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SPOTLIGHT

Lipid synthesis leads the way for invasive migration

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Invasive migration requires cells to break through extracellular matrix barriers, which is an energy-expensive process. In this issue, Park et al. (https://doi.org/10.1083/jcb.202402035) highlight the importance of biosynthesis of fatty acids, phospholipids, and isoprenoids in driving invasive migration of the *Caenorhabditis elegans* anchor cell through a basement membrane barrier during development.

Invasive migration occurs when cells need to breach barriers, such as the tight mesh of extracellular matrix (ECM) fibers that comprise a basement membrane. Invasion is widely studied in tumor cells and is considered a key measure of malignant potential. The role of signaling pathways and the actin cytoskeleton has been extensively characterized in cancer, and structures called invadopodia mediate cancer cell invasion. But many normal healthy cells have invasive capacity too, including the *C. elegans* anchor cell (AC). The AC uses both proteases and physical force to forge the uterine–vulva connection, which involves the fusion of two epithelial layers, each with separate basement membranes (BMs). The AC produces a single protrusion, which breaches the two BMs and gradually widens the gap between the two epithelial layers in a process involving local actin assembly as well as a striking polarization of mitochondria, other organelles, and metabolic enzymes to the leading invasive edge (1).

In new work, Park et al. extend earlier involvement of the actin and metabolic machinery in invasion to show that lipid biosynthesis is also amplified and polarized during BM breaching (2). Lipogenesis is orchestrated by the lipogenic transcriptional coordinator SBP-1 (also known as SREBP in mammals). Park et al. define fatty acid synthesis, phospholipid synthesis, and the production of isoprenoids, the building blocks for protein prenylation, as key lipid drivers of AC invasion. Their study raises several fascinating questions about how lipid biosynthesis might aid invasion, both in development and potentially also in cancer (see Fig. 1).

How does new lipid biosynthesis aid the formation of invasive protrusions?

Lipid biosynthesis might aid the formation of the anchor cell's invasive protrusion due to the need for physical membrane expansion and/or the assembly of a protrusion containing a specific membrane composition that orchestrates invasion. When the anchor cell protrudes through the BM and intercalates between the vulval cells, it undergoes a transient ∼20% expansion in cell size over a time course of about 1 h (3). The AC assembles a large protrusion that can span a whole cell length and harbors concentrated Rho GTPases and GPI-anchored matrix metalloproteinases that contribute to BM removal. The source of the new membrane appears to be from the lysosomes (3), and Park et al. suggest that lipid production is enhanced to increase the lysosomal storage of lipid membranes, which will then be transported to and incorporated into the newly expanding protrusion.

In addition to the need for rapid expansion of the plasma membrane, the invasive protrusion comprises a domain with a specific lipid composition, enriched in cholesterol and Rho-family GTPases (Fig. 1). This is akin to cancer cell invadopodia, which also resemble apical membranes rich in cholesterol and Rho GTPases (4, 5). This specialized protrusion represents a diffusion barrier in the AC, which likely directs the organization of proteins, including metalloproteases (ZMP-1 in *C. elegans*) and signaling proteins, as well as a platform for the docking of secretory vesicles. Production of signaling phosphoinositides, such as PI(4,5)P2 and PI(3,4,5)P3, is key for the invasion of cancer cells and is controlled by ARF5/6 (6), so may also be worth investigating in the AC. Park et al. find that the AC appears to have solved the problem of rapid expansion and invasive protrusion by a combination of fatty acid synthesis to supply lysosomal stores with phospholipids and sphingolipid generation to ensure a deposit of the unique plasma membrane domains. The GPI-anchored metalloprotease ZMP-1 is a key cargo of these membrane domains, providing a platform for rapid matrix remodeling.

Do Rho and Ras-family small GTPases require polarization of the prenylation machinery to promote invasion?

Small GTPases of the Rho family actively promote signaling that aids protrusion of the plasma membrane and coordinate membrane and cytoskeletal activities that lead to invasion and migration. Park et al. found that enzymes involved in the synthesis of prenylation precursors polarize toward the AC invasive front, suggesting that polarization of the protein lipidation

