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Angiomotin Regulates Integrin Beta 1-Mediated Endothelial Cell Migration and Angiogenesis

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Abstract : Angiogenesis describes that new blood vessels migrate from pre-existing ones to form 3D lumenized structure and remodeling. During directional migration toward the gradient of pro-angiogenic factors, the endothelial cells, especially the tip cells need filopodia to sense the environment and exert the pulling force. Of particular interest are the integrin proteins, which play an essential role in focal adhesion in the connection between migrating cells and extracellular matrix (ECM). Understanding how these biomechanical complexes orchestrate intrinsic and extrinsic forces is important for our understanding of the underlying mechanisms driving angiogenesis. We have previously identified Angiomotin (Amot), a member of Amot scaffold protein family, as a promoter for endothelial cell migration in vitro and zebrafish models. Hence, we established inducible endothelial-specific Amot knock-out mice to study normal retinal angiogenesis as well as tumor angiogenesis. We found that the migration ratio of the blood vessel network to the edge was significantly decreased in Amotec-retinas at postnatal day 6 (P6). While almost all the Amot defect tip cells lost migration advantages at P7. In consistence with the dramatic morphology defect of tip cells, there was a non-autonomous defect in astrocytes, as well as the disorganized fibronectin expression pattern correspondingly in migration front. Furthermore, the growth of transplanted LLC tumor was inhibited in Amot knockout mice due to fewer vasculature involved. By using MMTV-PyMT transgenic mouse model, there was a significantly longer period before tumors arised when Amot was specifically knocked out in blood vessels. In vitro evidence showed that Amot binded to beta-actin, Integrin beta 1 (ITGB1), Fibronectin, FAK, Vinculin, major focal adhesion molecules, and ITGB1 and stress fibers were distinctly induced by Amot transfection. Via traction force microscopy, the total energy (force indicater) was found significantly decreased in Amot knockdown cells. Taken together, we propose that Amot is a novel partner of the ITGB1/Fibronectin protein complex at focal adhesion and required for exerting force transition between endothelial cell and extracellular matrix.

Keywords : angiogenesis, angiomotin, endothelial cell migration, focal adhesion, integrin beta 1
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