IQGAP1 MEDIATES VE-CADHERIN-BASED CELL-CELL CONTACTS AND VEGF SIGNALING AT ADHERENCE JUNCTIONS LINKED TO ANGIOGENESIS

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INTRODUCTION. Vascular endothelial growth factor (VEGF) induces angiogenesis by stimulating reactive oxygen species (ROS) production primarily through the VEGF receptor-2 (VEGFR2) in endothelial cells (ECs) (1). One of the initial responses in established vessels to stimulate angiogenesis is loss of vascular endothelial (VE)-cadherin-based cell-cell adhesions. However, underlying regulatory mechanisms remain unknown. We recently identified IQGAP1 as a novel VEGFR2 binding protein in ECs (2). IQGAP1 is a scaffold protein that interacts directly with actin, cadherin, β-catenin, thereby regulating cell motility and morphogenesis (3).

METHOD and RESULTS. Using confocal microscopy, here we show that IQGAP1 colocalizes and forms complex with VE-cadherin at cell-cell contacts in unstimulated confluent human endothelial cells (ECs). VEGF stimulation reduces the staining of VE-cadherin and IQGAP1 at the adherens junction without affecting their interaction. IQGAP1 knockdown by siRNA inhibits localization of VE-cadherin at cell-cell contacts as well as VEGF-stimulated: 1) ROS production (79% decrease); 2) recruitment of VEGFR2 to and the dissociation of the α-catenin from the VE-cadherin/β-catenin complex; 3) ROS-dependent tyrosine phosphorylation of VE-cadherin (51% decrease) which is required for loss of cell-cell contacts; 4) downstream Akt activation (58% decrease); 5) EC migration (78% decrease), as measured by wound scratch assays; and 6) capillary tube formation in 3 dimensional typeI-collagen gels. Moreover, a mouse hindlimb ischemia model of angiogenesis demonstrates that IQGAP1 protein expression is significantly increased (1.7-fold increase) in newly-formed lectin-positive ECs in ischemic hindlimbs with concomitant increase in VEGF expression (5.4-fold increase), ROS production (29.3-fold increase) and capillary density (2.5-fold increase) at 7 days after operation.
DISCUSSION. The present study provides compelling evidence that IQGAP1 is required for establishment of VE-cadherin-based cell-cell contacts in quiescent ECs. It may also function as a scaffold protein to link VEGFR2 to the VE-cadherin/β-catenin complex at the adherens junctions, thereby promoting ROS-dependent tyrosine phosphorylation of VE-cadherin and loss of cell-cell contacts, which may contribute to postnatal angiogenesis. These findings suggest an essential role of IQGAP1 in organization of signaling at endothelial adherens junction and provide novel insight into IQGAP1 as an attractive therapeutic target for modulating development of neovasculature during angiogenesis.

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