Mechanochemistry of Single 2-Integrin-ICAM-1 Molecular Pair

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LFA-1 and Mac-1, two β_2 integrin members constitutively expressed on neutrophils (PMNs), mediate PMN recruitment *via* binding to their same ligand of intercellular cell adhesive molecule-1 (ICAM-1). The slow rolling and firm adhesion of PMNs rely on LFA-1 while the cell crawling is dependent on Mac-1, in which their distinct functions are hypothesized to be governed by their different binding capacities. Here we first applied an adhesion frequency approach to compare their kinetics in the quiescent and activated states using three different molecular species. Data indicate that the binding affinity A_cK_a for LFA-1 is much higher than those for Mac-1 both in the quiescent and activated states, mainly due to the highly-enhanced on-rate A_ck_f and, moreover, this on-rate difference between Mac-1 and LFA-1 is reduced after integrin activation. To understand the structural basis of integrin activation, we further performed the molecular dynamics simulations for binding of their I domains presenting on the top of each α subunit to the common ligand of ICAM-1. It was indicated that such the kinetics difference is likely attributed to the distinct conformations of key serine residues at the interface of Mac-1 or LFA-1 and ICAM-1. This work furthers the understandings in the binding differences between Mac-1 and LFA-1 and correlates the structural basis with the distinct functions of β_2 integrins from the viewpoint of allosteric pathways.

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