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A point mutation in the F-actin regulator p190A RhoGAP affects ciliogenesis and leads to glomerulo cystic kidney disease

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Rho family GTPases act as molecular switches regulating actin cytoskeleton dynamics. Attenuation of their signaling capacity is provided by GTPase activating proteins (GAPs), including p190A, that promote the intrinsic GTPase activity of Rho proteins. We recently identified a novel loss of function allele of the p190A gene *Arhgap35*, which introduces a Leu1396 to Gln substitution in the GAP domain. This change results in decreased GAP activity for the prototypical Rho-family members, RhoA and Rac1. Consequently, Arhgap35 deficient animals exhibit hypodysplastic and glomerulocystic kidneys. We show that p190A is required for appropriate primary cilium formation in proximal tubules. P190A localizes to the base of the cilia to permit axoneme elongation, which requires a functional GAP domain. Pharmacological manipulations further reveal that inhibition of either Rho kinase (ROCK) or F-actin polymerization is able to rescue the ciliogenesis defects observed upon loss of p190A activity. We propose a model in which p190A acts as a modulator of Rho GTPases in a localized area around the cilia to permit the dynamic actin rearrangement required for cilia elongation. Together, our results establish an unexpected link between Rho GTPase regulation, ciliogenesis and glomerulocystic kidney disease.

Biography

Maxime Bouchard has received his PhD from Laval University, Canada and pursued his Post-doctoral studies at the Institute for Molecular Pathology, Vienna, Austria. He has joined McGill University in 2003 and is currently an Associate Professor at the Goodman Cancer Research Centre and in the Department of Biochemistry. His research focuses on the developmental genetics of renal diseases using the mouse as a model system.

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