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SPOTLIGHT

When a PLC-γ1–based light switch tells a cell which way to go

Jichao Sun[1,2] and Mo Chen[3,4]

Appalabhotla et al. (https://doi.org/10.1083/jcb.202507177) engineer a light-controlled version of PLC-γ1 (PLC-γ1) and show that activating it in an illuminated region of the cell membrane drives directional migration. The work redefines PLC-γ1 as an instructive signal in control of cell polarity.

A migrating cell must do one simple thing: choose a direction. That choice emerges from a web of signals organized in space and time. For decades, the command system has been framed through the lens of phosphoinositide signaling, a lipid-based system that patterns the cell membrane and helps define the front and back of a cell (1).

Phosphoinositides are a family of membrane lipids that can be rapidly interconverted (2). Small changes in their phosphorylation state create distinct signals that recruit proteins, reshape the cytoskeleton, and guide movement. Among them, phosphatidylinositol 4,5-bisphosphate (PIP_2) occupies a central position. It is both a precursor and a regulator, sitting at a key branching point in the network (2).

One route converts PIP_2 into phosphatidylinositol 3,4,5-trisphosphate (PIP_3) through phosphatidylinositol 3-kinase (PI3K). This pathway feeds into the well-known PI3K-AKT-Rac1-Arp2/3 cascade, which helps define the leading edge and drive forward movement (3, 4). In many models, PIP_3 accumulates at the front of the cell, where it promotes microtubule polymerization and actin filament rearrangement to facilitate the protrusions (1). For years, this pathway has been viewed as the cell's primary compass.

But PIP_2 has another fate. It can also be cleaved by PLC into two secondary messengers, inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG) (2). These molecules trigger calcium signals and activate PKC, opening a parallel signaling branch (1). Compared with the PI3K pathway, this route has received less attention in the context of directional migration, with a lack of research tools. It is clearly important, but whether it can guide movement or support it has remained unclear.

That question has come into sharper focus with work on one member of the PLC family: PLC-γ1.

This enzyme is required for certain types of chemotaxis, particularly in mesenchymal cells (5). But the requirement does not imply control. The central question is whether PLC-γ1 can instruct direction. If activated in one region of the membrane, is that enough to pull the cell that way?

Testing this idea has been challenging because PLC-γ1 is tightly regulated. In resting cells, it is held in an autoinhibited conformation that prevents access to its substrate, PIP_2, at the plasma membrane (6). Simply increasing its abundance or bringing it closer to the membrane is not sufficient to turn it on (7).

Appalabhotla and colleagues addressed this problem with an optogenetic approach. They engineered a system, OptoPLC-γ1, that allows PLC-γ1 to be recruited to the plasma membrane with pulses of blue light (8) (Fig. 1). This setup could either bypass or amplify upstream receptors, providing precise control over where and when the enzyme is positioned.

As expected, when the wild-type enzyme is recruited to the membrane, it remains largely inactive.

There is little evidence of PIP_2 hydrolysis or downstream signaling. This highlights the strength of its autoinhibition and suggests that membrane localization alone is not enough to activate PLC-γ1. The outcome differed markedly for cancer-associated PLC-γ1 mutants (9, 10). One variant, S345F, is partially relieved of autoinhibition (8). When this mutant is recruited to the membrane, it becomes active. PIP_2 is rapidly hydrolyzed.

To track this activity directly, the authors use a live-cell biosensor that detects DAG, one of the products of PIP_2 cleavage (11). The signal appears within minutes and is confined to the illuminated region. This provides a clear, real-time link between local recruitment and local lipid signaling.

What does this local change in lipids do to the cell?

When PLC-γ1 is activated on one side, that side pushes outward. A protrusion forms at the site of activation, while the opposite side retracts. The cell becomes polarized, with a clear front and rear.

