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PDK1-mediated activation of MRCKα regulates directional cell migration and lamellipodia retraction

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Directional cell migration is of paramount importance in both physiological and pathological processes, such as development, wound healing, immune response, and cancer invasion. Here, we report that 3-phosphoinositide-dependent kinase 1 (PDK1) regulates epithelial directional migration and invasion by binding and activating myotonic dystrophy kinase–related CDC42-binding kinase α (MRCKα). We show that the effect of PDK1 on cell migration does not involve its kinase activity but instead relies on its ability to bind membrane phosphatidylinositol (3,4,5)-trisphosphate. Upon epidermal growth factor (EGF) stimulation, PDK1 and MRCKα colocalize at the cell membrane in lamellipodia. We demonstrate that PDK1 positively modulates MRCKα activity and drives its localization within lamellipodia. Likewise, the retraction phase of lamellipodia is controlled by PDK1 through an MRCKα-dependent mechanism. In summary, we discovered a functional pathway involving PDK1-mediated activation of MRCKα, which links EGF signaling to myosin contraction and directional migration.