Published in final edited form as:
Trends Cardiovasc Med. 2011 January ; 21(1): 1–5. doi:10.1016/j.tcm.2011.12.009.

The Role of Transcription Enhancer Factors in Cardiovascular Biology

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Abstract

The TEF (transcriptional enhancer factor) multigene family is primarily functional in muscle-specific genes through binding to MCAT elements that activate or repress transcription of many genes in response to physiological and pathological stimuli. Among the TEF family, TEF-1, RTEF-1 and DTEF-1 are critical regulators of cardiac and smooth muscle-specific genes during cardiovascular development and cardiac disorders including cardiac hypertrophy. Emerging evidence suggests that in addition to functioning as muscle specific transcription factors, members of the TEF family may be key mediators of gene expression induced by hypoxia in endothelial cells by virtue of its multi-domain organization, potential for posttranslational modifications and interactions with numerous transcription factors, which represent a cell-selective control mediator of nuclear signaling. We will briefly review the recent literature demonstrating the involvement of the TEF-family of transcription factors in the regulation of differential gene expression in cardiovascular physiology and pathology.

Introduction

The human transcriptional enhancer factor (TEF) multigene family includes transcriptional enhancer factor-1 (TEF-1, TEAD1) (Xiao et al. 1991), related transcriptional enhancer factor-1 (RTEF-1, TEAD4) (Jacquemin et al. 1996; Stewart et al. 1996), embryonic TEA domain-containing factor (ETF, TEAD2) (Jacquemin et al. 1999), and divergent transcriptional enhancer factor-1 (DTEF-1, TEAD3) (Azakie et al. 1996; Jiang et al. 1999) (for nomenclature of the TEF family, see Table 1). The TEFs share a highly conserved 68-amino acid TEA/ATTS DNA-binding domain within the N-terminal, which binds to SV40 GT-IIC (GGAATG), SphI (AGTATG), SphII (AGCATG), and muscle-specific M-CAT (GGTATG) enhancers. The tissue distribution of TEF1 family members has been examined and studies have found that TEF-1, RTEF-1 and DTEF-1 are widely expressed in multiple tissues including the skeletal muscle, pancreas, placenta, lung, and heart (Jiang et al. 1999; Stewart et al. 1996; Xiao et al. 1991; Yasunami et al. 1995). In contrast to these three factors, ETF is selectively expressed in a subset of embryonic tissues including the cerebellum, testis, and the distal portion of the forelimb and hindlimb buds, as well as the tail bud, yet it is essentially absent from adult tissues (Yasunami et al. 1995). Additionally,

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TEF transcription factors regulate gene expression by forming complexes with cofactors, including the basic helix loop helix protein MAX (Gupta et al. 1997), poly (ADP-ribose) polymerase (PARP) (Butler and Ordahl 1999), the serum response factor (SRF) (Gupta et al. 2001), myogenic enhancer factor 2 (MEF2) (Maeda et al. 2002a), the yes-associated protein (YAP) and transcriptional coactivator with PDZ domain (TAZ), transcriptional co-activators (Mahoney et al. 2005), the steroid receptor co-activator (SRC1) (Belandia and Parker 2000), the Vestigial-like (VGLL) family of co-factors (*Drosophila*) (Mahoney et al. 2005), and most recently discovered interferon response factor 2 binding protein 2 (IRF2BP2) (Teng et al. 2010).

In the cardiovascular system, TEF-1 is present in cardiac muscle and binds to the M-CAT motif (Azakie et al. 1996). TEF-1 knockout results in defective heart development and embryonic lethal phenotypes in mice (Chen et al. 1994), suggesting that TEF-1 is required for cardiac development. DTEF-1 is highly expressed in cardiac myocytes and augments the α_1-adrenergic activation of the skeletal muscle α-actin gene (Maeda et al. 2002b). DTEF-1 deficient mice have not yet been described. RTEF-1 was first cloned from the human heart cDNA library (Stewart et al. 1996) and ablation of the mouse RTEF-1 gene causes defects in the production of trophoblast stem cells, trophectoderm or blastocoel cavities and consequently, pre-implantation lethality (Nishioka et al. 2008; Yagi et al. 2007). As ETF-1 is largely absent from adult tissues, however, ETF-1 knockout mice reveal a phenotype with increased risk of exencephaly (neural tube closure defect) (Kaneko et al. 2007). For a table of the summarizing the TEF family transgenic mice and their phenotypes, see Table 2.

