Untangling STK40-MAPK interactions in endothelial and cancer cell migration

Ling-Yea Yu^{1,3}, Ting-Jen Tseng¹, Yung-Jen Xiao^{1,3}, Chia-Jung Tsai^{1,5,6}, Hsuan-Chao Lin², Feng-Chiao Tsai^{1,4}

¹Dept. of Pharmacology, National Taiwan University College of Medicine, Taipei, Taiwan, ²Dept. of Immunology, National Taiwan University College of Medicine, Taipei, Taiwan, ³Dept. of Medical Research, National Taiwan University Hospital, Taipei, Taiwan, ⁴Dept. of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, ⁵Ph. D Program in Human Biology, School of Integrative and Global Majors, University of Tsukuba, Tsukuba, Japan, ⁶International Institute for Integrative Sleep Medicine (WPI-IIS), University of Tsukuba, Tsukuba, Japan

Cell migration is important for embryonic development, tissue regeneration and cancer metastasis. Recent research identified cell migration-related genes, but how they crosstalk with each other remains unclear. To resolve this mystery, we conducted a "two-hit" cell migration screen using short hairpin RNA (shRNA) and small molecules inhibitors. The screen identified an interaction between MAPK signalling and STK40, a putative serine/threonine kinase. Suppression of both MAPK and STK40 synergistically blocked HUVEC cell migration, causing "synthetic immobility." Interestingly, previous literature reports showed that STK40 knockdown disrupted cell-cell interactions during cell migration, and that STK40 might affect cell differentiation through MAPK signalling. However, how STK40 regulates cell migration and how STK40 interacts with MAPK signalling are still unknown. We thus aim at elucidating the molecular mechanisms of STK40 and MAPK signalling during cell migration.

We started our exploration by tracing the migration of individual STK40-manipulated cells in monolayers or in scratch-wound healing assays. Interestingly, STK40 knockdown reduced the motility and cell-cell coordination in both cancer cells SAS and endothelial cells HUVEC, while STK40 over-expression caused opposite results. We further investigate how STK40 manipulated cell migration machinery, by inhibiting both STK40 and one of the actin-modulating molecules: alpha-catenin, Rac1, paxillin and myosin-light chain kinase. To our surprise, blocking Rac1 or paxillin completely eliminated STK40 effects on cell migration, indicating that STK40 modulated actin and focal adhesion dynamics. Such STK40-altered cytoskeletons might synergize with MAPK signalling to change cell motility and cell-cell interactions. We are currently working on their underlying mechanisms, with the ultimate goal to develop novel therapeutics targeting cell migration-related processes including wound healing, tissue repair, angiogenesis and cancer metastasis.