Editorial

Smooth Muscle Cells Move With Mitochondria

Ning Shi, Shi-You Chen

Vascular smooth muscle cells (SMCs) are essential components in blood vessel walls and responsible for maintenance of blood vessel structure and function. Normally, SMCs reside in medial layers of blood vessels and do not exhibit migration potential. Under pathological conditions, however, medial SMCs migrate to intimal space where they proliferate and secrete extracellular matrix, contributing to vascular remodeling and repair, the featured characteristics of several cardiovascular diseases including atherosclerosis and restenosis after angioplasty. PDGF (platelet-derived growth factor) is a potent stimulator for SMC migration and has been used widely to examine the underlying molecular mechanisms.[1] Although the research on SMC migration has mostly focused on the cellular regulation, recent studies have narrowed down to the subcellular levels, especially mitochondria.[2–6] However, the precise mechanisms underlying mitochondrial functions in SMCs remain largely unknown. The new study by Nguyen et al[7] in this issue makes the elegant and exciting discovery that mitochondrial Ca^{2+}/CaMKII (calmodulin-dependent kinase II), a serine/threonine-specific protein kinase necessary for cellular Ca^{2+} homeostasis, promotes mitochondrial motility, serving as an important regulator for PDGF-induced SMC migration.

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Mitochondria are double membrane-bound cytoplasmic organelles found in large quantities in most cell types and play a critical role in the generation of metabolic energy. A previous study has demonstrated that the increase in mitochondrial motility because of activation of Ca^{2+} signaling is essentially required for SMC proliferation.[8] As an energy-demanding process, SMC migration also necessitates the involvement of mitochondria. The imbalance between mitochondrial fission (division of a single mitochondrion into 2 or more mitochondria) and fusion (the opposite process) seems to have a profound effect on PDGF-induced SMC migration.[2] However, the molecular mechanisms underlying the mitochondrial dynamics beyond fission and fusion remain unclear, limiting our understanding of mitochondrial biology and thus impeding the development of potential therapeutic strategies treating cardiovascular diseases.

The study by Nguyen et al[7] provided new insights linking mitochondria dynamics to SMC migration. Using a series of gain- and loss-of-function assays, the authors delicately integrated disparate intramitochondrial molecular events into a novel CaMKII-mediated mechanism regulating SMC migration (Figure). PDGF-induced Ca^{2+} influx triggers reciprocal activation between CaMKII in the mitochondrial matrix and mitochondrial Ca^{2+} uniporter, and this feed-forward circuit enhances mitochondrial Ca^{2+} influx and thus ensures a highly efficient signal transmission to the downstream target GTPase Miro-1 at the outer mitochondrial membrane. The activated Miro-1 then facilitates the physical association of mitochondria with microtubules, promoting mitochondrial translocation to the leading edge of SMCs.[7]

Focal adhesion (FA) turnover and redistribution at the leading edge of SMCs because of the activation of pMLC (myosin light chain) is essential for SMC migration. The new study suggests that mtCaMKII (mitochondrial CaMKII)-mediated mitochondrial mobility to the leading edge is very important for FA turnover.[7] Indeed, inhibition of mtCaMKII reduces pMLC colocalization to FA, decreases FA kinase phosphorylation, and prevents the dynamic changes in FA redistribution.[7] The authors propose that mtCaMKII-facilitated mitochondrial translocation to the leading edge is an additional mechanism controlling the energy source necessary for dynamic FA turnover in SMCs,[7] which is consistent with a previous study demonstrating that local energy demands are coupled to the subcellular targeting of mitochondria during cell migration in cancer cells.[9]

The CaMKII-mediated mechanism seems to be a predominant one for the mitochondrial regulation of SMC migration because overexpression of CaMKII in mitochondria has significant positive while selective blockade of mtCaMKII has substantial negative effects on mitochondrial Ca^{2+} influx and SMC migration.[7] Importantly, consistent with the in vitro observations, transgenic CaMKII inhibition achieved by expressing a peptide inhibitor of CaMKII selectively in SMC mitochondria significantly attenuates vascular injury-induced neointimal hyperplasia,[7] a pathological process involving SMC migration. In the future, SMC lineage tracking mouse model combining with transgenic CaMKII inhibition in SMC mitochondria could be used to firmly establish the role of CaMKII in SMC migration in vivo.

