

Cell migration at a glance

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Cell migration is a fundamental process, from simple, uni-cellular organisms such as amoeba, to complex multi-cellular organisms such as mammals. Whereas its main functions comprise mating and the search for food in simple organisms (Manahan et al., 2004), complexity brings a requirement for specialization, which necessitates cell migration-mediated tissue organization, organogenesis and homeostasis (Ridley et al., 2003).

The past 15 years have witnessed

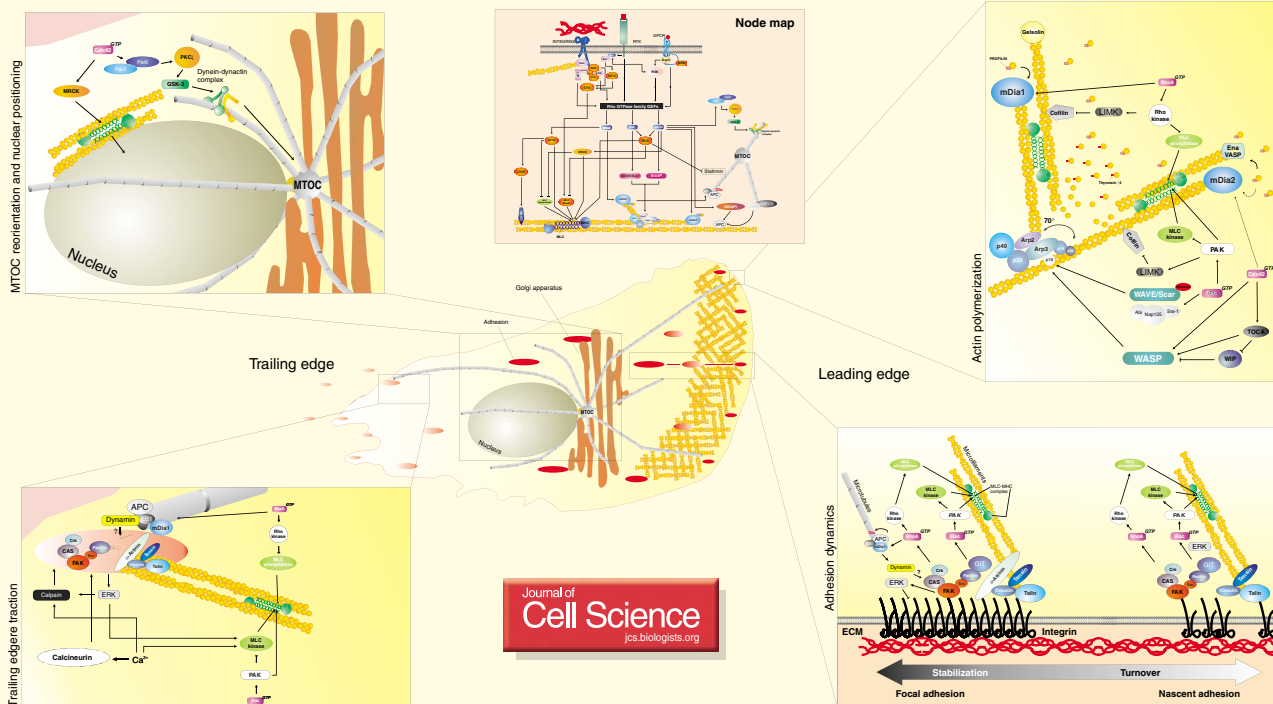
enormous advances in our understanding of the complexities and subtleties underlying the regulation of cell migration. This now includes the generation of temporal-spatial cues that result in cell adhesion, asymmetric polarization and individual and layered cell motility. A key discovery was the involvement of the actin cytoskeleton and its fine regulation in the maintenance of cellular integrity and the dynamic responses that drive migration. Such regulation requires multi-nodal control to ensure coordinated migration, which the organism can turn off and on depending on the requirements of a given situation. It also allows highly specialized modes of cell migration in different tissues. However, the overall process exhibits so many regulatory steps that any deficiency, either ectopic activation or hijacking by pathogens, can impair or enhance cell migration and have catastrophic consequences that include vascular disease, chronic inflammation, cancer, mental retardation, and virus and bacterial infection and dissemination.

Thus, a thorough understanding of the mechanisms underlying cell migration will facilitate development of therapies for the treatment of migration-related disorders.

