Lamellipodin cooperates with the Scar/WAVE complex and Ena/VASP proteins to regulate cancer cell invasion.

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Abstract

Cell migration is essential for development while its deregulation causes cancer metastasis. Increased expression and activation of ErbB/EGF-receptors is a hallmark of many cancers including breast cancer. Lamellipodin is required for EGF-induced increase in cell proliferation[1] and is a key signalling hub linking growth factor receptors to effectors of the actin cytoskeleton: Lamellipodin is in complex with the EGF-receptor[2] and directly binds to Ena/VASP proteins (regulating actin filament elongation) and the Scar/WAVE complex (regulating F-actin branching) to control lamellipodia formation and cell motility[3-5].

The ability of cancer cells to invade through extracellular matrix is a prerequisite for metastasis. We found using a confocal microscopy-based invasion assay that Lamellipodin overexpression massively increases and knockdown impairs 3D migration/invasion of MDA-MB231 breast cancer cells into matrigel. Lamellipodin is recruited to the leading edge of cells by its Ras-association RA domain and phospholipid-binding PH domain[4]. Furthermore, we have recently shown that Lamellipodin is a novel RacGTP effector since RacGTP binds directly to Lamellipodin's RA-PH domains thereby positively regulating the Lamellipodin-Scar/WAVE interaction[3]. Consequently, we found that the RA or PH domains are required for Lamellipodin's function to increase breast cancer cell invasion.

Tyrosine kinases such as c-Src and c-Abl are proto-oncogenes and activated downstream of growth factor receptors. Lamellipodin is phosphorylated by c-Abl and this positively regulates Lamellipodin-Ena/VASP interaction[5]. We now discovered that Lamellipodin is also phosphorylated by c-Src and this positively controls Lamellipodin-Scar/WAVE interaction but not Lamellipodin-Ena/VASP interaction. We had previously shown that Lamellipodin regulates 2D migration via the direct interaction with Scar/WAVE but not Ena/VASP. Surprisingly we found that Lamellipodin controls 3D migration/invasion into matrigel via both Scar/WAVE and Ena/VASP. This suggests that Lamellipodin is a key switch to coordinate actin filament branching upon c-Src phosphorylation via Scar/WAVE with actin elongation upon c-Abl phosphorylation via Ena/VASP thereby controlling breast cancer cell invasion.

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