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Offline: Jukhyun Bio Auditorium (RM.121)

Online: Zoom ID 315 451 8934 (Password: 101320)

ECM regulates endothelial phenotypes through assembly of a PP2A complex

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Abstract

Fibronectin (FN) is deposited in subendothelial basement membranes in athero-prone regions of arteries with disturbed flow, where it promotes endothelial NFkB activation and expression of inflammatory mediators. We previously reported that integrin α5 cytoplasmic tail directly bound phosphodiesterase (PDE) 4D. Mice bearing mutation of the integrin α5 cytoplasmic tail or the integrin binding site in PDE4D had markedly reduced atherosclerosis. Further analysis showed binding of PDE4D to α5 led to dephosphorylation of PDE4D by the phosphatase complex PP2A, which increased PDE and NFkB activity. Further, PDE4D directly bound the B55α subunit of PP2A to localize PP2A to sites of adhesion. These experiments unexpectedly showed that the PDE4D promoted the PP2A-B55α complex assembly and led us to hypothesize that focal adhesion-localized PP2A may have other substrates. We therefore performed phosphoproteomic analysis to compare phosphoprotein profiles between (1) ECs on FN vs. matrigel (MG, basement membrane matrix) or (2) ECs expressing WT PDE4D vs. a mutant PDE4D with deletion of the PP2A-binding domain. Among 205 hits showing >1.5-fold changes in phosphorylation from FN vs. MG analysis, 63 phosphorylation events were also changed in PDE4D WT vs. mutant analysis. Functional annotation for the hits with differential phosphorylation from FN vs MG analysis revealed that ‘cell-cell adhesion’ and ‘mRNA splicing’ are the top two GO terms. These terms were also ranked top two from PDE4D-wild type vs mutant analysis. This suggests that PDE4D-depenent PP2A activation could be a major mechanism for FN roles in inflammatory signaling and also mediate novel function of FN on endothelial junctional molecules and alternative splicing.

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