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ANGIOPOIETIN-2-INDUCED LYMPHATIC ENDOTHELIAL CELL MIGRATIO DRIVES LYMPHANGIOGENESIS VIA THE B1 INTEGRIN-RHOA-FORMIN AXIS

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Lymphangiogenesis is an essential physiological process but also a determining factor in vascularrelated pathological conditions. Angiopoietin 2 (Ang2) plays an important role in lymphatic vascular development and function and its upregulation has been reported in several vascularrelated diseases, including cancer. Given the established role of the small GTPase RhoA on cytoskeleton-dependent endothelial functions, we investigated the relationship between RhoA and Ang2-induced cellular activities. This study shows that Ang2-driven human dermal lymphatic endothelial cell (HDLEC) migration depends on RhoA. We demonstrate that Ang2-induced migration is independent of the Tie receptors, but dependent on β1 integrin-mediated RhoA activation with knockdown, pharmacological approaches, and protein sequencing experiments. Although the key proteins downstream of RhoA, Rho kinase (ROCK) and myosin light chain (MLC), were activated, blockade of ROCK did not abrogate the Ang2-driven migratory effect. However, formins, an alternative target of RhoA, were identified as key players, and especially FHOD1. The Ang2-RhoA relationship was explored in vivo, where lymphatic endothelial RhoA deficiency blocked Ang2-induced lymphangiogenesis, highlighting RhoA as an important target for anti-lymphangiogenic treatments.

Biography

Dr. Mikelis has completed his PhD from University of Patras in Greece and postdoctoral studies at the National Institutes of Health. He set up his research program in Texas Tech University Health Sciences Center (TTUHSC), where reached the Associate Professor level at the School of Pharmacy of TTUHSC and recently moved to the Department of Pharmacy at the University of Patras as an Associate Professor. He has published more than 60 papers in reputed journals and has been serving as reviewer and editorial board member of many scientific journals.