The Translation of Transcription

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Defining the factors that mediate the phenotype of vascular smooth muscle cells (VSMCs) is important in the identification of new therapeutic targets for vascular diseases that are associated with VSMC phenotypic modulation. This modulation is characterized by a switch from a quiescent “contractile” state to an activated “synthetic” state and is an integral part of the acute response to vascular injury.1 This phenotypic switch is the result of a complex pattern of gene regulation suggesting an important role for regulation at a transcriptional level. As such, transcription factors involved in this regulation may be “druggable” targets for the prevention and treatment of vascular diseases. In this issue of Circulation Research, an article by Fujiu and colleagues2 adds an important new chapter in a translational story that began with the identification of Kruppel-like zinc-finger transcription factor 5 (KLF5) and its role in transcriptional regulation of VSMCs. KLF5 is a key determinant of smooth muscle phenotype3 through regulation of expression of a number of proteins associated with a quiescent or contractile phenotype including SMemb/non-myosin heavy chain-B (NMMHC-B), platelet-derived growth factor-A (PDGF-A), and smooth muscle α-actin. This new study demonstrates that inhibition of this transcription factor may represent an exciting new modality to prevent or treat the vascular response to injury associated with phenotypic modulation of VSMCs including restenosis.

Soon after Andreas Gruentzig presented the first human experience with percutaneous coronary angioplasty, it was recognized that the initial success of coronary interventions is lost in a significant number of patients because of renarrowing or restenosis.4,5 The advent of coronary stenting marked the first substantial departure from the high restenosis rates observed with balloon angioplasty.6,7 Improvements in the science of biomaterials and an increased understanding of vascular biology led to the development of drug eluting stents (DES) that have had a major impact on restenosis after coronary stenting.5–10 Four years and more than a million drug-eluting stent implantations later, it appears that DES, although safe and very effective in a majority of lesions, still have a number of limitations.11 Significant restenosis rates are observed in certain situations, such as in side branches of bifurcation lesions, small vessels, and diabetics, with restenosis rates sometimes as high as 10% to 38%.12,13 Additional concerns have been raised regarding delayed healing after DES with associated coronary aneurysm formation, late neointima proliferation, and a small number of late in-stent thrombosis.11–14 Therefore, the report of Fujiu and coauthors in the current issue of this journal is timely and deserves attention.

In 1999 in 2 articles in Circulation Research, this group led by Nagai reported that KLF5 was activated by inflammatory stimuli through the mitogen-activated protein–kinase pathway15 and was markedly induced in “synthetic” smooth muscle cells present within the neointima after balloon injury in the rat aorta.3 Three years later this same group of investigators demonstrated that mice in which one KLF5 allele was deleted (Klf5<sup>−/−</sup>) had an attenuated response to arterial cuffing.16 Furthermore, they demonstrated that angiotensin II administration induced KLF5 expression associated with activation of PDGF-A and TGF-B in hearts and that this process was decreased in Klf5<sup>−/−</sup> mice.

A critical step in the translation of these important original studies was the identification of small molecules that regulate KLF5 activity. These same investigators demonstrated that a synthetic retinoic acid receptor alpha (RARα) agonist, Am80, reduced PDGF-A promoter activity in cells overexpressing KLF5 whereas LE135, a synthetic retinoic acid receptor alpha (RARα) antagonist, enhanced PDGF-A activity. They report that Am80 has been safely used to treat promyelocytic leukemia in humans. With these valuable reagents in hand, they showed that Am80 administration reduced neointimal thickening after arterial cuffing.

The current study from Fujiu and colleagues2 extends their important work in a translational fashion by further exploring the role of KLF5 in controlling SMC phenotype while applying Am80 to a more clinically relevant model of vascular injury (neointimal formation after stenting). They demonstrate that RARα and RXRα bind the PDGF-A promoter via an interaction with KLF5. Am80 was shown to disrupt this transcriptional complex formed by KLF5, RAR, and RXR on the PDGF-A promoter (Figure). Am80 was also shown to upregulate the expression of smooth muscle myosin heavy chain (SM-MHC) and smooth muscle α-actin consistent with favoring the SMC “contractile” phenotype. These phenotypic changes were associated with reduced VSMC migratory and proliferative capacity. Importantly, the oral administration of Am80 reduced intimal formation and associated SMC phenotypic modulation in a rabbit model of iliac stenting. Thus the fundamental understanding of the regulation of this transcriptional complex has led to a promising translational strategy for vascular disease.

Of course, much work remains in the basic science and translation of these studies. It remains to be determined whether the effects of Am80 and KLF5 are through autocrine or paracrine effects and to describe the coordinated complex...
of proteins that are regulated by KLF5. Testing for safety and efficacy of Am80 in larger animal models of stenting and development of a delivery strategy remain important barriers to clinical translation.

This rapid translation of these transcriptional studies highlights the importance of basic science and the essential and important step of identifying small molecule regulators of key biological pathways. In less than a decade, this group has generated promise of an orally active molecule with potential inherent pharmacology, pharmacokinetics, and safety profile as well as the mundane but important issue of financial backing, intellectual property, and ownership. Regardless, based on the rapid progression of this translational story, we have not likely heard the last chapter of KLF5 modulation in vascular disease.

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References


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