

Cell coordination of collective migration by Rab11 and Moesin

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Cell migration is an important process involved in developmental events and in pathologies such as cancer. Cell migration can be classified into two types: individual and collective cell movements. Compared with individual migration, collective cell migration is less understood and has drawn increasing attention lately because of its emerging role in cancer spreading. We have recently established that Rab11 is absolutely required for spatial control of Rac1 activity through the control of cell-cell communication during collective movements (Ramel et al. 2013). Moreover, we demonstrated that Rab11 acts through the control of Moesin activity. Here, we discuss how Rab11 and Moesin could cooperate to transfer forces from cell to cell in order to insure coordinated collective cell migration.

Cell migration is crucial during development, but it is also involved in pathologies such as inflammation or tumor metastasis.^{1,2} Different types of cell migration exist including single cell migration, amoeboid migration and collective cell migration. Individual cell migration has been extensively studied and greatly benefited from the in vitro culture of migratory cells. Collective cell migration is much less understood and has drawn increasing attention lately because of its emerging role in development and cancer spreading.^{3,4} The small GTPase Rac is a key regulator of actin dynamics and cell migration. However, the mechanisms regulating Rac in time and space during collective cell migration are poorly understood. Here, we discuss our recent evidence that endocytic

trafficking coordinates Rac activity during collective cell movements.

Currently, few models have been applied to study collective cell migration. However, most of these in vivo models are very complex and cannot be easily genetically manipulated. For our study, we used *Drosophila* ovary. During *Drosophila* oogenesis, the so-called border cells perform a stereotypic migration between germ cells toward the oocyte to form the future sperm-entry point.^{5,6} As a simple and genetically tractable in vivo model, border cell migration provides a good platform for our understanding of collective cell movement.⁷ Four major signaling pathways have been identified by traditional genetic studies to regulate the different aspects of border cell migration: the JAK/STAT pathway, a global steroid-hormone pathway, cell-cell contact dependent Notch signaling, and Receptor Tyrosine Kinase (RTK) signaling. In addition to these four major signals, hedgehog⁸ and JNK⁹ signaling pathways have been implicated in the control of border cell migration. The hedgehog pathway regulate different factors necessary for BC but its direct target has to be determined.⁸ JNK signaling is implicated in the control of cell-cell communication restricting Rac activity at the front of the cluster.⁹ However the molecular mechanism achieving this restriction of Rac was still largely misunderstood. Our recent study provides the first elements of the molecular basis regulating cell-cell communication during collective cell movements.¹⁰

Endocytosis has been considered for a long time as a way to simply attenuate signaling by receptor displacement from the

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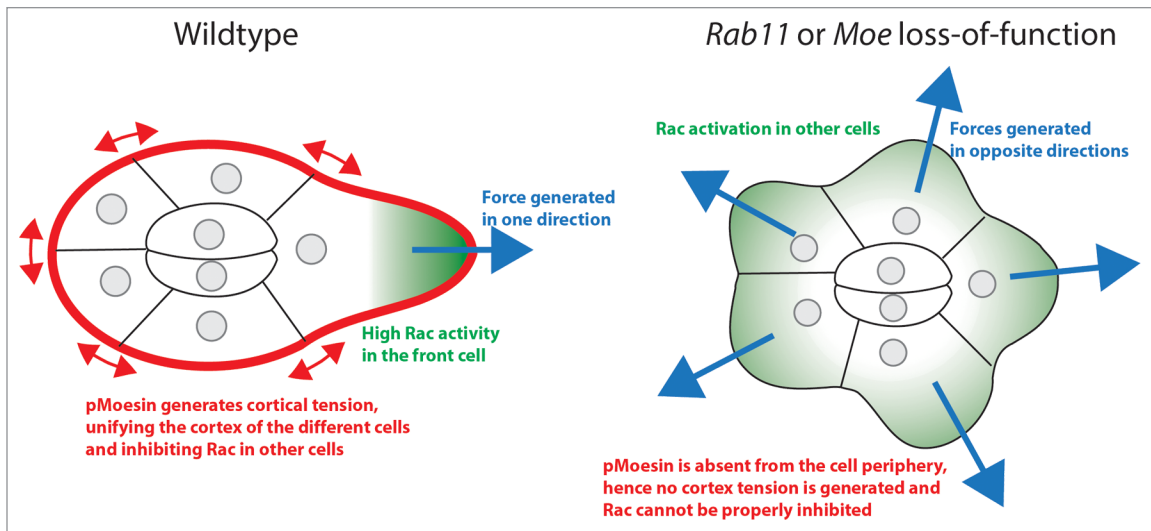


Figure 1. Working model explaining the mechanism by which Rab11 and Moesin restrict Rac activity to the lead cell.

plasma membrane. However, it is now appreciated as a major regulator of signaling outcome. In collective migration, endocytosis has been shown to restrict RTK signaling at the leading edge, either by controlling lateral diffusion of signaling molecules or by recycling RTKs to active regions of the plasma membrane at the leading edge.¹¹⁻¹³ Our results demonstrate that Rac is also an important target of endocytosis during collective cell migration. With the use of advanced imaging techniques, we first determined that Rab11 is a key regulator of cell-cell communication during collective movements. Second, we outlined a new role for Rab11 in the regulation of Moesin activity and we demonstrated that a phosphomimetic form of Moesin is able to rescue migration phenotypes induced by Rab11 loss of function. Finally, we showed that Moesin activation is necessary for normal cell-cell communication during collective cell migration.¹⁰ Thus, our work places Rab11 at the center of these processes and provides new insights into the role of endocytosis in the organization of individual cells in a coherent multicellular motile structure.

Indeed, one of the key findings of our study is the identification of Rab11 as a regulator of cell-cell communication in collective movements. Wang and colleagues have shown that cell-cell communication is required for proper restriction

of Rac in the leading cell and that this is key for directionality of the cluster migration.⁹ The mechanism by which cells are able to sense the relative level of Rac activity in neighboring cells remains unclear. This study identifies both Rab11 and Moesin as major regulators of this process. Moesin plays a critical role in organizing the epithelial architecture and in the regulation of membrane tension through regulation of the acto-myosin cytoskeleton.¹⁴ Recently, it has been proposed that membrane tension could be a mechanism to restrict signaling to the leading edge of neutrophils.¹⁵ Indeed, Houk and colleagues have shown that plasma membrane tension is generated by the formation of protrusions at the leading edge. This tension is subsequently transmitted to the cell body to inhibit formation of other leading edges. The molecular basis of this mechanism is still unknown but it might be possible to parallel neutrophils and border cells. Indeed, during border cell migration, there is emission of one major protrusion at the leading edge. Moreover, photo-activation of Rac has been shown to induce formation of protrusions in the photo-activated cell and inhibit formation of protrusions in the other cells of the group. Formation of protrusions in the leading border cell might thus increase plasma membrane tension that is subsequently transmitted around the cluster to inhibit Rac

signaling in other cells. Conversely, photoactivation of the dominant negative form of Rac in the leading cell leads to retraction of the protrusions and apparition of protrusions in other cells of the cluster suggesting that relaxing tension at the leading edge allows formation of protrusions in the other cells. We propose that Rab11 and Moesin could regulate this mechanical effect (Fig. 1), but it remains challenging to understand the molecular mechanism that controls the transmission of tension from one cell to a group of migrating cells.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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