It is worth noting that microtubule inhibitor nocodazole, but not the actin inhibitor cytochalasin D, inhibits the mitochondrial mobility to the leading edge of SMCs, suggesting that mitochondrial translocation is selectively dependent of microtubule dynamics.[7] The results also suggest that the mitochondrial translocation and actin filament assembly may be independently regulated during the SMC migration. Thus, it would be interesting to determine whether CaMKII and actin cytoskeleton assembly are activated through distinct PDGF downstream signaling pathways and whether they are activated at different stages during SMC migration.

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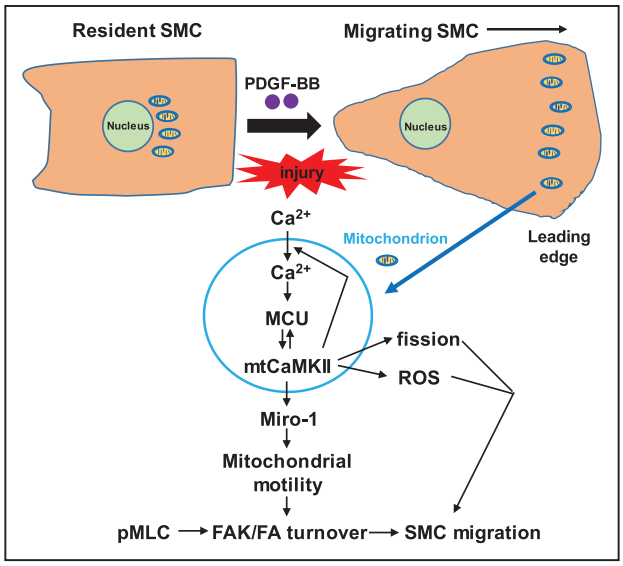

Figure. CaMKII (calmodulin-dependent kinase II)-dependent regulation of PDGF (platelet-derived growth factor)-induced smooth muscle cell (SMC) migration. PDGF promotes Ca^{2+} influx into mitochondria and elicits CaMKII activation in a mitochondrial Ca^{2+} uniporter (MCU)–dependent manner, which in turn regulates MCU activity and Ca^{2+} influx. Activated CaMKII then (1) promotes mitochondrial motility via Miro-1, which promotes focal adhesion (FA) turnover; (2) stimulates mitochondrial fission at the leading edge; and (3) induces mitochondrial reactive oxygen species (ROS) production. These events together lead to SMC migration. mtCaMKII indicates mitochondrial CaMKII; and pMLC, myosin light chain.

SMC migration is an integral process of SMC phenotypic modulation that is characterized by downregulation of SMC contractile proteins with enhanced cell migration, proliferation, and matrix-synthesizing abilities under the influence of various environmental cues.[10] PDGF regulates SMC phenotypic modulation at transcriptional, post-transcriptional, and epigenetic levels.[11–15] Besides SMC migration, CaMKII is also involved in other segments of SMC phenotypic modulation. CaMKII has 4 isoforms termed α, β, γ, and δ. CaMKIIγ isoform correlates with the contractile phenotype and thus regulates the contractile activity and Ca^{2+} homeostasis.[16] On the other hand, synthetic SMCs seem to primarily express CaMKIIδ. CaMKIIδ is important for SMC migration and proliferation both in vitro and vascular hyperplastic remodeling in vivo.[16] Because CaMKII isoform(s) that are present or predominant in mitochondria are currently unknown, the new study by Nguyen et al[7] has used the peptide inhibitor to block all isoforms to test the role of CaMKII in mitochondria translocation and SMC migration. It will be of interest to determine whether CaMKIIδ is the main isoform present in mitochondria and whether blocking CaMKIIδ can achieve a similar effect as blocking all isoforms.

In addition to mediating active mitochondrial translocation, Nguyen et al[7] found that mtCaMKII also regulates mitochondrial fission and the production of reactive oxygen species that are known to play critical roles in SMC migration,[17] suggesting that mtCaMKII may serve as a master mitochondrial regulator in SMC migration. Most importantly, CaMKII is found in mitochondria of SMC in the intimal and subintimal thickening of human coronary arteries from autopsy samples,[7] suggesting that the findings may not only help us better understand the mechanism underlying SMC migration, but also offer a new perspective on the identification of potential therapeutic targets for treating cardiovascular diseases.

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Disclosures

None.

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