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The mechanisms of spatial and temporal patterning of cell-edge dynamics

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Adherent cells migrate and change their shape by means of protrusion and retraction at their edges. When and where these activities occur defines the shape of the cell and the way it moves. Despite a great deal of knowledge about the structural organization, components, and biochemical reactions involved in protrusion and retraction, the origins of their spatial and temporal patterns are still poorly understood. Chemical signaling circuitry is believed to be an important source of patterning, but recent studies highlighted mechanisms based on physical forces, motion, and mechanical feedback.

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Types and patterns of cell edge activity

Protrusion and retraction at the cell edge depend mostly on the activity of the actin cytoskeletal system [1,2]. Three major types of cell protrusions are leaf-like lamellipodia filled with a branched actin network, cylindrical filopodia containing actin filament bundles, and blebs, rounded membrane bulges that are driven by cytosolic pressure due to the contraction of the cortical actin–myosin network [3–6]. Retraction, on the other hand, is thought to depend on contraction of the actin–myosin network and/or network disassembly allowing it to collapse under the load of membrane tension [7–9]. In this review, we focus on the control over the patterns of protrusion and retraction of the lamellipodia — one of the most common and well-studied types of edge activity — but these control mechanisms could also be applicable to other types of edge dynamics.

The cells exhibit various spatial and temporal patterns of protrusion and retraction related to their shape and migration behavior [10]. Many migrating cells display formation of lamellipodia preferentially or exclusively at the leading edge, while the trailing edge exhibits continuous retraction. A perfect example of this behavior is fish epidermal keratocytes, which are among the most persistent cells in nature [10,11]. Keratocyte edge activity is believed to be stable in time and precisely graded in space to maintain a nearly constant cell shape. By contrast, in cells exploring their environment, for example, spreading fibroblasts and epithelial cells, edge activity is on average spatially isotropic, but fluctuates in time between protrusion and retraction [12–19]. These fluctuations could be either synchronous along the edge or propagate in a wave-like manner [16,17,20]. Many migrating cells exhibit a mixed pattern of activity with protrusion–retraction cycles and a net prevalence of protrusion at the leading edge [17,18,21]. The cells of the same type can switch between different patterns of activity depending on the conditions: for example, fish epidermal keratocytes that are typically persistent exhibit protrusion–retraction waves during polarization [22], when migrating on the substrates with high adhesiveness [23], and at a particular stage of development [24•].

Signaling networks versus feedback within the cytoskeletal machinery

One important class of mechanism of biological patterning is based on coupled chemical reactions involving substances with different diffusivities. This mechanism was proposed by theoreticians [25–27] more than half a century ago and has since been shown to operate in diverse biological processes [28–30]. In migrating cells, reaction–diffusion mechanisms are probably responsible for amplifying and sustaining polarization of edge activity induced by external directional signals, for example, by a gradient of chemical attractant [31,32]. Many variants of such mechanisms have been proposed; most involve a local autocatalytic activator and global diffusible inhibitor [30,33]. Recently, the circuitry necessary for patterning through reaction–diffusion mechanisms was dissected through a combined modeling/synthetic biology approach in a model of non-motile yeast cells [34]. Minimal circuits involving just a single positive or negative feedback loop were shown to be sufficient, but the robustness of the mechanism increased when more than one feedback loop was involved.

The main signaling entities believed to participate in the patterning of edge activity in motile cells are the enzymes and lipids of the phosphoinositide signaling system and