Since the initial report describing the TEF family as a regulator of muscle specific genes, several studies have recently reported that TEFs show expression in a wide range of cell lines and tissues in response to a variety of stimuli. For instance, RTEF-1 mRNA expression is induced by hypoxia in vascular and ocular endothelial cells, and is involved in promoting the angiogenic response through the Sp1 element in the VEGF promoter (Appukuttan et al. 2007; Shie et al. 2004). RTEF-1 also transcriptionally regulates HIF-1α (Jin et al. 2011) and DSCR1-1L (Liu et al. 2011; Liu et al. 2008).

In this review, we will summarize recent advances in understanding the molecular biology and physiological functions of the TEF family members and discuss their role in the transcriptional control of cardiovascular biology.

TEF family in the regulation of cardiovascular development

TEF-1 is essential for cardiac development. TEF-1 knockout in mice caused embryonic lethality (E12.5) and they exhibited an enlarged pericardial cavity, bradycardia, and a dilated fourth ventricle in brain (Chen et al. 1994). Histological examination revealed that the ventricular wall in the heart of TEF-1 knockout mouse embryos was abnormally thin with a reduced number of trabeculae. These results indicate that TEF-1 is required for cardiac morphogenesis and that the other TEF-1 family members cannot compensate for a lack of TEF-1 function during embryogenesis. TEF-1 interacts with SRF, a protein that is essential for cardiac development (Carson et al. 1996; MacLellan et al. 1994).

DTEF-1 is a unique member of the TEF-1 multigene family with highly abundant transcripts in cardiac but not in skeletal muscle (Azakie et al. 1996). DTEF-1 proteins are highly expressed as early as 16–18 h of chick embryogenesis, after which DTEF-1 becomes abundant in the sinus venosus and is expressed in the trabeculated ventricular myocardium and ventricular outflow tracts (Azakie et al. 2005). DTEF-1 interacts with the cardiac troponin T (cTnT) promoter in embryonic cardiocytes, yet not in embryonic skeletal myocytes or fibroblasts. DTEF-1 also interacts with MEF-2 by co-immunoprecipitation and *trans*-activates the cTnT promoter (Azakie et al. 2005). Additionally, DTEF-1 consists of

two isoforms, A and B, and its RNA expression pattern suggests cardiac but not skeletal muscle enrichment, implicating a role for DTEF-1 in cardiac-specific MCAT-dependent gene expression, as evidenced by DTEF-1 *trans*-activation of cardiac-specific promoters. Specifically, murine DTEF-1 is important in mediating the effects of α-adrenergic stimulation of cardiac myocytes, potentially contributing to pathophysiological responses of the myocardium to states of increased afterload (Maeda et al. 2002b).

RTEF-1 knockout transgenic mice caused pre-implantation embryonic lethality (Nishioka et al. 2008; Yagi et al. 2007), which might mask the other functions of RTEF-1 in adult mice. Although inactivation of RTEF-1 expression in post-implantation embryos did not show significant morphological defects (Yagi et al. 2007), transgenic mice with cardiac specific overexpression of RTEF-1 developed heart conduction defects associated with altered connexin phosphorylation (Chen et al. 2004). ECGs revealed prolongation of the PR, QRS, and AH intervals and the appearance of progressive atrial arrhythmias in RTEF-1 mice. Conduction defects were correlated with the dephosphorylation of connexin40 (Cx40) and connexin43 (Cx43), as well as the up-regulation of protein phosphatase 1β (PP1β). Increased levels of dephosphorylated Cx43 at the cardiac gap junctions in alpha-MHC/RTEF-1 mice indicated that defective conduction is a result of impaired gap-junction conductance. Additionally, recent literature suggests that RTEF-1 is required for proper initiation of myoblast differentiation through regulation of myogenin (Benhaddou et al. 2011). More recently, a cofactor IRF2BP2, was discovered in a complex with TEF-1 in myoblasts to facilitate activation of VEGFA expression (Teng et al. 2010). Additionally, RTEF-1 is also able to interact with IRF2BP2, but requires an additional cofactor, the vertebrate VGLL4, to coactivate the VEGFA promoter (Teng et al. 2010).

