Novel role of NANOG in smooth muscle cell phenotypic modulation during aortic dissections

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Central Message

The regulatory role of NANOG offers a novel molecular pathway in thoracic aortic dissection.

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Stanford acute type A aortic dissection (TAD) is a life-threatening process that has remained a persistent challenge for cardiovascular surgeons. Although the most common initiating physiological event is an intimal tear after a sudden increase in blood pressure, mechanisms predisposing to aortic wall degeneration and dissection remain undefined. An improved molecular understanding of aortic dissection pathophysiology will facilitate the identification of individuals who may benefit from early surgical intervention.

Vascular smooth muscle cells (VSMCs) play a key role in maintaining the integrity and regulation of the aortic wall. Because there is a paucity of in vivo aortic dissection animal models, in vitro VSMC model systems provide a powerful tool to study the molecular mechanisms of TAD. VSMCs can shift from a normal quiescent contractile phenotype toward a synthetic phenotype, characterized by proliferation, migration, and extracellular matrix remodeling. This VSMC dedifferentiation has been reported to play an important role in aneurysm formation.¹

In this issue of the *Journal*, An and colleagues² expand their earlier findings regarding the molecular pathways involved in TAD.^{3,4} They report greater levels of NANOG and osteopontin (OPN) in both surgical aortic specimens and VSMC cultures derived from patients with TAD compared with control patients. In a series of elegant experiments on VSMCs, the authors demonstrate that NANOG mediates the phenotypic switch to synthetic phenotype in vitro and positively controls the expression of OPN. Furthermore, they show that knock down of OPN significantly decreases NANOG-induced phenotypic switch, suggesting the mediatory role of OPN in the process.

Despite its advantages, in vitro modeling of TAD using VSMCs has obvious downsides, including the fact that surgical specimens are obtained after the disease state already has occurred; therefore, it is challenging to study early mechanisms of dissection formation. Furthermore, the current study does not demonstrate a causal link between development of TAD and NANOG-mediated

phenotypic switch. Whether the greater expression of NANOG in VSMCs eventually leads to aortic dissection or instead represents a triggered response mechanism after the dissection occurred remains to be determined. Finally, although the authors focus on VSMC, the aorta consists of more cell types, including endothelial cells and fibroblasts, which may prove to be important.

Nevertheless, in line with the well-established role of NANOG in proliferation and biology of pluripotent stem cells^{5,6} and its emerging role in cancer biology,⁷ the current study highlights the promise of NANOG as a biomarker for synthetic VSMCs and TAD. Furthermore, considering the role of OPN as a marker for synthetic phenotype in SMCs,^{8,9} demonstration of the regulatory role of NANOG upstream of OPN offers a novel molecular pathway for the phenotypic switch. For surgeons who investigate and operate on patients with TAD, this article represents an intriguing breakthrough. Although not yet ready for clinical application, in the era of precision medicine, these basic science findings will help stimulate and test new hypotheses, with the ultimate goal of identifying patients at increased risk to dissection.

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