Initially, smooth muscle cell differentiation is induced in lateral plate mesoderm-derived cells; however, this population is replaced by paraxial mesoderm (somites) derivatives (Esner et al., 2006; Pouget et al., 2006; Wasteson et al., 2008; Wiegreffe et al., 2009). Individual somites build up locally restricted spatial domains of the "segmental" aortic wall (Majesky, 2007).

Despite the mosaic origin of the component cells, no evident segmental expression pattern of TNC is observed during development of the aorta. In E12-13 mouse embryos, very weak expression of TNC is observed in the ascending aorta and pulmonary truncus, in contrast to the strong expression in outflow and pulmonary arteries (Fig. 4A). Expression of TNC in medial smooth muscle cells of the aorta is upregulated after ED14-15 (Fig. 4B) when the systemic circulatory system is established, and becomes stronger after birth. This upregulated expression may reflect the increased hemodynamic stress on the aortic wall. Similarly, increased mechanical stress produced by ligation of pulmonary arteries –increased TNC expression (Jones et al., 2002).

Development of coronary artery and tenascin-C

Most cells of coronary vessels originate from extracardiac tissue known as the proepicardial organ. Mesenchymal cells from-this region attach to and migrate along the surface of the heart to form a nascent epicardium. Subsequently, the epithelial epicardium undergoes epithelial-mesenchymal transition and seeds pluripotent mesenchymal cells into the subepicardial space, which differentiate into coronary smooth muscle cells, perivascular fibroblasts, myocardial interstitial cells, and possibly part of the endothelial cells (Dettman et al., 1998; Mikawa and Gourdie, 1996;

Perez-Pomares et al., 1998) (also see (Nakajima and Imanaka-Yoshida, 2013) for review). TNC is upregulated at the epithelial-mesenchymal transition of epicardial cells. Epicardium-derived endothelial precursors form the vascular plexus. Once the primitive coronary endothelial tubes connect with the aortic sinuses of the ascending aorta, VSMCs s are recruited. While VSMC s of the coronary arteries are mainly derived from the proepicardial organ, the preotic neural crest contributes to the septal coronary artery (Arima et al., 2012). Strong expression of TNC is detected, closely associated with the formation of the thick α-smooth muscle actin (αSMA) positive vascular wall (Ando et al., 2011) (Fig. 5), which suggests that TNC may be involved in maturation of the coronary artery.

Maturation of the vascular wall includes the differentiation of mural cells from the undifferentiated mesenchyme, mural cell proliferation, and recruitment. Addition of TNC to epicardial cells in culture changes their phenotype to smooth muscle cells (Ando et al., 2011). Various signaling pathways are involved in the regulation of mural cell recruitment. Among them, the PDGF-BB/PDGF receptor (PDGFR) β signaling loop is known to be a key regulator (Andrae et al., 2008; Armulik et al., 2011; Gaengel et al., 2009). *In vitro*, treatment of VSMCs with TNC arguments PDGF signaling by cross-talk between PDGFR-β and integrin αvβ3 with activation of focal adhesion kinase and Src tyrosine kinase, followed by enhancing cell proliferation and migration (Ishigaki et al., 2011) (Fig. 6). Therefore, TNC may promote smooth muscle cell development through regulation of smooth muscle precursor expansion and differentiation by enhancing PDGF-BB/ PDGFR-β signaling. It is also suggested that TNC upregulates *Pdgfra* and *Pdgfrb* at downstream of Wnt7b/catenin in the development of lung smooth muscle cells (Cohen et al., 2009).

Vascular disease and tenascin-C

TNC expression is linked to a range of vascular pathologies. A growing number of studies have reported transient upregulation of TNC associated with the development of intimal hyperplasia, pulmonary artery hypertension, atherosclerosis aortic aneurysm, renal transplant vasculopathy, varicose veins and angiogenesis (reviewed in (Golledge et al., 2011; Midwood et al., 2011; Van Obberghen-Schilling et al., 2011)).

