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LFA-1 / ICAM-1 ligation in T-cells influences both notch and TGF-β pathways

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Introduction: The T-cell integrin LFA-1 interacts with the ligand ICAM-1 expressed on endothelium and this interaction is important in T-cell motility. But downstream signalling pathways triggered by LFA-1/ICAM-1 ligation in T-cells are not clear. Here, we show that LFA-1-signalling for T-cell migration modulates gene expression, induces notch and TGF-β pathways and influences T-cell differentiation.

Methods: Primary human T-cells or T-cell line Hut78 were stimulated via LFA-1 by incubating on immobilised recombinant ICAM-1. Standard molecular, biochemical and imaging techniques including Affymetrix Gene Chip® microarrays, real-time PCR, Western-immunoblotting, siRNA, confocal microscopy and high content analysis were utilized.

Results: LFA-1/ICAM-1 ligation in T-cells induced genomic signatures associated with Notch and TGF-β pathways. We verified the activation of notch signalling by nuclear translocation of its cleaved intracellular domain and up-regulation of target genes Hey1 and Hes1. Moreover, a subset of molecules associated with reduced TGF-β responsiveness including Smad7, Smurf2 and Ski were found to be up-regulated, which was dependent of Stat3 and/or JNK activation. While LFA-1/ICAM-1 promoted Notch-dependent Tbet$^+$ Th1 polarization, LFA-1-stimulated T-cells were refractory to TGF-β-mediated induction of Foxp3$^+$ iTreg or RORγt$^+$ Th17 differentiation. Pre-treatment of cells with blocking anti-LFA-1 antibody, specific inhibitors or siRNA against identified molecules substantially suppressed LFA-1-mediated modulation of T-cell functional phenotypes.

Conclusion: We demonstrate a novel mechanism by which LFA-1/ICAM-1 ligation regulates immune response through notch and TGF-β pathways concurrent with its role in T-cell migration. These new findings have implications for normal immunologic functions and may also have therapeutic relevance for immune-mediated diseases.

Biography

Navin K Verma completed his PhD and Post-doctoral training in Clinical Medicine at Trinity College Dublin, Ireland. In 2013, he joined Lee Kong Chan School of Medicine, Nanyang Technological University, Singapore, where he is currently an Assistant Professor of Immunology and Cell Biology. His research is focused on molecular processes involved in T-cell motility. In particular, he is investigating biological roles and functional significance of the integrin LFA-1 signalling for T-cell migration in health and immune-medicated diseases.

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