TEF family in the regulation of cardiac hypertrophy

Cardiac hypertrophy occurs in response to stress on the heart, caused by increased workload or injury. At the cellular level, it is characterized by increases in cell size, protein synthesis and by reactivation of the fetal cardiac genes, such as β-myosin heavy chain (β-MHC) and skeletal α-actin (SKA) (Kariya et al. 1994). Stimulation of the α_1-adrenergic response induces hypertrophy in cardiac myocytes and activates SKA and β-MHC expression (Kariya et al. 1994). TEF-1 and RTEF-1 are both involved in the α_1-adrenergic-stimulated hypertrophy of cultured cardiac myocytes by regulating the α_1-adrenergic activation of SKA and β-MHC (Stewart et al. 1998). The promoter of SKA and β-MHC both require an M-CAT element for activation of the α_1-adrenergic stimulation (Kariya et al. 1994; Karns et al. 1995). The TEF-1 overexpression trans-activated the minimal β-MHC promoter and interfered with the minimal SKA promoter and that RTEF-1 trans-activated both the minimal β-MHC and SKA promoters. RTEF-1 potentiated the α_1-adrenergic responses of the SKA promoter whereas TEF-1 had no effect. The β-MHC promoter required an intact M-CAT element to respond to TEF-1 and RTEF-1, whereas the SKA promoter M-CAT was required for the TEF-1 response, but not for the RTEF-1 response. These results indicate a possible role of RTEF-1 in mediating the α_1-adrenergic response in hypertrophic cardiac myocytes, in which SKA promoter–specific cofactors may be involved.

Studies on TEF-1 gene inactivation and retroviral gene trapping in embryonic stem cells demonstrated an essential role for TEF-1 in proper heart development (Chen et al. 1994; Sawada et al. 2008). Further research in TEF-1 transgenic mice demonstrated slower skeletal muscle contractile and increased glycogen synthase kinase-3 activity (Tsika et al. 2008). Additionally, Tsika *et al*. reported that the TEF-1 mice revealed an increase in TEF-1 can induce characteristics of cardiac remodeling that occur over time, such as significantly increased levels of βMyHC, SKA, ANP, and BNP in both neonatal and adult hearts, and can be associated with pathological hypertrophy and the failing heart (Tsika et al. 2010).

Furthermore, assessment of cardiac function by MRI analysis revealed that at 10 months of age, the hearts of TEF-1 transgenic mice displayed a significant reduction in cardiac output, stroke volume, ejection fraction, and percent fractional shortening with an increase in end systolic volume, consistent with impaired systolic function of the left ventricle (Tsika et al. 2010).

Previously described as a cardiac-enriched TEF family member that regulates cardiac gene expression that is expressed in the early embryo, DTEF-1 is also up-regulated during biomechanical stress on the heart, such as the cardiac hypertrophic response, consistent with its chromatin binding and transactivating properties. During volume loading of the left ventricle and pressure loading of the right ventricle, DTEF-1 is up-regulated more on the right side of the heart. DTEF-1 up-regulation during biomechanical stress could be an asymmetric, chamber-specific response or may act as a pressure-responsive rather than volume-responsive transactivator (Azakie et al. 2006). PARP, a known coactivator of TEF-1, has been implicated in myocardial cell hypoxic-ischemic injury and cardiomyocyte survival (Butler and Ordahl 1999). Furthermore, TEF-1 becomes heavily ADP-ribosylated, a process amenable to inhibition, and therefore a potential target for pharmacotherapy of heart failure (Szabo 2005).

A recent report from our lab demonstrated a role for RTEF-1 in cardiac hypertrophy using endothelial-specific RTEF-1 transgenic mice (VE-CAD/RTEF-1). VE-CAD/RTEF-1 mice exacerbated cardiac hypertrophy via the mechanism of RTEF-1 transcriptional up-regulation of VEGF-B. VE-CAD/RTEF-1 mice had elevated VEGF-B expression and developed more significant cardiac hypertrophy after the pressure overload stimulus. Additionally, RTEF-1 stimulated VEGF-B promoter activities via binding to MCAT elements and regulated VEGF-B expression in endothelial cells (Xu et al. 2011).

