

PIP1a REGULATES RAC1 AND AKT ACTIVATION TO PROMOTE CELL MIGRATION AND PROLIFERATION

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Introduction. Rac1 activity is concentrated at the front of migrating cells where it initiates signaling processes necessary for cell migration in normal and pathological situations. The signaling pathways downstream of Rac1 are well characterized. However, how Rac1 activation is regulated to confer cell movement is incompletely understood.

Materials and methods. We examined the molecular mechanisms underlying Rac1 membrane localization and activation in osteosarcoma and breast cancer cell lines using a combination of cell biological, biochemical and knockdown approaches. PIPK1a expression in various human cancer types was analyzed using public databases.

Results and discussion. We discovered that Rac1 activation is regulated through complex formation with Type I phosphatidylinositol 4-phosphate 5-kinase alpha (PIPK1a), an enzyme that generates the second messenger phosphatidylinositol-4,5-bisphosphate. Formation of the PIPK1a-Rac1 complex led to the recruitment of Rac1 from the cytoplasm to the plasma membrane in response to the local activation of integrin receptors at the cell front (1). Significantly, the PIPK1a-dependent recruitment of Rac1 was essential for Rac1 activation in response to both, integrins and growth factors. Consequently, loss of PIPK1a impaired normal cell adhesion and directional cell movement (1). Thus, our studies identified a new molecular mechanism that regulates Rac1 signaling spatially and is essential for cell migration. Importantly, the regulation of Rac1 by PIPK1a may be clinically relevant. Only a small fraction of total Rac1 protein (<5%) is associated with the plasma membrane at any given time (8). Hence, genetic alterations that lead to a gain in PIPK1a may increase Rac1 activity and promote tumor cell motility and invasiveness. Indeed, PIPK1a expression is upregulated in motile, metastatic tumor cell lines compared to nonmetastatic ones. Importantly, elevated levels of PIPK1a correlate with enhanced Rac1 activation and contribute to cancer cell migration, invasion into Matrigel. Compared to normal tissue, PIPK1a expression is also increased in various types of tumors where aggressiveness correlates with increased Rac1 activity, including metastatic ductal breast carcinoma. In addition to its role in cell migration, PIPK1a is also required for the activation of the survival kinase Akt, suggesting that PIPK1a also promotes the proliferation and survival of tumor cells.

Conclusions. Our results suggest that PIPK1a may be a suitable target for the treatment of advanced breast cancer. In this context, we identified a natural compound, Bogol, with promising anti-proliferative and anti-migratory effects that inhibits PIPK1 activity and PIPK1-associated migration, and Akt activation.

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