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EDITORIAL COMMENT

TCF7L1 Exacerbates Abdominal Aortic Aneurysm Prevalence and Severity*

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Abdominal aortic aneurysm (AAA) is the second most prevalent aortic disease after atherosclerosis and is the ninth leading cause of death, claiming 200,000 lives per year worldwide.[1] Aneurysm weakens the aortic wall, which can lead to rupture and subsequent massive internal bleeding and death. There is currently no effective nonsurgical treatment for AAA. It has long been known that vascular smooth muscle cell (VSMC) migration, proliferation, and apoptosis contribute to the pathogenesis of AAA. VSMCs in normal blood vessels display a contractile phenotype, which helps maintain vascular tone, tensile strength, and blood pressure. Through a process referred to as phenotypic switching or modulation, VSMCs can dedifferentiate into a synthetic phenotype, characterized by reduced contractile protein expression and increased production of matrix metalloproteinases, leading to a loss of tensile strength. Recent work has established that dedifferentiated VSMCs can express certain genes and functions associated with fibroblasts, macrophages, adipocytes, and osteoblasts (reviewed in Sawada et al[2]).

In this issue of *JACC: Basic to Translational Science*, Wang et al[3] examined AAA tissue from human aortae and from a mouse model of AAA and found increased expression of TCF7L1 messenger RNA and protein. TCF7L1 (also known as TCF3) is a member of the T-cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors and, like several other members of the TCF/LEF family, regulates transcription downstream of the canonical Wnt/β-catenin pathway via direct binding to *cis*-acting elements in promoters and enhancers of Wnt signaling-dependent genes.

While it was previously known that TCF7L1 is strongly expressed in adult human aortic tissue, there is comparatively little known about the role of TCF7L1 in VSMCs. TCF7L2, on the other hand, is associated with atherosclerosis and type 2 diabetes and its overexpression in mice inhibits intimal hyperplasia. Thus, the present study by Wang et al[3] introduces TCF7L1 as a new possible regulator of AAA. Indeed, the increased expression of TCF7L1 in AAA tissue prompted the investigators to hypothesize that TCF7L1 activity might contribute to the pathophysiology of AAA. Using knockdown and overexpression strategies in mice, the investigators show that TCF7L1 activity promotes AAA formation. Wang et al[3] found that knockdown of TCF7L1 reduced AAA incidence, whereas overexpression of TCF7L1 increased AAA incidence. Interestingly, they found that TCF7L1 expression also correlated with MMP2 expression and cell migration. In contrast, they found that TCF7L1 negatively correlated with markers of VSMC differentiation, such as α-smooth muscle actin (SMA) and SM22-α. Together, these observations suggest that TCF7L1 promotes phenotypic switching of VSMCs from the differentiated, contractile phenotype to a proliferative, migratory phenotype. If correct, this model suggests that TCF7L1 expression could

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contribute to the pathophysiology of AAA by compromising the structural integrity of the aortic wall by down-regulation of the VSMC contractile phenotype.

To test their model, Wang et al[3] conducted in vitro experiments in which TCF7L1 was either knocked down or overexpressed in cell culture. Knockdown of TCF7L1 suppressed the stimulatory effect of angiotensin II on VSMC migration in Transwell and scratch wound assays. In contrast, TCF7L1 overexpression stimulated VSMC migration in both these systems. Together, these results support the idea that TCF7L1 activity promotes VSMC phenotypic switching to the migratory phenotype. The investigators further found that the stimulatory effect of TCF7L1 overexpression on VSMC migration was inhibited by overexpression of serum response factor (SRF), which increased α-SMA and SM22-α expression. Conversely, the inhibitory effect of TCF7L1 siRNA knockdown on VSMC migration was blocked by knockdown of SRF, which increased migration. These results are potentially interesting because SRF is a ubiquitous transcription factor that drives the expression of VSMC contractile genes and promotes the VSMC differentiation phenotype.

To gain insight into possible mechanisms for how TCF7L1 activity might antagonize SRF, Wang et al[3] used luciferase assays to show that TCF7L1 can suppress the activity of the *SRF* promoter in cell culture studies. Specifically, they found that mutation of a putative TCF7L1 binding site (site 1) in the *SRF* promoter resulted in loss of TCF7L1-dependent repression of the *SRF* promoter. These preliminary observations suggest that the mechanism of action of TCF7L1 on VSMC phenotype, at least in part, might be caused by suppression of *SRF* expression. While the possible regulatory relationship between TCF7L1 and SRF is interesting, further experiments extending these findings should determine more conclusively whether inhibition of *SRF* promoter activity by TCF7L1 involves direct interaction with DNA by chromatin immunoprecipitation of the *SRF* promoter in VSMCs and actual tissue and whether the suppression of *SRF* promoter activity by TCF7L1 involves interactions with other proteins. For example, it is known that TCF7L1 depletion stimulates TCF7L2 and β-catenin binding to the *DKK4* promoter in human colorectal cancer cells.[4] In those same studies, it was also shown that TCF7L1 can recruit histone deacetylase 1 and C-terminal binding proteins to the *DKK4* promoter to repress *DKK4* transcription.[4] It would be interesting to learn whether similar mechanisms involving TCF7L1 are functioning at the *SRF* promoter in VSMCs.

The present study by Wang et al[3] indicates that TCF7L1 expression contributes to AAA formation, at least in a mouse model involving angiotensin II infusion, and suggests that TCF7L1 may serve as a novel therapeutic target in AAA. This opens several possible lines of future investigation. For example, the effect of TCF7L1 knockdown should also be studied in other models of AAA (such as extraluminal calcium chloride, elastase infusion, or anterior patch models) to determine whether the observations presented in the current study apply broadly to AAA or if the role of TCF7L1 is more restricted. It will also be interesting to learn whether variants in human *TCF7L1* are associated with increased or decreased risk of AAA, and if so, how any identified variants affect TCF7L1 expression and function.

In addition, single-cell transcriptomics should better define whether TCF7L1 function and its interaction with SRF affects all VSMCs or whether there are VSMC subtypes that selectively express TCF7L1. This type of analysis might also help to clarify the involvement of other transcription factors and transcriptional cofactors. For example, single-cell RNA-sequencing identified extensive phenotypic plasticity in atherosclerotic lesions with KLF4 controlling transition to different phenotypes, including osteogenic cells.[5] It would be interesting to understand the transcriptional profile of VSMCs that express higher levels of TCF7L1 to gain insight into possible mechanisms, other than SRF regulation, that might contribute to the observed phenotypic switching.

The role of β-catenin and canonical Wnt signaling in SMC migration and AAA formation mediated by TCF7L1 also remains unresolved. For example, what effects do mutation or deletion of the β-catenin interaction domain in TCF7L1 have on its ability to suppress the *SRF* promoter, decrease α-SMA and SM22-α levels, increase MMP2 expression, promote VSMC migration, and accelerate AAA formation?

Finally, because Wang et al[3] injected mice with an adeno-associated virus 3 weeks before infusion with angiotensin II, the AAA model used in this study tested the ability of TCF7L1 to affect AAA formation rather than to treat established disease, a limitation identified by others.[2] Indeed, there did not appear to be a change in mouse survival when TCF7L1 was overexpressed or knocked down, compared with respective control animals, possibly suggesting that TCF7L1 may contribute to the aneurysm itself and

that other factors may be involved in rupture and subsequent morbidity and mortality caused by AAA. Ultimately, a detailed mechanistic understanding of how TCF7L1 regulates AAA formation, what factors it interacts with, and what genes it regulates in VSMCs may provide opportunity for therapeutic intervention for AAA and potentially other vascular disorders.

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