In the poster, we try to convey the overflow of information pertinent to the regulation of cell migration. It is based on a classical model of cell migration, an individual fibroblast-like cell migrating on a 2D environment. Other cell types adopt different morphologies during migration, such as leukocytes, which display amoeba-like movement and morphology, keratocytes, which display a gliding motion, and cells that retain cell-cell contacts during motility, such as epithelial monolayers during gastrulation and wound healing. In addition, there is a nascent but increasing literature on cells migrating in 3D environments; although little is known about the molecular details, there appears to be differences (Beningo et al., 2004; Gunzer et al., 2000; Knight et al., 2000). Although each of these modes of

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Abbreviations: APC, Adenomatous polyposis coli; Cdk, cyclin-dependent kinase; Cdc, Cdc124; Eph, Eph receptor tyrosine kinase; EMT, epithelial-mesenchymal transition; FAK, focal adhesion kinase; GTP, G-protein-coupled receptor; Integrin, integrin; LIMK, LIM domain kinase; mDia, mDia1; mDia2, mDia2; mDia3, mDia3; mDia4, mDia4; mDia5, mDia5; mDia6, mDia6; mDia7, mDia7; mDia8, mDia8; mDia9, mDia9; mDia10, mDia10; mDia11, mDia11; mDia12, mDia12; mDia13, mDia13; mDia14, mDia14; mDia15, mDia15; mDia16, mDia16; mDia17, mDia17; mDia18, mDia18; mDia19, mDia19; mDia20, mDia20; mDia21, mDia21; mDia22, mDia22; mDia23, mDia23; mDia24, mDia24; mDia25, mDia25; mDia26, mDia26; mDia27, mDia27; mDia28, mDia28; mDia29, mDia29; mDia30, mDia30; mDia31, mDia31; mDia32, mDia32; mDia33, mDia33; mDia34, mDia34; mDia35, mDia35; mDia36, mDia36; mDia37, mDia37; mDia38, mDia38; mDia39, mDia39; mDia40, mDia40; mDia41, mDia41; mDia42, mDia42; mDia43, mDia43; mDia44, mDia44; mDia45, mDia45; mDia46, mDia46; mDia47, mDia47; 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motility exhibits some unique features, they also have much in common, which is the focus of this poster.

The model shown represents a polarized cell that has distinct leading and trailing edges. This is a common feature of both fibroblastic and amoeboid motility. The leading edge points in the direction of movement and is driven by actin-polymerization-mediated protrusion. Red spots represent points of interaction of the cell with the substrate. The larger spots represent stable adhesions (a classic feature of fibroblastic motility that is absent in faster-moving cells), and smaller spots at the periphery represent nascent adhesion complexes. Colour gradients within the spot represent the dynamics of adhesion turnover (at the front) and disassembly (at the back). Other structures depicted include the nucleus (light brown), the Golgi apparatus (dark brown) and the microtubule-organizing center (MTOC), from which the microtubule network (grey) radiates, as well as an actin-rich lamellipodium at the front. Insets show specific features within the migrating cell, such as the regulation of actin polymerization at the protrusion sites, adhesion dynamics, MTOC- and nucleus-based cell polarity and tail retraction, as well as a node map depicting some of the key molecules involved in regulation of the process.

Actin polymerization

Actin polymerization controls protrusion of the cell in the current paradigm for cell migration (Pollard and Borisy, 2003). There are two main types of nucleator of actin polymerization: the Arp2/3 complex and the formins mDia1 and mDia2 (other formins have described in different cellular systems). Arp2/3 binds to the sides of existing actin filaments and promotes the extension of a new actin filament from its pointed end, forming a 70° angle with the pre-existing filament (Weaver et al., 2003). Arp2/3 regulation is controlled by WAVE/Scar, WASP and N-WASP proteins, whose mutation or truncation is related to the Wiskott-Aldrich syndrome immune disease. WAVE/Scar is part of a multimeric complex including Abi, Nap125, Sra-1 and HSPC-300. This complex is under the control of the small

GTPase Rac, which induces the dissociation of Abi, Nap125 and Sra-1 from WAVE, thus mediating its activation. WASP and N-WASP are regulated by Cdc42. These proteins are also regulated by phosphorylation, phosphoinositides and other molecules, such as WIP and TOCA, which also negatively regulate WIP (Vartiainen and Machesky, 2004).

Unlike the Arp2/3 complex, formins bind to the barbed end of actin filaments and promote actin growth in a linear fashion. Formins are regulated by small GTPases (RhoA and Cdc42 for mDia1 and mDia2, respectively) and require interaction with G-actin-bound profilin to promote actin polymerization (Watanabe and Higashida, 2004). Profilin is also required for Ena/VASP-mediated actin polymerization at the barbed end, although its mode of action seems more related to anti-capping activity (Krause et al., 2003). Both profilin and thymosin β 4 are G-actin-binding proteins. Whereas profilin can bind to different actin nucleators, thymosin β 4 cannot, and thus is regarded as a G-actin reservoir that can shuttle G-actin to profilin to promote actin filament growth (dos Remedios et al., 2003).

