6. Introduction to

"Diacylglycerol Kinase-α mediates HGF-induced epithelial cell scatter by regulating Rac activation and membrane ruffling"

by

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submitted to Molecular Biology of the Cell

Cell migration is a critical step in tumor invasion and metastasis, and understanding the regulation of this process will lead to appropriate therapies for treating cancer.

The molecular mechanisms underlying cell migration are common to both non-neoplastic cells and cancer cells. As summarized above, cell migration involves multiple processes that are regulated by various signaling molecules. The actin cytoskeleton and its regulatory proteins are crucial for cell migration. During cell migration, the actin cytoskeleton is dynamically remodelled, and this reorganization produces the force necessary for cell migration. Because the inhibition of these processes decreases cell motility, the elucidation of the molecular mechanisms of actin reorganization is important for the development of anti-cancer drugs.

Due to the demonstration of the crucial role played by Dgkα downstream of tyrosine kinase receptors in the contest of cell migration, we analyzed the effect of Dgkα inhibition on several well-characterized morphological changes and signaling cascades upon HGF-induced migratory signal. For this purpose, MDCK epithelial cells were chosen as a model epithelium. Dgkα inhibition was achieved both by cell treatment with the pharmacological inhibitor R59949 and by stable expression of a dominant-negative mutant of Dgkα. We demonstrated for the first time that Dgkα is involved in the specific subset of events triggered by HGF contributing to spreading and early protrusion of membrane ruffles, while it is not involved in the disruption of E-cadherin mediated cell-cell adhesions. As a consequence, the clustering of newly-formed focal adhesion in the direction of migration is altered by Dgkα inhibition. Finally, in this paper we demonstrated that upon Dgkα inhibition, the activation of

the small GTPase Rac by HGF is impaired, thus providing a novel link between RTKs to small GTPases regulation in the context of cell migration.