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A novel role for heterotrimeric G proteins and formins in microtubule-based cell polarity and migration

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Cell polarity is a necessary process observed in all cells. It is tightly regulated during directed migration. Cells need to reorganize their actin and microtubule cytoskeleton and reorientate the microtubule-organizing-center (MTOC). Heterotrimeric $G\alpha_{12}$ and $G\alpha_{13}$ proteins are involved in Rho-mediated regulation of the actin cytoskeleton in various processes, however it is unclear if they are also involved in regulation of the microtubule cytoskeleton.

The findings presented here are based on studies using $G\alpha_{12/13}$-deficient mouse embryonic fibroblasts (MEFs). They reveal that $G\alpha_{12}$ and $G\alpha_{13}$ proteins are necessary for directed migration. In addition, $G\alpha_{12/13}$ signaling regulates microtubule dynamics during migration and is necessary for MTOC polarization.

To characterize the signaling pathway involved, components downstream of $G\alpha_{12/13}$ were investigated for their potential involvement. Surprisingly, cell polarization and migration involve the RhoA guanine nucleotide exchange factor leukemia-associated (LARG), which belongs to the family of RhoGEFs that can directly bind to $G\alpha_{12/13}$ subunits. Interestingly, LARG associates with the MTOC and moves along microtubule tracks, suggesting a continuous trafficking of LARG to and from the leading edge to link cell surface receptors to the microtubule cytoskeleton. The data presented here suggest a biological role for LARG in the control of cell polarity during migration downstream of $G\alpha_{12/13}$.

Furthermore, the RhoA effector and actin polymerizing formin Diaphanous 1 (Dia1) is necessary for successful migration. RNA interference studies demonstrate that Dia1 influences microtubule dynamics and is involved in MTOC reorientation in migrating cells, which appears to depend on its actin nucleating activity. These findings along with localization of Dia1 to the leading edge of migrating cells suggest an important role for LARG and Dia1 as mediators of actin-microtubule crosstalk in polarized migration.