 6, 349-353.

Vaughan L., Weber P., D'Alessandri L., Zisch A.H. and Winterhalter K.H. (1994). Tenascin-contactin/F11 interactions: a clue for a developmental role? Perspect. Dev. Neurobiol. 2, 43-52.

Virdis A. and Schiffrin E.L. (2003). Vascular inflammation: a role in vascular disease in hypertension? Curr. Opin. Nephrol. Hypertens. 12, 181-187.

Weber K.T., Pick R., Jalil J.E., Janicki J.S. and Carroll E.P. (1989). Patterns of myocardial fibrosis. J. Mol. Cell Cardiol. 21, 121-131.

Wenk M.B., Midwood K.S. and Schwarzbauer J.E. (2000). Tenascin-C suppresses Rho activation. J. Cell Biol. 150, 913-920.

Willems I.E., Arends J.W. and Daemen M.J. (1996). Tenascin and fibronectin expression in healing human myocardial scars. J. Pathol. 179, 321-325.

Yamada S., Ichida T., Matsuda Y., Miyazaki Y., Hatano T., Hata K., Asakura H., Hirota N., Geerts A. and Wisse E. (1992). Tenascin expression in human chronic liver disease and in hepatocellular carcinoma. Liver 12, 10-16.

Yamamoto K., Dang Q.N., Kennedy S.P., Osathanondh R., Kelly R.A. and Lee R.T. (1999). Induction of tenascin-C in cardiac myocytes by mechanical deformation. Role of reactive oxygen species. J. Biol. Chem. 274, 21840-21846.

Yamamoto K., Dang Q.N., Maeda Y., Huang H., Kelly R.A. and Lee R.T. (2001). Regulation of cardiomyocyte mechanotransduction by the cardiac cycle. Circulation 103, 1459-1464.

Yoshida T., Matsumoto E., Hanamura N., Kalembeyi I., Katsuta K., Ishihara A. and Sakakura T. (1997). Co-expression of tenascin and fibronectin in epithelial and stromal cells of benign lesions and ductal carcinomas in the human breast. J. Pathol. 182, 421-428.

Yoshida T., Yoshimura E., Numata H., Sakakura Y. and Sakakura T. (1999). Involvement of tenascin-C in proliferation and migration of laryngeal carcinoma cells. Virchows Arch. 435, 496-500.

Zagzag D., Shiff B., Jallo G.I., Greco M.A., Blanco C., Cohen H., Hukin J., Allen J.C. and Friedlander D.R. (2002). Tenascin-C promotes microvascular cell migration and phosphorylation of focal adhesion kinase. Cancer Res. 62, 2660-2668.