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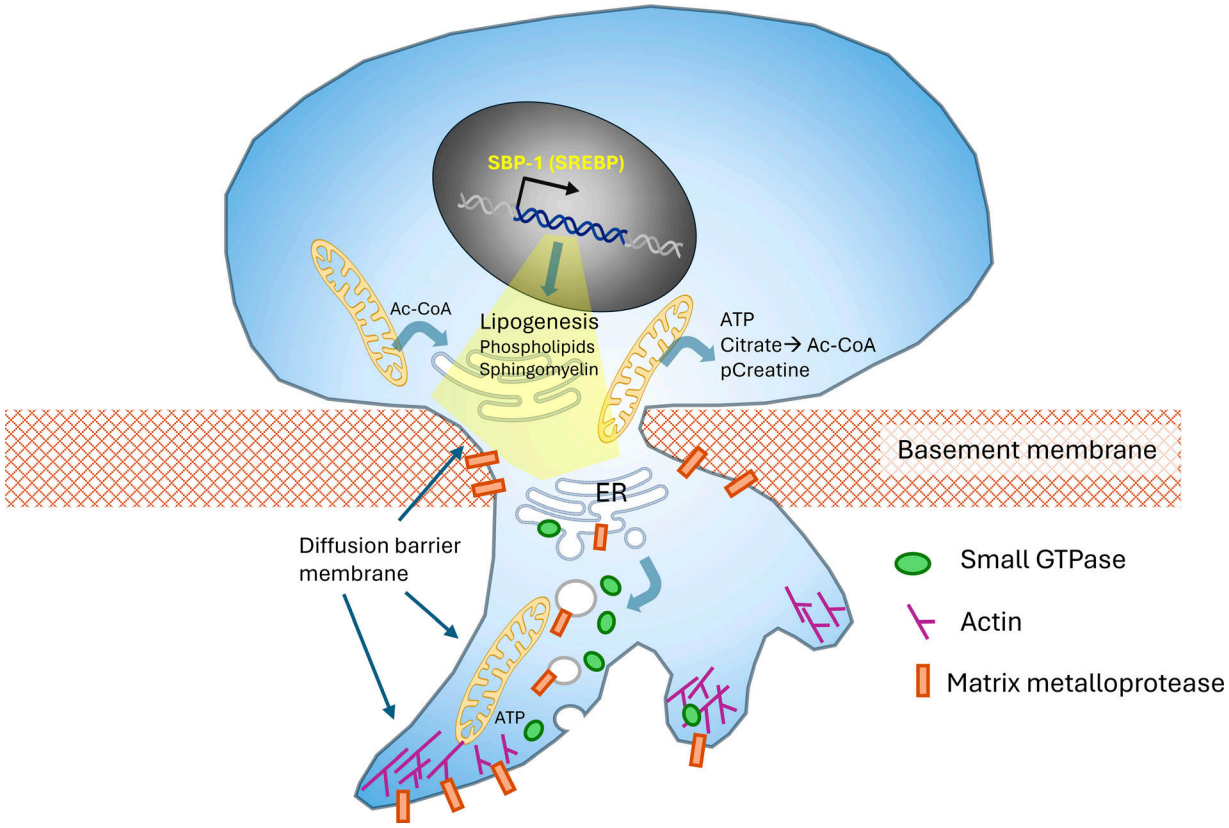

Figure 1. **Cartoon showing invasion through the basement membrane in the *C. elegans* anchor cell (AC).** SBP-1 transcription promotes transcription of key lipogenic enzymes, leading to enhanced production of phospholipids and sphingomyelin. Mitochondria are also recruited to the protrusion, where they produce ATP and potentially phosphocreatine to power actin-based force generation and citrate/acetyl-CoA to produce the building blocks for protein prenylation. The ER and ER exit sites are also recruited to the protrusion site to enhance polarized trafficking into the protrusion. Rho-family GTPases and the metalloprotease Zmp-1 are trafficked into the protrusion to facilitate signaling and matrix remodeling.

machinery could further drive protrusion. This raises questions about the rate of turnover of prenylation moieties on GTPases and whether/why new biosynthesis is key to providing a ready supply to the nascent AC protrusion. Previous studies in cancer cells showed that delivery of new GTP-bound Rac1 to the plasma membrane was crucial for protrusion formation (7), but did not address prenylation. Furthermore, it has been suggested by other studies that cycles of palmitoylation and depalmitoylation can regulate the association of Ras GTPases to recycling endosomes (8). Rac1 undergoes both prenylation at the C-terminus and palmitoylation at a more internal cysteine residue (9), indicating that it may cycle between lipidated states and require turnover and new lipid synthesis to maintain leading edge activation of targets. The study by Park et al. highlights the need to further investigate how polarization and activation of lipid biosynthesis may regulate the availability of active GTPases for signaling.

How and why does the secretion machinery, including the endoplasmic reticulum processing machinery and lysosomal stores of lipids, polarize to promote invasion?

Park et al. reported polarization of ER exit sites and lysosomal lipid stores toward the invasive front of the AC, indicating that delivery of specific lipid or lipid-associated cargoes towards the expanding edge may enhance invasion. While Park and colleagues did not observe lipid droplets in the AC, these have previously been shown to enhance invasion in pancreatic cancer cells and to provide energy to fuel invasion (10). This may be a key difference between cancer cells and the AC, where there is no evidence that lipids provide fuel for invasive behavior. In mammalian cells, Rab6-mediated polarized secretion from the Golgi directs lysosomal cargoes toward adhesion sites (11). This could be an efficient way to direct trafficking in the AC, but it is unknown how the secretion machinery polarizes into the AC protrusion.

What is the role of mitochondria, which also polarize to the leading edge and generate ATP and key metabolites?

Mitochondria track into leading edge and invasive pseudopodia, where they are thought to provide ATP to fuel actin and myosin dynamics (12–14). Park et al. add a new twist to this idea by suggesting that mitochondria produce metabolic building blocks, such as citrate, which is readily converted into acetyl coA, which feeds into the mevalonate pathway and into the biosynthesis of prenyl moieties for lipid modification of proteins. This could integrate our picture of how the biosynthesis machinery and the trafficking machinery polarize to allow the AC to perform its journey through the BM barriers.

Overall, an exciting new picture is emerging suggesting that cells can organize

their metabolic machinery to maximize synergy with production and secretion as well as energy utilization by active motors and actin (Fig. 1). This coordination can make invasive migration more efficient and help to avoid energy stress. The *C. elegans* AC is a fascinating example of a normal healthy invasion event that has many parallels with cancer invasion. This study should inspire new efforts to uncover how cancer invasion might also depend on polarized lipid biosynthesis. As well as enhancing our knowledge of how normal developmental migration takes place, this could uncover new weaknesses in tumor cells that could be exploited to combat metastatic spread.

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