TEF family in the regulation of vascular smooth muscle cells

In addition to cardiac myocytes, M-CAT elements play a key role in the transcriptional activation of multiple genes in myofibroblasts, smooth muscle cells and skeletal muscle cells, specifically cardiac troponin T (Mar and Ordahl 1988), SKA (Karns et al. 1995), and smooth muscle α-actin (Gan et al. 2007), by binding with TEF family members.

In particular, smooth muscle α-actin (SM α-actin) is first expressed in vascular SMCs during differentiation of the outflow tract and formation of the aortic arch. Yet in adult animals, it is highly restricted to SMCs under normal circumstances (Li et al. 1996). Moreover, expression of SM α-actin is activated in myofibroblasts within granulation tissue as part of the stromal response with neoplasia and during tissue fibrosis (Gabbiani 2003). Results from transgenic mice containing an SM α-actin promoter–enhancer–LacZ reporter gene containing M-CAT element mutations showed that mutations of M-CAT elements selectively abolished LacZ transgene expression in myofibroblasts within granulation tissue of skin wounds (Gan et al. 2007). Furthermore, siRNA experiments and chromatin immunoprecipitation (ChIP) assays revealed RTEF-1 regulates SM α-actin transcription in myofibroblasts, but not in differentiated SMCs. However, TEF-1 did bind to the same region in differentiated SMCs (Gan et al. 2007).

TEF family in the regulation of endothelial function

Endothelial cells are modulators of cardiovascular function. Endothelial dysfunction during the pathological process can induce loss of homeostasis in the cardiovascular system and cause cardiovascular diseases such as hypertension, cardiac infarction, hypertrophy and heart failure, etc. Hypoxia/ischemia triggers metabolic and angiogenic responses in endothelial cells. RTEF-1 is up-regulated in endothelial cells and activates transcription of

VEGF by binding to its promoter (Shie et al. 2004). Interestingly, RTEF-1 stimulates VEGF expression via binding to the Sp1 element in a GC-rich region of VEGF promoter instead of an M-CAT element. Appukattan *et. al.* reported that in addition to 1305-bp and 937-bp RTEF-1 transcripts found in human ocular vascular endothelial cells during normoxia, a 447-bp novel transcript is present in cells under hypoxic conditions (Appukuttan et al. 2007). Additionally, alternatively spliced products are also produced under normoxia compared with hyperoxic and hypoxic conditions in mouse neural retina cells (Appukuttan et al. 2007). These alternatively spliced variants of human RTEF-1 transcripts are able to potentiate expression of VEGF (Appukuttan et al. 2007).

Hypoxia-inducible factor-1α (HIF-1α) which is degraded under normoxia but stabilized in hypoxia, controls genes that are involved in the hypoxic response, such as erythropoietin (EPO), vascular endothelial growth factor (VEGF), and glucose transporter-1 (Glut1). RTEF-1 is one of the key regulators that activated HIF-1α transcription directly in hypoxic endothelial cells. Forced over-expression of RTEF-1 in endothelial cells helps maintain HIF-1α mRNA levels in hypoxia conditions (Jin et al. 2011). RTEF-1 activated HIF-1α promoter activity by binding to the M-CAT like sequence located down-stream of the NF-κB site on the 5′ untranslated region (5′UTR). Transgenic mice that specifically over-express RTEF-1 in endothelial cells showed higher levels of HIF-1α and a higher angiogenic ability in the hind limb ischemia model than wild type mice (Jin et al. 2011).

As stated previously, novel RTEF-1 transcripts have been reported to be present within human ocular vascular endothelial cells and mouse neural retina during normal and oxygen-induced retinopathy (OIR) development, and these alternatively spliced products are produced under hyperoxic and hypoxic conditions. Alternative spliced variants of human RTEF-1 transcripts are able to potentiate expression from the VEGF proximal promoter region. Analysis with deletion promoter constructs determined that all isoforms required the presence of Sp1 elements for efficient activation and that the hypoxia response element (HRE) was not essential for enhancement (Appukuttan et al. 2007; Shie et al. 2004).

