

Kaori Yamada

The University of Illinois at Chicago
USA



KIF13B mediates VEGFR2 recycling to modulate vascular permeability in neovascular age-related macular degeneration

Abstract:

Choroidal neovascularization (CNV) leads to irreversible blindness in age-related macular degeneration (AMD). CNV is triggered by elevated levels of vascular endothelial growth factor (VEGF). Current anti-VEGF therapies need repeated intravitreal injections of anti-VEGF drugs, which is a burden for old patients with impaired vision. We have developed a peptide-based inhibitor that can be used as an eyedrop and showed efficacy in mouse models of neovascular AMD (nAMD). The strategy is based on our finding that VEGFR2 trafficking to the cell surface is mediated by the kinesin-3 family protein KIF13B, and it is essential to respond to VEGF-A when inducing angiogenesis. However, the precise mechanism of how KIF13B regulates VEGF-induced signaling and its effects on endothelial permeability is largely unknown. Here, we show that KIF13B-mediated recycling of internalized VEGFR2 through Rab11-positive recycling vesicle regulates endothelial permeability. Phosphorylated VEGFR2 at the cell-cell junction was internalized and associated with KIF13B in Rab5-positive early endosomes. KIF13B mediated VEGFR2 recycling through Rab11-positive recycling vesicle. Inhibition of the function of KIF13B attenuated phosphorylation of VEGFR2 at Y951, SRC at Y416, and VE-cadherin at Y685, which are necessary for endothelial permeability. Failure of VEGFR2 trafficking to the cell surface induced accumulation and degradation of VEGFR2 in lysosomes. Furthermore, in the animal model of nAMD, inhibition of KIF13B-mediated VEGFR2 trafficking also mitigated vascular leakage. Thus, the present results identify the fundamental role of VEGFR2 recycling to the cell surface in mediating vascular permeability, which suggests a promising strategy for mitigating vascular leakage associated with inflammatory diseases.

Biography

Kaori Yamada has completed her PhD from the University of Tokyo in Japan and postdoctoral studies at the University of Illinois at Chicago, College of Medicine. She is an Assistant Professor of Pharmacology and Ophthalmology at UIC. She has published more than 15 papers in reputed journals.