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Dictyostelium discoideum: A model organism for G protein coupled receptor-mediated chemotaxis in human diseases

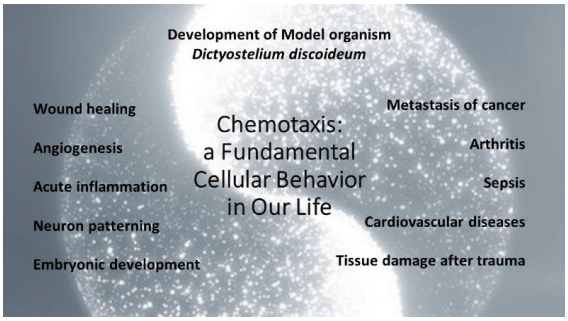

Figure-1: *Development of model organism Dictyostelium discoideum*

Chemotaxis is a directional cell migration guided by extracellular chemoattractant gradients. This cellular behavior plays critical roles in many physiological processes, such as neuron patterning, immune responses, angiogenesis, metastasis of cancer cells, and the early development of the model organism *Dictyostelium discoideum*. Inappropriate recruitment and dysregulated activation of human neutrophils contribute to tissue damage and cause autoimmune and inflammatory diseases. Neutrophils and *D. discoideum* sense and migrate to sites of inflammation using G Protein-Coupled Receptors (GPCRs) and share remarkable similarity in signaling pathways of governing this cellular behavior. During the last two decades, it has been proven that the latter provides a powerful model system to identify new components and develop novel theories to understand the molecular mechanism underlining chemotaxis. To accurately navigate through an enormous concentration-range gradient of various chemoattractants, neutrophils and *D. discoideum* cells employ a mechanism called adaptation, in which they no longer respond to present stimuli but remain sensitive to stronger stimuli. Homogeneous, sustained chemoattractant stimuli trigger transient, adaptive responses in many steps of the GPCR-mediated signaling pathway, that adaptation is a fundamental strategy for eukaryotic cell chemotaxis through large-range gradients of chemoattractants. Abstract modules and computational simulations have proposed some temporal dynamics of adaptation: An increase in receptor occupancy activates two antagonistic signaling processes, namely, a rapid excitation that triggers cellular responses and a temporally delayed inhibition that terminates the responses and results in adaptation. Many excitatory components have been identified; however, the inhibitor(s) largely remain elusive. The small GTPase Ras mediates multiple signaling pathways that control directional cell migration in both neutrophils and *D. discoideum*. Here, we identified Ras GAP protein that mediates Ras adaptation and chemotaxis in both *D. discoideum* and neutrophils. Our findings reveal a general inhibitory mechanism for chemotaxis and provide the potential therapeutic targets for inflammation-related diseases and cancer.

Recent Publications

1. X Xu, X Wen, D M Veltman, I Keizer-Gunnink, H Pots, A Kortholt and T Jin (2017) GPCR-controlled Membrane Recruitment of C2GAP1 Locally Inhibits Ras Signaling for Adaptation and Long-range Chemotaxis. *Proc Natl Acad Sci USA*; 114(47): e10092-e10101.
2. X Xu and T Jin (2017) ELMO Proteins Transduce G Protein Coupled Receptor Signal to Control Reorganization of Actin Cytoskeleton in Chemotaxis of Eukaryotic Cells. *Small GTPases*, DOI: 10.1080/21541248.2017.1318816.

Biography

Xuehua Xu has her expertise in developing and applying state-of-the-art imaging technologies to monitor the signaling network of GPCR-mediated chemotaxis in the model organism *Dictyostelium discoideum*, human neutrophils and breast cancer cells. The interplay between computational simulation and experimental verification allow her to identify new components and novel signaling pathways essential for chemotaxis. Her research focuses on understanding the molecular mechanisms of GPCR-mediated chemotaxis in multiple systems and identifying new therapeutic strategies for inflammatory diseases and metastasis of breast cancer.

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