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Abstract

The Rab11 Family Controls Signalling to the Cytoskeleton for Cell Migration and Invasion †

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Abstract: Endocytic recycling controls the return of internalised cargos to the plasma membrane to coordinate their positioning, availability and downstream signalling. The Rab4 and Rab11 small GTPase families regulate distinct recycling routes, broadly classified as fast recycling from early endosomes (Rab4) and slow recycling from perinuclear recycling endosomes (Rab11), and both routes handle a broad range of overlapping cargos to regulate cell behaviour. We have previously shown that Rab11 regulates the recycling of integrins to promote cancer cell migration and invasion, at least in part by controlling RhoGTPase activity at the leading edge, but the mechanisms that underpin cytoskeleton regulation by Rab11 family members are still unclear. We adopted a proximity labelling approach, BioID, to identify and compare the protein complexes recruited by Rab4a, Rab11a and Rab25 (a Rab11 family member implicated in cancer aggressiveness), revealing robust protein–protein interaction networks of well-characterised, new cargos and trafficking machinery in migratory cancer cells. Gene ontological analysis of these interconnected networks revealed that these endocytic recycling pathways are intrinsically connected to cell motility and cell adhesion, and we demonstrate that several of these new Rab11 and Rab25 associated proteins are required for efficient cancer cell migration in a 3D matrix. Rab11 and Rab25 vesicles are found at the perinuclear recycling compartment but also in the tips of protrusions in cells moving in a 3D matrix. This leads us to speculate that these recycling pathways deliver cargos to directly promote protrusion formation and extension. To test this, we established a magneto-genetic approach to physically re-localise Rab25 vesicles in cells in 2D and 3D matrices. Using this technique, we are able to show that repositioning of Rab25 vesicles to the cell cortex promotes the formation of protrusions in a manner dependent on actin-polymerising protein formins, but not Arp2/3. Together, these data reveal a direct role for Rab11 family members in directing cytoskeletal signalling to promote cancer cell invasion.

Keywords: cell migration; cytoskeleton; endocytic recycling; Rab11; formins

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