[1]Department of Critical Care Medicine, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University, The First Affiliated Hospital, Southern University of Science and Technology), Shenzhen, China; [2]Department of Geriatrics, Guangdong Provincial Clinical Research Center for Geriatrics, Shenzhen Clinical Research Center for Geriatrics, Shenzhen People's Hospital, Shenzhen, China; [3]Department of Pharmacology, Joint Laboratory of Guangdong-Hong Kong Universities for Vascular Homeostasis and Diseases, School of Medicine and SUSTech Homeostatic Medicine Institute (SHMI), Southern University of Science and Technology, Shenzhen, China; [4]Laboratory of Oral Homeostatic Medicine, School of Medicine and SUSTech Homeostatic Medicine Institute (SHMI), Southern University of Science and Technology, Shenzhen, China.

Correspondence to Mo Chen: chenm7@sustech.edu.cn; Jichao Sun: sunjichao@mail.sustech.edu.cn.

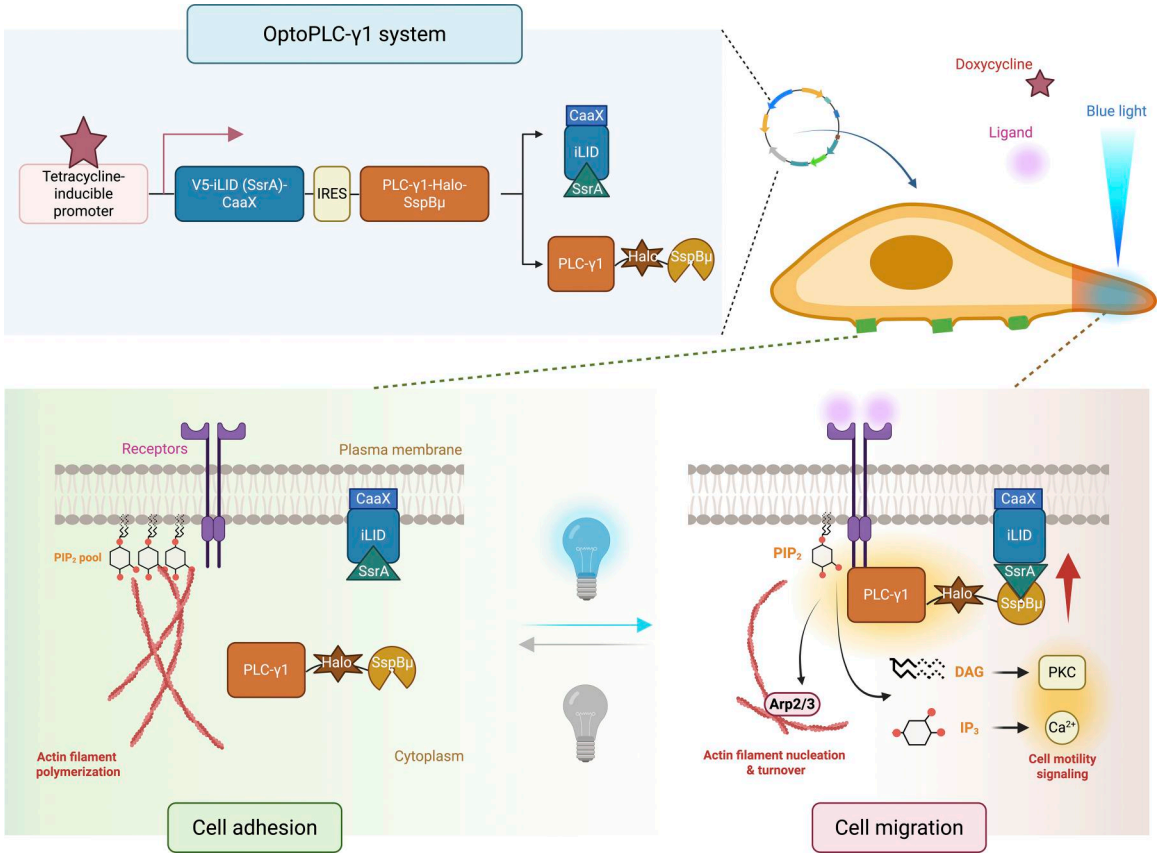

Figure 1. **Optogenetic control of PLC-γ1 directs localized lipid signaling and cell migration.** An optogenetic system (OptoPLC-γ1) enables light-controlled recruitment of PLC-γ1 to the plasma membrane. In the dark, PLC-γ1 remains cytosolic and autoinhibited and cells maintain a non-polarized, adhesive state with stable focal adhesions. Blue light induces the membrane localization of PLC-γ1, triggering local hydrolysis of the PIP_2 pool and production of DAG and IP_3. This spatially confined lipid remodeling promotes downstream signaling governing cell motility and Arp2/3-dependent actin dynamics, leading to protrusion at the illuminated edge and reduced adhesion at the rear. The balance shifts from stable adhesion to polarized migration, and graded stimulation drives persistent, directional cell movement. BioRender generated this figure.

This asymmetry arises from a single, localized signal.

The next question is whether this polarity can drive movement. Cells often form transient protrusions that do not lead to migration. To test this, the authors impose a light gradient across the cell. Instead of a fixed spot, they create a series of regions with increasing intensity.

The response is striking. Cells begin to move, and they keep moving. They follow the light gradient over extended periods, effectively using it as a directional cue. This shows that localized PLC-γ1 activity is not only sufficient to generate protrusions but can also sustain directed migration.

How does this happen? One might expect the answer to lie in the classic outputs of PLC signaling, PKC activation, and calcium release. Yet blocking these pathways only weakens the response.

Even when both are inhibited, cells can still polarize and move.

