Regulation of Actin Polymerization and Cell Motility by IQGAP1

George S. Bloom, Scott C. Mateer, Ningning Wang, Lorena B. Benseñor, Leah E. Morris, and Dorothy A. Schafer;

Departments of Biology, and Cell Biology; University of Virginia; Charlottesville, Virginia, USA.

The scaffolding protein, IQGAP1, is ideally suited to regulate stimulation of actin polymerization during cell migration by Rho family GTPases because its direct binding partners include F-actin and activated forms of the Rho GTPases, Cdc42 and Rac1, and it is concentrated in lamellipodia. Nevertheless, the mechanisms by which IQGAP1 influences cell motility have not been described. Cell motility is often coupled to lamellipodial protrusion, which is driven by the assembly of branched actin filaments that deform the plasma membrane in the direction of cell migration. Branched actin filaments are nucleated by Arp2/3 complex and other factors, such as N-WASP, whose activity is stimulated by binding activated Cdc42, phosphatidylinositol 4,5-bisphosphate, or both. We now demonstrate that IQGAP1 directly regulates this pathway. In vitro, IQGAP1 potently stimulates actin assembly in the presence of Arp2/3 complex and N-WASP, does so additively with activated Cdc42 or Rac1, and is prevented from stimulating assembly by calmodulin, which also binds directly to IQGAP1. When IQGAP1-YFP is expressed in cultured mammalian cells, it specifically enriches in motile lamellipodia, and endogenous IQGAP1, Arp3 and N-WASP associate intracellularly, as judged by immunofluorescent co-localization and co-immunoprecipitation out of cell extracts. The involvement of IQGAP1 in actin assembly is evidently controlled upstream by growth factors and their cognate cell surface receptors. In the case of endothelial cells, stimulation of VEGFR2, the type 2 receptor for vascular endothelial growth factor (VEGF), leads to recruitment of IQGAP1 to the cytoplasmic tail of VEGFR2, formation of activated Rac1/IQGAP1 complexes, and directed cell migration. Furthermore, reducing IQGAP1 protein levels with siRNA potently inhibits the ability of VEGF to induce endothelial cell motility. These results establish IQGAP1 as a major, but previously unrecognized regulator of actin assembly and cell motility mediated by Arp2/3 complex and N-WASP.