

論文の内容の要旨

論文題目 A study on phosphorylated FROUNT protein mediated CCR2/CCR5 chemokine receptor-dependent chemotaxis

(リン酸化フロントタンパクが制御する CCR2/CCR5 ケモカイン受容体依存的細胞遊走の研究)

氏名 陳 旻岑 Chen, Ming-Chen

The chemokine system is well known for its role in regulating directed cell migration (chemotaxis) that orchestrates the immune system. Upon chemokine stimulation, chemokine receptors, a type of G-protein coupled receptors, activate class IB PI3K to induce leukocyte infiltration into inflammation and tumor sites. However, among the subclasses of PI3K, the involvement of class IA PI3K (PI3KIA) in chemokine receptor signaling remains elusive. FROUNT, a CCR2 and CCR5 chemokine receptor-binding protein, was identified to activate the PI3K pathway to facilitate macrophage chemotaxis in the pathogenesis of cancer and inflammatory diseases, but how FROUNT directly connects to PI3K still remains unknown. Hence, my aim here was to unveil the connection of FROUNT with PI3K in a chemokine receptor activation-dependent manner. The PI3KIA-binding motif (YxxM) in FROUNT (residue 598–601) was found. Further, the tyrosine-phosphorylated FROUNT at residue 598 located on the binding motif (FROUNT-Y598P) was found to regulate the CCR2-mediated chemotaxis via PI3KIA. Co-immunoprecipitation experiments revealed that FROUNT-Y598P interacts with CCR2 and p85, the regulatory subunit of PI3KIA. Moreover, expression of the dominant-negative form of mutated p85 or 598th tyrosine-point mutated FROUNT inhibits CCR2-dependent chemotaxis. Furthermore, immunocytochemical analysis using the antibody against FROUNT-Y598P revealed that FROUNT-Y598P is translocated from the cytoplasm to the cell membrane in response to chemokine stimulation, where it co-localizes with Akt and filamentous actin at the leading edge of the lamellipodia. Conclusively, chemokine-induced FROUNT-Y598P translocation regulates formation of the CCR2/5-FROUNT-PI3KIA complex (named “chemotaxisome”) at the leading edge, which amplifies cellular polarization signaling for directional cell migration.