An evolutionary perspective on cell migration: Digging for the roots of amoeboid motility

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Fritz-Laylin et al. (2017. J. Cell Biol. https://doi.org/10.1083/jcb.201701074) take advantage of the deep knowledge of mechanisms of actin-based motility and a growing number of sequenced genomes across the tree of life to gain insight into the machinery needed for pseudopod-based amoeboid motility and how it evolved.

The growing number of sequenced genomes across a diverse range of organisms has stimulated great interest in phylogenetic analyses of widely expressed proteins with critical roles in cell biology. Such phylogenetic studies of multi-gene protein families have long been used to assess conservation of biochemical functions across organisms or, alternatively, to identify where functions have diverged (Goodson and Spudich, 1993). Even deeper insight can be obtained from phylogenetic studies of cell biological processes: It has become clear that suites of proteins involved in a particular structure or function are often maintained or lost in tandem. These observations can define the proteins involved in particular cellular functions and provide mechanistic insight; they also allow researchers to predict on the basis of sequence alone which structures and/or functions may exist in otherwise uncharacterized organisms. When patterns of protein identification are compared across the tree of life, these approaches provide insight into when particular processes evolved. For example, studies of genes associated with cilia/flagellar motility have established a signature for the presence of these structures, ascribed flagellar functions to several previously uncharacterized genes, and provided strong evidence that the last eukaryotic common ancestor contained motile flagella (Carvalho-Santos et al., 2011). In this issue, Fritz-Laylin et al. take advantage of the recent explosion of sequenced genomes and use an evolutionary approach to study amoeboid motility.

Actin-dependent cell crawling is an ancient form of motility and likely a defining feature of early eukaryotes. It is driven by actin-powered extension of membrane protrusions (such as pseudopodia or lamellipodia) or by blebbing that results from actomyosin contractility (Fig. 1). It is easy to imagine that the different types of actin-based motility vary in name only or perhaps represent minor variations on the same theme. However, pseudopodia are associated with rapid amoeboid motility (~10 μm/min) and involve weak and/or nonspecific surface interactions, whereas lamellipodia are used for slower mesenchymal motility (~1 μm/min), which typically depends on strong and specific adhesions (Fritz-Laylin et al., 2017). Pseudopodia and lamellipodia differ in their morphology: Pseudopodia are 3D, actin-filled structures, whereas lamellipodia are thinner, sheet-like, 2D membrane extensions. These phenotypic differences hint at the existence of as-yet poorly-understood mechanistic differences underlying their formation. Fritz-Laylin et al. (2017) gain insight into this problem by looking at it from an evolutionary cell biology perspective.

The mechanisms of actin-based motility have been the subject of intense study for decades, but the functional relationship between pseudopod-associated and mesenchymal motility has been difficult to study because both forms of motility have been thought to require Arp2/3. Thus, it has not been possible to predict which mode of motility might be used by a given cell type based solely on the presence of Arp2/3. Study of this question has also been hampered by the fact that Arp2/3 contributes to other actin-based processes such as endocytosis (Rotty et al., 2013). Fritz-Laylin et al. (2017) approached this problem by examining the phylogenetic distribution of key regulators of actin-based motility. They found a correlation between organisms that move by a mode that they term “α motility” (amoeboid movement involving actin-rich pseudopods) and the presence of two regulators of Arp2/3: WASP and SCAR (SCAR is also known as WAVE; Rotty et al., 2013). Fritz-Laylin et al. (2017) hypothesized that α motility exists in organisms that have both WASP and SCAR but are unknown to exhibit such motility. They focused their attention on chytrid fungi, deeply diverging fungi that produce flagellated spores and are best known for devastating effects on amphibians. The researchers collected infectious flagellated zoospores from the zoosporangium of Batrachochytrium dendrobatidis. These flagellated zoospores lack cell walls and make dynamic extensions that strikingly resemble pseudopodia. The authors observed that these extensions are filled with actin, and their formation is abolished by inhibitors of either actin polymerization or the Arp2/3 complex. Remarkably, when placed in a confined chamber, these fungi spores did exhibit amoeboid α motility with a speed comparable to that of fast moving neutrophils or Dictyostelium discoideum (mean of ~20 μm/min; Fritz-Laylin et al., 2017).

