A024 Role of Epsin and Dab2 in Trafficking of Vascular Endothelial Growth Factor Receptor During Angiogenesis

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Introduction: Cardiovascular diseases are often associated with impaired angiogenesis. VEGF-A and VEGFR2 is a prominent ligand-receptor complex involved in proliferation, migration, and survival of endothelial cells leading to angiogenesis. VEGFA-VEGFR2 undergoes dimerization and activation followed by internalization through endocytosis. Internalized VEGFR2 has two potential fates: recycling to the plasma membrane or degradation via lysosomes. We hypothesized that the endocytic proteins epsin 1, epsin 2, and Dab2 play crucial roles in the dynamics of receptor recycling and degradation. **Results:** Using inducible endothelial cell-specific epsin and Dab2 knockout mice, we showed that epsins and Dab2 interact with VEGFR2 via a mutually exclusive mechanism during receptor trafficking. Mice lacking endothelial epsins showed heightened VEGF signaling and angiogenesis; while Dab2 loss dramatically decreased VEGF signaling and angiogenic responses. Interestingly, simultaneous loss of epsin and Dab2 rescued both phenotypes, indicating antagonistic roles of these proteins during receptor internalization. Confocal imaging showed rapid co-localization of VEGFR2 with lysosomal-associated membrane protein 1-positive lysosomal vesicles in Dab2-depleted endothelial cells compared to controls after ligand activation. Co-immunoprecipitation showed enhanced interaction of VEGFR2 with epsins in the absence of Dab2, while Dab2 had a stronger interaction with VEGFR2 without epsins. We also found PKCi knockdown diminishes VEGFR2 degradation due to dephosphorylation of Dab2 upstream signals generated by sphingosine-1-phosphate receptors governed endocytic adaptor switching in presence of S1P ligand. **Conclusions:** Our study indicates that Dab2 loss facilitates degradation of VEGFR2 and attenuation of angiogenic signaling mediated by epsins. Stabilizing Dab2 can amplify VEGF signaling in endothelial cells, driving angiogenesis, and providing a therapeutic target for a variety of cardiovascular diseases.