Korean Circ J. 2020 Jul;50(7):625-627
https://doi.org/10.4070/kcj.2020.0197
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Editorial

The New Weapon to Inhibit Proliferation and Migration of Smooth Muscle Cell in Neointimal Formation

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▸ See the article "Inhibition of Smooth Muscle Cell Proliferation and Migration by a Talin Modulator Attenuates Neointimal Formation after Femoral Arterial Injury" in volume 50 on page 613

Received: May 7, 2020
Accepted: May 20, 2020

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Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Funding acquisition: Kwon YW; Supervision: Kwon YW; Writing - original draft: Chae CW, Kwon YW; Writing - review & editing: Kwon YW.

Neointimal formation known as thickening of the intima is initiated by mechanical damage to the arterial endothelium, which then promotes local inflammatory cell recruitment, chemokine production and vascular smooth muscle cell (VSMC) migration to the intimal layer. Talin, one of the proteins strong relative to focal adhesions, has a crucial role in VSMC proliferation and migration, thereby promoting progression of atherosclerosis. Therefore, many therapeutic strategies for anti-atherosclerotic drugs have been focused on controlling talin related signaling pathway.

CVD including atherosclerosis is one of the leading causes of mortality globally. Several risk factors such as elevated circulating low-density lipoprotein, obesity, smoking, hypertension, diabetes and ageing contribute atherosclerosis progression.

These external factors cause shear stress, which is directly related to neointimal formation after vascular injury.[1)]

Atherosclerosis is characterized by migration and excessive proliferation of VSMC to the inner membrane due to neointimal formation caused by vascular damage.[2)] Therefore, suppression of activity of VSMC has been one of hot topic in treatment of arteriosclerosis.[2)]

During cell migration, the actin cytoskeleton constantly repeats assembly and disassembly.[3)] This progression could regulate contractile filament directly.[3)] The dynamic actin architecture could be modulated by a variety of signaling pathways and actin-associated protein.[3)] Cell movement modulated by actin-associated protein has mainly been known to adhesive contacts between ECM and transmembrane integrins.[3)] Especially, integrins including α and β subunits directly connect with the ECM and have an important role in migration.[1)] Integrin's intracellular tails could bind to linker proteins such as talin and vinculin.[3)]

During cell adhesion and migration, integrin aggregation is induced and focal adhesion assembly is triggered by recruiting structural proteins such as talin, vinculin, integrin-linked kinase.[4)] The α-actinin as well as focal adhesion related signaling proteins for example,

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focal adhesion kinase (FAK), paxillin, and Rac1 are also necessary for migration in the cell membrane.[5] The recruitment of these proteins that make up focal complexes could lead to large complexes which have the potential to strengthen the linkage of actin filaments.[6] Meanwhile, in order to promote actin polymerization, signaling proteins are required to initiate cascade action. At this time, FAK activation, one of the most cardinal proteins for migration and proliferation of smooth muscle cell (SMC), proceeds, which in turn can activate actin polymerization regulating protein, such as Neural Wiskott-Aldrich syndrome protein.[3]

The above mentioned talin plays a crucial role in focal adhesion assembly.[3] Talin can be a potential key target for the treatment of atherosclerosis because it induces various proteins to gather in the extracellular matrix in combination with integrin. In addition, research has been conducted as one of the proteins that bind to the tail portion of integrin. Subsequently, it was found to bind to actin and more specifically, the complex involved in cell migration.[1]

Talin is a very large protein composed of 2,500 amino acids.[4] Talin consists of a large C-terminal rod domain that contains bundles of alpha helices and N-terminal protein 4.1, ezrin, radixin, moesin (FERM) domain.[4] FERM domain has been studied as a transmembrane protein that binds to the cytoskeleton. The FERM domain consists of 3 subdomains.[7] Each subdomain has a different binding partner, of which the site pivotal in function is the integrin-binding site1 domain.[4] It can bind to the β-integrin subunit, T-lymphoma invasion and metastasis-inducing protein 1, especially FAK, which plays a critical role in cell migration.[3]

Although canonical models also support role of talin in the recruitment and activation of FAK at focal adhesion complex, factors that regulate talin-related downstream signaling molecules have not been identified.[8] Recently, Lim et al.,[2] reported the talin modulator significantly inhibited cell proliferation and suppressed migration of SMC. To be more specific, the talin modulator definitelyinhibited the phosphorylation of FAK at Y397 and at Y925.[2] Autophosphorylation of FAK at Y397 has been previously studied to induce phosphorylation of other sites of FAK, eg Y925. In addition, FAK downstream signaling is induced differently according to phosphorylation of each FAK residue. Therefore, it is very impressive result that the talin modulator inhibits the phosphorylation of various sites of the FAK. Notably, subsequent downregulation of FAK downstream signaling proteins such as mitogen-activated protein kinase and phosphoinositide 3-kinase was dramatically inhibited by talin modulator in human aortic SMC. In addition, the animal model of apolipoprotein E knockout showed remarkable recovery of blood flow by the talin modulator, which showed a promising aspect for future drug development.[2] Talin-FAK-integrin binding is an essential complex for inducing atherosclerosis, and neointimal formation is markedly reduced through a talin modulator that suppresses SMC migration. Therefore, as they suggested, tallin modulators seem to be attractive candidate for anti-atherosclerotic drug development.

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