Recent studies on RTEF-1 have confirmed its angiogenic properties in endothelial cells; Liu, *et al*. demonstrated a novel transcriptional mechanism that mediates VEGF-A^{165}-induced Down Syndrome Candidate Region 1 isoform L (DSCR1-1L) expression, in which VEGF-A^{165} induced the interaction of RTEF-1 with the M-CAT *cis* element of the DSCR1-1L promoter (Liu et al. 2008). Interestingly, DSCR1 is up-regulated in cultured vascular endothelial cells by VEGF-A^{165} and provides a negative feedback loop that inhibits VEGF-A^{165}-induced angiogenesis (Hesser et al. 2004; Liu et al. 2003; Minami et al. 2004). Furthermore, RTEF-1 was shown to be required for VEGF-induced HUVEC proliferation, migration, tube formation, and angiogenesis (Liu et al. 2011).

Clinical Perspectives and Conclusions

Cellular and molecular mechanisms of cardiovascular diseases have been studied *in vitro* and *in vivo* in hopes to provide molecular targets for a therapeutic purpose. However, therapeutic clinical trials using recombinant protein or gene therapy formulations of a single target have yielded only modest success to date. Emerging evidence indicates that a transcriptional regulator with the ability to coordinate multiple signaling molecules may be an improved therapeutic strategy. Multiple lines of evidence indicate that the TEF family of transcription factors plays important roles in the regulation of genes in cardiovascular system. As stated earlier, TEF-1 is required for cardiac morphogenesis (Chen et al. 1994). RTEF-1 altered connexin phosphorylation to impact cardiac conduction (Chen et al. 2004). RTEF-1 is also involved in hypoxia-induced angiogenesis (Shie et al. 2004), which could lead to a potential therapeutic target to enhance collateral vessel formation in coronary artery

disease and cardiac hypertrophy (Xu et al. 2011). Additionally, the discovery that ETF-1 controls myocardin expression in the cardiac and smooth muscle cell lineages can offer possibilities for manipulating myocardin expression in various therapeutic settings (Creemers et al. 2006). DTEF-1 expression occurs very early in embryogenesis and activates cardiac promoters, that could be an early marker of the myocardial phenotype (Azakie et al. 1996). As a transcription factor that plays an important role in cardiovascular function, the members of the TEF family are potential therapeutic and diagnostic targets for cardiovascular disease.

Acknowledgments

We thank Ms. Melissa Philbrick for editing the manuscript. This work was supported by NIH grants HLR01082837 (Li), and T32 training award, HL007917 (Messmer-Blust).

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Table 1

Nomenclature of TEF family members. In this review, names listed in the first column will be used.

TEF Family	Synonyms	References
TEF-1	TEAD1, NTEF-1	Xiao, et al. 1991
RTEF-1	TEAD4, TEF3, ETFR-2, FR-19	Jacquemin, et al. 1996; Stewart, et al. 1996
ETF	TEAD2, TEF4	Jacquemin et al. 1999 Yasunami et al. 1995
DTEF-1	TEAD3, TEF5, ETFR-1	Azakie, et al. 1996; Jiang, et al. 1999

Table 2

Transgenic mice with modified TEF family genes.

Genetic modification	Method	Effects	References
TEF-1 knock-out	Retroviral gene trap in ES cells	Lethality from defective heart development at E12.5: enlarged pericardial cavity bradycardia, a dilated fourth ventricle in brain, and an abnormally thin ventricular wall	Chen, Friedrich et al. 1994, Genes & Development
Skeletal muscle over-expression TEF-1	HA-tagged TEF-1 driven by MCK promoter	Slower skeletal muscle contractile and increased glycogen synthase kinase-3 activity	Tsika, Schramm et al. 2008, and Tsika, Ma et al. 2010, JBC
RTEF-1 knock-out	Retroviral gene trap in ES cells	Pre-implantation embryo lethality; Defects in the production of trophoblast stem cells	Yagi, Kohn et al. 2007, Development
Cardiac over expression of RTEF-1	RTEF-1 driven by a rat α-myosin heavy promoter	Heart conduction defects associated with altered connexin phosphorylation	Chen, Baty et al. 2004, Circulation
Endothelial over expression of RTEF-1	RTEF-1 driven by VE Cadherin promoter	Cardiac hypertrophy and increased angiogenesis from ischemia	Xu, Jin et al. 2011, Cardiovas. Res. and Jin, Wu et al. 2011, JBC
ETF conditional knock-out	Cre/Lox recombination	Increased risk of exencephaly (neural tube closure defect)	Kaneko, Kohn et al. 2007, Genesis