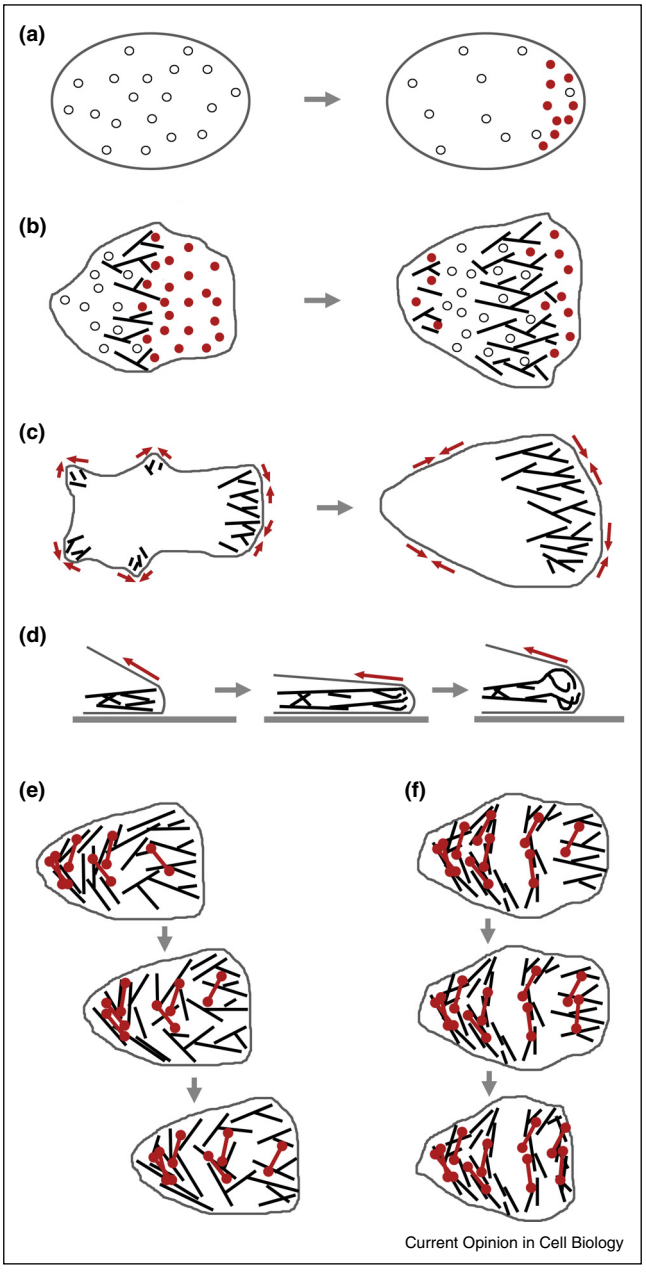
small GTPases of the Rho family [35–38]. Molecules of these signaling pathways are particularly suitable for reaction–diffusion circuits because they cycle between active membrane-bound forms and inactive cytosolic species. Several theoretical studies have suggested mechanisms of polarization of motile cells based on self-sorting of these molecules [33,39]. Experimentally, self-organizing gradients of small GTPases and the components of the phosphoinositide system are observed in migrating cells [40–43] (although they may be dispensable for chemotaxis [44,45]), and the cycles of activation of these molecules correlate with the cycles of protrusion and retraction at the edge [46–48,49•].

The pathways from the signaling molecules to their cytoskeletal targets are often complex, with activators and inhibitors of protrusion activated downstream of the same pathway [50•,51]. Another intriguing example of signaling complexity is that protrusion phases of cyclical edge activity correlate with the activation of Rho A, a member of the small GTPase family that promotes retraction when activated globally in the cell [46,47]. The regulation of cytoskeletal dynamics by signaling molecules has been a subject of several recent reviews [5,35–38,51] and will not be considered in detail here.

At the same time, an increasing body of evidence suggests that important feedback relationships responsible for patterning are realized at the level of the cytoskeleton itself rather than at the signaling level [21,51–55]. A recent study reported a universal coupling between velocity and directional persistence of migrating cells, suggesting that motion is part of the feedback maintaining polarity [56••]. Another indication that reaction–diffusion of signaling molecules is not sufficient for patterning of edge activity is the observation that polarity is maintained in cellular geometries that are not compatible with reaction–diffusion mechanisms. Neutrophils maintain a single protruding region even if it is separated from the bulk of the cell by a thin and long stalk, making communication between the protrusive domain and the rest of the cell through diffusion virtually impossible, but leaving the possibility of mechanical force transmission [57].

If feedback mechanisms are realized on the cytoskeletal level, the outcomes of cytoskeletal activity should serve as readouts for the control circuits. The main outcomes of protrusion are build-up of the actin network; deformation and tensioning of the plasma membrane [58•]; and the motion of the actin network and the cell as a whole. This list is not exhaustive, but most of the hypotheses and experimental works on edge activity patterning indeed focus on the feedback from these three sources (Figure 1). These mechanisms are not mutually exclusive and can cooperate with reaction–diffusion mechanisms at the signaling level [59–61] as has been shown in other systems, for example, synergy of actin flow and reaction–diffusion in

Figure 1



Schematics of the mechanisms of patterning cell edge activity. **(a)** Signaling molecules self-sort through reaction–diffusion. **(b)** Actin polymer inhibits activators of actin nucleation, resulting in actin polymerization waves. **(c)** Membrane tension quenches small patches of actin assembly resulting in the emergence of a single dominant protrusion. **(d)** Actin assembly extends and flattens cell edge resulting in the increase of membrane resistance and eventual collapse of the protrusion. **(e)** Actin flow swaps myosin filament assemblies to the back of the cell, reinforcing cell polarity. **(f)** Myosin assembly at the cell front causes periodic retraction of the protrusion. Red-filled and open dots indicate, respectively, active and inactive forms of signaling molecules and of actin nucleators; black lines, actin filaments; red dumbbell figures, myosin filaments; red arrows, membrane tension.