Bleb Expansion in Migrating Cells Depends on Supply of Membrane from Cell Surface Invaginations

Graphical Abstract

Pre-bleb

bleb

Retraction

Highlights
- Migrating zebrafish PGCs allows for in vivo study of cellular protrusions
- Rapid expansion of bleb-type protrusions required for cell motility occurs locally
- Bleb expansion requires the unfolding of membrane invaginations as a membrane source
- The formation of plasma membrane invaginations depends on Cdc42

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In Brief
Blebs are cellular protrusions that play key roles in a range of physiological and disease processes. Employing the primordial germ cells of zebrafish as an in vivo model for cell migration, Goudarzi et al. show that the rapid expansion of protrusions of this type depends on unfolding of membrane invaginations.

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Bleb Expansion in Migrating Cells Depends on Supply of Membrane from Cell Surface Invaginations

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SUMMARY

Cell migration is essential for morphogenesis, organ formation, and homeostasis, with relevance for clinical conditions. The migration of primordial germ cells (PGCs) is a useful model for studying this process in the context of the developing embryo. Zebrafish PGC migration depends on the formation of cellular protrusions in form of blebs, a type of protrusion found in various cell types. Here we report on the mechanisms allowing the inflation of the membrane during bleb formation. We show that the rapid expansion of the protrusion depends on membrane invaginations that are localized preferentially at the cell front. The formation of these invaginations requires the function of Cdc42, and their unfolding allows bleb inflation and dynamic cell-shape changes performed by migrating cells. Inhibiting the formation and release of the invaginations strongly interfered with bleb formation, cell motility, and the ability of the cells to reach their target.

INTRODUCTION

Protrusions in motile cells can be formed by polarized actin polymerization at the cell front or by hydrostatic pressure generated in the cytoplasm by the contractile actomyosin cortex (Charras and Paluch, 2008; Paluch and Raz, 2013; Small et al., 2002; Diz-Munoz et al., 2016; Friedl and Wolf, 2010; Fackler and Grosse, 2008; Welch, 2015). Blebs are generated in regions of the cell circumference where the plasma membrane detaches from the cell cortex or at locations where membrane-to-cortex attachment is reduced. Such “weak spots” can result from local reduction in the level of molecules such as ezrin/radixin/moesin (Fehon et al., 2010; Paluch and Raz, 2013), or as a consequence of an increase in local contractility of the cell cortex (Keller and Eggli, 1998; Paluch et al., 2005). Certain models describing cell-shape changes during protrusion formation assume that the cell volume is preserved and generally consider the plasma membrane to behave as a flat elastic substance (Kabaso et al., 2011; Strychalski and Guy, 2013). In a recent study, however, Taloni et al. (2015) suggest that protrusion formation involves an increase in cell volume and surface, further highlighting the need for a membrane source for the bleb formation. Since stretching of a flat plasma membrane just prior to its rupture is limited to 2%–3% (Kleinschmidt, 2006; Kwok and Evans, 1981; Sheetz et al., 2008) and given that the force needed for such expansion is 2–3 orders of magnitude greater than the force cells can generate (Sheetz et al., 2008), the question that arises concerns the source of the additional membrane required for bleb inflation.

Here we used primordial germ cells (PGCs) that migrate through the developing embryo (Barton et al., 2016) as an in vivo model for investigating the cellular mechanisms contributing to protrusion formation in single-cell migration. We find that the rapid expansion of the bleb-type protrusions in zebrafish PGCs depends on invaginations found around the cell circumference. Unfolding of these structures provides the membrane for protrusion inflation in the direction of cell migration.

RESULTS

During the first day of embryonic development, zebrafish PGCs migrate from the positions at which they are specified toward the region where the gonad develops (Barton et al., 2016; Paksa and Raz, 2015). The migrating zebrafish PGCs can be visualized within the developing embryo by expression of fluorescent protein fusions that label specific cellular structures (Blaser et al., 2005; Kardash et al., 2010). It was shown that as PGCs migrate in live embryos, they extend bleb-type protrusions (Blaser et al., 2006; Goudarzi et al., 2012). Bleb expansion is characterized by rapid flow of cytoplasm driven by hydrostatic pressure, leading to outward deformation of the cell membrane (Paluch and Raz,
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