Vasospasm after subarachnoid hemorrhage *and tenascin-C*

Vasospasm is the sudden abnormal contraction of VSMCs, leading to vasoconstriction and subsequent tissue ischemia. Cerebral vasospasm after subarachnoid hemorrhage (SAH) is a major cause of poor patient outcomes. SAH is associated with TNC upregulation in the spastic cerebral arteries. Clinically, elevation of TNC in patient serum (Suzuki et al., 2010) and cerebrospinal fluid (Suzuki et al., 2011b) after SAH is associated with cerebral spasm. In a rat model, TNC expression is markedly increased in the smooth muscle cell layer of spastic cerebral arteries on day 1 after SAH, and decreases on day 3 as vasospasm improved (Suzuki et al., 2013). In this experimental model, SAH induces PDGFR-β upregulation, PDGFR phophorylation, and consiquently activaties p38 and ERK1 in cerebral arteries (Shiba et al., 2012). Inhibition of the tyrosine kinases of PDGFRs by imatinib reduces post-SAH vasospasm, being associated with suppressing the expression level of PDGFR-β, TNC and p38 activation (Shiba et al., 2012). Direct injections of recombinant TNC into subarachnoid induces prolonged constriction of rat basilar arteries (Fujimoto et al., 2013; Shiba et al., 2013), being accompanied by upregulation of PDGFR-β and endogenous TNC, and enhanced

PDGFR phosphorylation (Shiba et al., 2013).

PDGFs can induce TNC expression via phosphoinositide 3-kinase/Akt pathways (Jinnin et al., 2006) and MAPK pathways (Chiquet et al., 2004). Conversely, TNC enhances PDGF signaling (Ishigaki et al., 2011), as discussed above (in coronary development section). Therefore, PDGF and TNC may act as positive feedback, causing PDGFR activation and leading to a vicious cycle of cerebral vasospasm.

Furthermore, TLR4 has been implicated in the pathogenesis of cerebral vasospasm after SAH (reviewed in (Suzuki et al., 2011a)). TNC administration also upregulates TLR4 expression in the endothelial, smooth muscle, and adventitial cells of cerebral arteries, which are blocked by TLR4 antagonists (LPS-RS) (Fujimoto et al., 2013). TNC is an endogenous TLR4 ligand in macrophages and fibroblasts (Midwood et al., 2009; Monaco et al., 2011). Taken together, it seems likely that TNC and TLR4 activation may also have positive feedback in cerebral vasospasm.

Pulmonary arterial hypertension and tenascin-C

Considerable attention has been directed toward TNC in pulmonary arterial hypertension. Progressive pulmonary hypertension is characterized by smooth muscle proliferation and migration of the medial layer, leading to medial hypertrophy and occlusive neointimal formation in muscular arteries that is associated with inflammation and fibrosis (Hassoun et al., 2009; Morrell et al., 2009). TNC is expressed with proliferating smooth muscle cells in the medial layer of remodeling pulmonary arteries in an animal model and human patients (Ihida-Stansbury et al., 2006; Jones et al., 1997a; Jones and Rabinovitch, 1996). *In vitro*, TNC amplifies the proliferative response to epidermal growth factor and basic fibroblast growth factor of smooth muscle cell by

the clustering of integrin αvβ3, (i.e. formation of focal adhesion) along with enhanced autophosphorylation (Jones et al., 1997b). Conversely, an antisense RNA suppressing TNC induces VSMCs apoptosis and regression of pulmonary vascular lesions in monocrotaline-exposed pulmonary hypertensive rats (Cowan et al., 2000). Recently, gene mutation of bone morphogenetic protein (BMP) type II receptor (BMPR2) has been linked to familial human pulmonary arterial hypertension (Lane et al., 2000). Loss-of function mutation of BMPR2 leads to a reduction in BMP-induced Smad signaling and an increase in MAPK signaling pathways (Ihida-Stansbury et al., 2006). Moreover, recent data have indicated that one family of pulmonary arterial hypertension contains a truncating mutation of SMAD8 (Shintani et al., 2009). Deletion of *smad*8 in mice results in characteristic changes in pulmonary arterial hypertension, associated with increased levels of Prx-1-dependent expression of TNC in VSMC (Huang et al., 2009). Together, these studies suggest the involvement of TNC in the progression of vascular lesions of pulmonary arterial hypertension.

Stenosis/restenosis and tenascin-C

Intimal hyperplasia is a major common pathogenic component of not only PAH but also various other stenotic vascular diseases, including atherosclerosis, restenosis after coronary angioplasty, stenting, and bypass grafting. Stenotic neointima is formed by abnormal migration, proliferation, and matrix synthesis by VSMCs and myofibroblasts modulated by inflammatory mediators and growth factors in response to intimal injury (Forte et al., 2010). Myofibroblasts are specialized mesenchymal cells with prominent contractile microfilament bundles and high contractile activity, appearing in pathophysiological conditions for tissue repair (Klingberg et al., 2013). Myofibroblasts

and smooth muscle cells share common functional properties and a number of markers, including αSMA. Vascular myofibroblasts can be derived from not only from the transdifferentiation of VSMCs resident in the tunica media but also from adventitial fibroblasts, endothelial cells through endothelial–mesenchymal transition, and circulating precursors defined as fibrocytes (Forte et al., 2010).

