Transient receptor potential cation channel subfamily C member 6 participates in functional regulation of vascular smooth muscle cells

Ljubica Matic, MSc, PhD, *Stockholm, Sweden*

Endovascular interventions trigger a healing response in the intima (intimal hyperplasia, restenosis, and in stent stenosis after angioplasty), which is characterized by a burst of smooth muscle cell (SMC) activity. SMCs have traditionally been recognized as the main structural cell responsible for preserving vessel integrity and stability, whereas their reparative function is based on the phenotypic plasticity and capacity to dedifferentiate into migroproliferative synthetic cells that invade the intima and secrete extracellular matrix. Studies into the molecular mechanisms of SMC activation upon arterial injury are therefore vital, because they may lead to novel therapies to modulate and control the vascular healing response.

With this aim, Hart Smith et al[1] have focused on investigating the function of transient receptor potential cation channel subfamily C member 6 (TRPC6) motivated by a body of literature showing that calcium channels are essential regulators of key SMC properties.[2] Previous studies from this group have shown improved endothelial healing upon arterial injury in TRPC6$^{-/-}$ compared with wild-type mice, and this effect was specific to the high-fat diet condition because TRPC6 is potently activated by lipid oxidation products.[3] Here, the authors further this data showing that the depletion of TRPC6 also promotes SMC response and intimal hyperplasia formation. The expression of contractile SMC markers after vascular challenge by carotid wire injury in vivo was decreased in TRPC6$^{-/-}$ mice and associated with SMC phenotypic switch, which was also confirmed in isolated primary SMC cultures. Although this data should be contrasted against the fact that after 4 weeks of injury there was surprisingly little healing response triggered in the intima of wild-type animals,[4] it is important that the study by Smith et al[1] has used an in vivo model for assessment of SMC response. In contrast, Numaga-Tomita et al[5] recently used pharmacologic inhibition of TRPC6 in vitro and showed that this approach facilitated contractile differentiation of SMCs through plasma membrane hyperpolarization. These results may be reconciled by the fact that more complex systemic mechanisms could be activated in vivo to compensate for the loss of TRPC6, but clearly some of the main questions around the role of TRPC6 in SMC phenotypic modulation under different conditions remain unresolved. Nevertheless, it seems clear that TRPC6 contributes to the regulation of SMC phenotype and the article by Smith et al[1] paves the way for more detailed investigations in this direction.

Interestingly, defects from gain-of-function TRPC6 mutations, reflected as enhanced TRPC6 expression and protein activity, have also been shown to contribute to both cardiac and renal disease, where angiotensin II, reactive oxygen species and other factors can stimulate drastic increases in calcium influx through this channel causing, that is, fibrosis and podocyte hypertrophy.[6] Furthermore, the process of intimal hyperplasia shares features with fibrous cap formation in atheroma, where SMCs have recently been shown to act as the predominant cell fraction.[7,8] Taken together, this particular calcium ion channel may present an attractive avenue for exploration into the therapeutic modulation not only of vascular SMC activity, but also in other diseases that may share common mechanisms on cellular and molecular level.

The opinions or views expressed in this commentary are those of the authors and do not necessarily reflect the opinions or recommendations of the Journal of Vascular Surgery: Vascular Science or the Society for Vascular Surgery.

REFERENCES

1. Suri P, Birnbaumer L, Rosenbaum MA, et al. Canonical transient receptor potential 6 channel deficiency promotes smooth muscle cells dedifferentiation and increased proliferation after arterial injury. JVS-Vascular Science 2020;1:136-50.
2. Wamhoff BR, Bowles DK, McDonald OG, Sinha S, Somlyo AP, Somlyo AV, et al. L-type voltage-gated Ca2+ channels modulate expression of smooth muscle differentiation marker genes via a rho kinase/myocardin/SRF-dependent mechanism. Circ Res 2004;95:406-14.
3. Rosenbaum MA, Chaudhuri P, Graham LM. Hypercholesterolemia inhibits re-endothelialization of arterial injuries by TRPC channel activation. J Vasc Surg 2015;62:1040-7.e2.

From the Vascular Surgery, Department of Molecular Medicine and Surgery, Karolinska Institute.

Author conflict of interest: none.

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS-Vascular Science policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

JVS—Vascular Science 2020;1:166-7

2666-3503

https://doi.org/10.1016/j.jvssci.2020.07.004

4. Rykaczewska U, Suur BE, Rohl S, Razuvaev A, Lengquist M, Sabater-Lleal M, et al. PCSK6 is a key protease in the control of smooth muscle cell function in vascular remodeling. Circ Res 2020;126:571-85.
5. Numaga-Tomita T, Shimauchi T, Oda S, Tanaka T, Nishiyama K, Nishimura A, et al. TRPC6 regulates phenotypic switching of vascular smooth muscle cells through plasma membrane potential-dependent coupling with PTEN. FASEB J 2019;33:9785-96.
6. Staruschenko A, Spires D, Palygin O. Role of TRPC6 in progression of diabetic kidney disease. Curr Hypertens Rep 2019;21:48.
7. Shankman LS, Gomez D, Cherepanova OA, Salmon M, Alencar GF, Haskins RM, et al. KLF4-dependent phenotypic modulation of smooth muscle cells has a key role in atherosclerotic plaque pathogenesis. Nat Med 2015;21:628-37.
8. Perisic Matic L, Rykaczewska U, Razuvaev A, Sabater-Lleal M, Lengquist M, Miller CL, et al. Phenotypic modulation of smooth muscle cells in atherosclerosis is associated with downregulation of LMOD1, SYNPO2, PDLIM7, PLN, and SYNM. Arterioscler Thromb Vasc Bio 2016;36:1947-61.