CDB SEMINAR

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Role of Rho-kinase in cell polarization and directional migration

Summary

Polarized cell migration is a fundamental process in all organisms and is stringently regulated during tissue development, chemotaxis, wound healing, and development of some diseases. A polarity complex of Par3, Par6 and atypical protein kinase C (aPKC), functions in various cell polarization events including cell migration. Signaling crosstalks among the Rho family small GTPases, RhoA, Rac1 and Cdc42, play roles in directed cell migration. Activated Cdc42 binds to Par complex through the interaction with Par6. Par3 directly interacts with Tiam1/Taim2 (STEF), Rac1-specific guanine nucleotide exchange factors, and forms a complex with aPKC-Par6-Cdc42•GTP, leading to Rac1 activation. RhoA antagonizes Rac1 in certain types of cells, and Rho-kinase/ROCK/Rok (an effector of Rho) is involved in Rac1 inactivation. Recent advances reveal that the mutual antagonism between RhoA and Rac1 is important for polarized cell migration. However, the molecular mechanisms underlying Rho-kinase-induced Rac1 inactivation remain elusive.

We found that Rho-kinase phosphorylated Par3 and thereby disrupted its interaction with aPKC and Par6. Phosphorylated Par3 was observed in the leading edge, and central and rear portions of migrating cells. Knockdown of Par3 by small interference RNA (siRNA) inhibited cell migration and the Par complex-mediated Rac1 activation, which were recovered with siRNA-resistant Par3 but not with the phospho-mimic Par3 mutant. Our results indicate that RhoA/Rho-kinase inhibits Par complex formation through phosphorylation of Par3, resulting in Rac1 inactivation. We propose that RhoA/Rho-kinase regulates cell polarity through Par complex during directional migration

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