Deposition of TNC has been reported at an early stage of neointimal formation in human patients and various animal models associated with VSMC proliferation and ECM deposition (Fujinaga et al., 2004; Hedin et al., 1991; Imanaka-Yoshida et al., 2001; Sawada et al., 2007; Wallner et al., 1999; Wallner et al., 2002; Wallner et al., 2001; Yamamoto et al., 2005; Yamamoto et al., 2007). An artery graft model using a TNC reporter mouse has demonstrated that TNC-expressing VSMCs in the media migrate into the neointima through the internal elastic lamina, suggesting that deposition of TNC can be, at least partly, a local reaction by medial VSMCs. Furthermore, in this model, it has also been demonstrated that TNC-producing cells may pass from the recipient into the neointima of transplanted grafts, and that TNC produced by both donor and recipient cells may contribute to stenotic neointimal hyperplasia (Sawada et al., 2007). In fact, deletion of TNC reduces neointimal hyperplasia after aortotomy and artery grafting (Sawada et al., 2007; Yamamoto et al., 2005). Alternatively, inhibition of intimal hyperplasia by, for example, prostaglandin E2 deficiency (Wang et al., 2011) or a phosphodiesterase inhibitor, cilostazol (Fujinaga et al., 2004), reduces TNC expression.

In contrast, recent reports have demonstrated that deletion of TNC in Apo-E-deficient mice exacerbate atherosclerotic intimal lesions (Wang et al., 2013; Wang et al., 2012), suggesting that TNC signaling may reduce intimal lesion by

modulating the interaction of inflammatory cells and endothelial cells. Therefore, it seems likely that TNC has both harmful and protective effects on neointimal hyperplasia in a context dependent manner.

Aortic aneurysm and tenascin-C

Abdominal aortic aneurysm is a common disease causing segmental expansion and rupture of the aorta. The central pathogenesis is chronic inflammation and degradation of ECM by proteolytic enzymes, such as matrix metalloproteinases (reviewed in (Yoshimura and Aoki, 2012)).

Not surprisingly, TNC is highly upregulated and associated with inflammation and tissue destruction in patients with abdominal aortic aneurysm (Didangelos et al., 2011; Paik et al., 2004; Satta et al., 1997) as well as in an animal model (Kimura et al., 2011). VSMCs of the medial layer of the involved aortic wall produce TNC stimulated possibly by inflammatory cytokines and mechanical stress. Upregulation of TNC is also reported in ascending aortic aneurysm (Majumdar et al., 2007).

Acute aortic dissection is another common destructive aortic disease; however, its molecular mechanism for tissue destruction is largely unknown except for congenital diseases, including Marfan's syndrome (reviewed (Gillis et al., 2013)). Marfan's syndrome is a systemic disorder of connective tissue caused by mutations in FBN1 (Dietz et al., 1991), the gene encoding fibrillin-1. FBN1 molecules assemble into microfibrils, which have an important structural function. Mutation of FBN1 causes structural deficiency as well as excessive TGF-β signaling, which leads to aneurysm formation and rupture of the aortic wall (Habashi et al., 2006). Overexpression of TNC has been reported to be associated with VSMC apoptosis in Marfan's syndrome

(Nataatmadja et al., 2003). Recently, two reports have shown upregulation of TNC in a dissecting aneurysm (Nozato et al., 2013; Trescher et al., 2013), suggesting that serum TNC may be a diagnostic biomarker for aortic dissection. However, its biological significance, and whether TNC is harmful or protective for VSMCs, remains to be elucidated.

Conclusion

VSMCs synthesize TNC in response to developmental and environmental cues, leading to regulation of cell responses such as proliferation, migration and survival in an autocrine/paracrine fashion. These roles are important for building the proper structure during the development and progression of pathological processes. Although understanding the clinical significance of TNC may not be straightforward, since it may contribute to both favorable and undesirable effects on pathological events in a context-dependent manner, it is clear that TNC is a key molecule controlling cellular activity during tissue remodeling and is a potential therapeutic target.

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