Actomyosin-based contraction is controlled by the small Rho GTPases Cdc42, Rac and RhoA (Jaffe and Hall, 2005). Regulation by these GTPases is antagonistic. RhoA activates Rho-kinase (also called ROCK), which in turn phosphorylates and inactivates the phosphatase that dephosphorylates MLC, resulting in increased contractility. A similar mechanism has been shown for Cdc42, acting through MRCK. Conversely, Rac activates PAK, which phosphorylates and inactivates MLC kinase, thus leading to decreased contractility and promoting spreading. However, PAK may also phosphorylate MLC directly, which would increase contractility. The predominance of the first or the second mechanism seems to be regulated by spatial considerations or differential regulation of PAK activity. In addition, PAK also regulates cell polarity, through the activation of a PIX/PAK complex that is targeted to the leading edge during G-protein-coupled receptor-dependent migration (Li et al., 2003). Finally, PAK regulates microtubules

through stathmin phosphorylation, which results in decreased microtubule catastrophe (Wittmann et al., 2004).

Capping proteins such as gelsolin block actin polymerization at the barbed end and are mainly regulated by phosphoinositides (Zigmond, 2004). Finally, cofilin severs actin filaments, and its activity is regulated by phosphorylation induced by LIMK, which is in turn regulated by PAK- or Rho-kinase-mediated Ser/Thr phosphorylation (Maciver and Hussey, 2002).

Adhesion dynamics

Adhesions are points of molecular interaction between the cell and the substrate. They assemble and disassemble in response to extracellular cues and regulate cell motility. During migration, adhesions assemble at the leading edge and disassemble at the trailing edge. However, adhesions also disassemble at the front during protrusion and feed components to nascent adhesions at the leading edge in a process called adhesion turnover (Webb et al., 2004). Thus, in protruding regions of cells, as new adhesions form, they can disassemble (adhesion turnover) or stabilize and grow into more mature, larger adhesions. Most highly motile cells, especially those in vivo, do not have the large adhesions that characterize less motile cells in 2D cultures. The molecular components of stable and nascent adhesions are similar, although there are molecules present in one type that are absent in the other. Among the structural molecules, talin directly links integrins to actin and also activates them (Nayal et al., 2004). Many actin- and signal-transduction-related molecules have also been reported to bind to integrins, regulating signalling from integrins to the actin cytoskeleton and also integrin activation. For example, zyxin binds α -actinin and regulates Ena/VASP function on neighbouring actin barbed ends (Zaidel-Bar et al., 2004).

The molecular mechanisms underlying the 'decision' of an adhesion to mature or turnover are unclear. Rho GTPases are critical effectors in this process. They in turn are controlled by signals

emanating from adhesion-related signalling modules, such as a multi-protein complex that includes FAK, Src, paxillin, Crk, CAS, PAK and GIT. Cleavage of adhesion components by proteases, such as calpain, also regulates disassembly at the front, although its role has been established more clearly in rear adhesions during detachment (Franco et al., 2004). Finally, relaxation signals emanating from the tips of microtubules that target adhesions, probably involving dynamin, are also implicated in adhesion disassembly (Ezratty et al., 2005).

MTOC reorientation and nuclear positioning

Cell polarity, which is essential for directed migration, is defined not only by actin-mediated protrusion and trailing edge retraction but also by positioning of the nucleus and reorientation of the Golgi apparatus and MTOC towards the leading edge. Different sets of molecules regulate these processes. The small Rho GTPase Cdc42 regulates MTOC positioning through Par proteins and PKC ζ , which regulate the dynein-dynactin complex, probably by phosphorylation (Jaffe and Hall, 2005). Recent data support the notion that MTOC reorientation depends on nuclear movement and that the Par/PKC pathway is involved in keeping the MTOC immobile with respect to the moving nucleus. Nuclear repositioning occurs through myosin-dependent actin rearward flow and is catalyzed by Cdc42 acting through MRCK (Gomes et al., 2005).

Trailing edge retraction

For cells to translocate forward, adhesions at the rear must disassemble and the trailing edge retract, otherwise tension would rip the cell apart. Several mechanisms promote disassembly; these include microtubule-dependent targeting of dynamin and subsequent endocytosis of some adhesion components (Ezratty et al., 2005); myosin-mediated

contractility contributes through regulation of MLC phosphorylation by RhoA and Rac acting through Rho-kinase and PAK. Finally, dissolution of the adhesive contacts at the rear edge is also achieved through affinity downregulation by phosphorylation by phosphatases, such as calcineurin, or simply by proteolysis of molecules such as talin by proteases, for example, calpain (Franco et al., 2004). Calcium is a key modulator in rear edge retraction, probably acting through its regulation of calpain and calcineurin.

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