These results are worth noting for several reasons. First is the idea that actin-based motility can be organized into several different subtypes, at least one of which (the one that the authors have termed α motility) can be predicted on the basis of
the suite of proteins present in the genome. In the case of α motility, both WASP and SCAR must be present. It remains to be seen what the signature actin regulators evolutionarily associated with the lamellipodial or bleb-based forms of actin-based motility are. Second, and perhaps more interestingly, α motility likely existed in the last eukaryotic common ancestor. This conclusion is based on the evidence that both WASP and SCAR likely existed in the last eukaryotic common ancestor (Kollmar et al., 2012) and that presence of the WASP/SCAR pair in a genome is a signature of α motility (Fritz-Laylin et al., 2017). In addition, many will find it surprising that organisms classified as fungi are capable of amoeboid motility. However, amoeboid motility has previously been observed in zoospores of other chytrid fungi (Heath and Steinberg, 1999). Regardless, this knowledge does not take away the significance of the predictive power of the analysis in this manuscript, because the chytrid fungi are a deeply diverging (and divergent) group. Indeed, the findings from Fritz-Laylin et al. (2017) provide dramatic support for the idea, originally posed in 1892, that fungi are “tube-dwelling amoebae” (cited in Heath and Steinberg, 1999). Although striking to many cell biologists, this conclusion is consistent with the idea that fungi, amoebozoa (e.g., organisms such as Dictyostelium), and animals share a relatively recent common ancestor that displayed both amoeboid and flagellar motility.

The work by Fritz-Laylin et al. (2017) raises several interesting questions. From a mechanistic perspective, it is striking to see that both WASP and SCAR are needed for α motility. Why? This is quite puzzling given that both are activators of Arp2/3 and might seem redundant. The strong signature of co-conservation across approximately one billion years in organisms exhibiting α motility suggests that there is some deep and fundamental level of cooperation between these proteins. In support of a potential cooperation between SCAR and WASP, Fritz-Laylin et al. (2017) observed that depletion of WASP or SCAR reduces but does not abolish motility of either neutrophils (Fritz-Laylin et al., 2017) or Dictyostelium (Veltman et al., 2012). Fritz-Laylin et al. (2017) suggest that amoeboid cells require both regulators to enable good control over when and where a pseudopod is formed and that activation of Arp2/3-based polymerization of actin at the membrane must exceed a specific threshold in order for a pseudopod to form. WASP and SCAR may both also be needed to ensure that the type of protrusion formed by a cell is optimized for its migration (Leithner et al., 2016). Another question is what network regulates the regulators? Pseudopod extension is activated by Ras GTPTases controlled by activity of GTPTase-activating proteins and guanine nucleotide exchange factors. It is interesting to speculate that there may be a subset of pseudopod-specific Ras regulators required for the activity of WASP and SCAR. However, it is possible that the same general activation pathways are used for both pseudopodia and lamellipodia formation, and that the key determinant of the phenotype solely rests with the presence of select actin regulators as suggested by Fritz-Laylin et al. (2017).

The role of actin-based protrusions in cell migration is significant, but efficient motility also appears to require myosin-based contraction that is generated by filament-forming class II (conventional) myosins. These myosins are critical for formation of cell polarity and retraction of the rear of a cell in animal cells and Dictyostelium amoebae. Interestingly, the distribution of conventional myosins on phylogenetic trees is similar to that of WASP/SCAR, even though myosin II is thought to have arisen after the initial eukaryotic diversification (Odronitz and Kollmar, 2007; Kollmar et al., 2012). Although it is not yet known if myosin II plays a distinct role in pseudopodial versus lamellipodial migration, it should be noted that myosin II–based forces generated at the cortex are required for blebbing motility (Paluch and Raz, 2013). Little is known at present about what dictates how fast-moving cells deploy their myosin II to cooperate with actin-based pseudopodia formation or how myosin II acts to generate blebs. The work by Fritz-Laylin et al. (2017) draws clear distinctions between different modalities of actin-based movement and identifies an underlying molecular signature for α motility. It will undoubtedly inspire further investigation into bleb- and lamellipodia-based motility and wider searches for evolutionarily conserved cytoskeletal regulators responsible for these processes.

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