This shifts attention back to PIP_2 itself. Beyond its role as a precursor, PIP_2 helps anchor the plasma membrane to the actin cortex. It binds proteins that link the membrane to the cytoskeleton and regulates factors that control actin dynamics (12). Local hydrolysis of PIP_2 could therefore loosen membrane-cortex attachment and free actin regulators, facilitating actin nucleation and turnover to make it easier for the membrane to protrude.

Consistent with this idea, the authors find that the Arp2/3 complex is essential for the response.

This complex drives the formation of branched actin networks at the leading edge. In its absence, light-induced protrusions do not form. Thus, PLC-γ1 acts upstream of the actin machinery, but not primarily through PKC or calcium.

The study also revisits a common assumption in the field. Phosphorylation of PLC-γ1 at tyrosine 783 (pTyr783) has often been used as a marker of activation. Here, that relationship breaks down. The S345F mutant shows strong lipase activity with only modest phosphorylation, while a catalytically moderate active P867R mutant can be more phosphorylated than S345F. In contrast, the lipase-dead S345F/H335A mutant harbors the strongest pTyr783 level. Phosphorylation appears to reflect a conformational change rather than enzymatic activity. To directly assess catalytic activity, the authors complement this analysis by measuring OptoPLC-γ1-dependent PIP_2 hydrolysis through the accumulation of isotopically labeled inositol phosphates following lithium treatment. This functional readout provides a clearer picture of enzymatic efficiency, revealing a consistent ranking of activity (S345F > P867R > wild type) that is not captured by phosphorylation status alone.

Finally, these findings offer insight into relative diseases. Cancer-associated PLC-γ1 mutants are more responsive to membrane recruitment, converting local signals into sustained movement (8, 9, 10). This could help explain their link to invasive behavior, where cells gain the ability to polarize and migrate more efficiently. Several questions remain. How exactly does local PIP_2 depletion trigger actin assembly? How does PLC-γ1 converge with other pathways, such as PI3K, within the same cell? And what physical changes, such as membrane tension or cortical attachment, mediate the transition from signal to motion?

What this study makes clear is that direction can arise from a simple principle: where a signal happens matters. By showing that localized PLC-γ1 activity is sufficient to drive cell migration, Appalabhotla et al. (8) shift PLC-γ1 from a supporting to a leading role. More broadly, the OptoPLC-γ1 strategy for spatially controlled PIP_2 modulation may be adaptable to other subcellular PIP_2 pools, including the nucleus (1), where phosphoinositide signaling plays significant roles in oncogenesis and chemoresistance.

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