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The role of small GTPases in neutrophil migration during inflammation

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Abstract

Immune cells are the first line of cellular defense against infecting microorganisms by moving rapidly toward sites of infection. Neutrophils are most abundant leukocytes and the first immune cell to reach at the site of infection/inflammation. Impaired neutrophil recruitment and functions can cause life-threatening infections, while excessive neutrophil tissue infiltration contributes to inflammatory disorders and tissue injury. Cell migration is multistep process of rolling, adhesion and polarization with cytoskeletal reorganization. The small GTPases are key regulators of cytoskeletal reorganization, but their roles in neutrophil migration remained largely unknown. Our research dissects out key role of small GTPase Cdc42 and Rap1b in neutrophil migration. Cdc42 deficient neutrophils exhibited defective neutrophil polarity. By using a Cdc42 mutant for WASp Binding (Cdc42S71P), We then examined the role of the Cdc42 effector Wiskott Aldrich Syndrome protein (WASp) that failed to rescue neutrophil polarity. Furthermore, WASp–/– neutrophils also exhibited loss of polarity. Together, we show that Cdc42- WASp reorganize the plasma membrane into discrete lipid raft domains to induce CD11b clustering that capture and stabilize microtubules to regulate neutrophil polarity. In addition, Cdc42 loss dramatically reduced neutrophil recruitment to LPS-induced acute lung injury model.

Furthermore, proteomics analysis of neutrophil lipid rafts revealed putative regulators of neutrophil migration including GTPase Rap1b. We investigated its role in neutrophil migration based on its integrin-mediated functions. Detailed analysis discovered that surprisingly Rap1b loss enhanced neutrophil emigration into lungs, associated with increased susceptibility to endotoxin shock. Interestingly, Rap1b-deficient neutrophils exhibited increased transcellular migration that was selectively mediated by enhanced PI3K-Akt activation and invadopodia-like protrusions. Importantly, Akt inhibition in vivo suppressed excessive Rap1b–/– neutrophil migration into lungs and associated endotoxin shock. Recent data from 2-photon intra-vital imaging uncover functions of these small GTPase in interstitial migration. These findings uncover novel role of GTPase Cdc42 and Rap1b during inflammation-derived neutrophil migration and have far reaching importance for inflammatory processes.