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TLR2/MyD88 pathway-dependent regulation of dendritic cells by dengue virus promotes antibody-dependent enhancement *via* Th2-biased immunity

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Possible risk mediators in primary dengue virus (DenV) infection that favor secondary DenV infection to life-threatening dengue hemorrhagic fever (DHF) and shock syndrome (DSS) *via* antibody-dependent enhancement (ADE) have not yet been described. Here, DenV infection enhanced the expression of inflammatory mediators and activation molecules in dendritic cells (DCs) through TLR2/MyD88 pathway. TLR2 appeared to facilitate DenV infection in DCs that were less permissive than macrophages for viral replication. In experiments using separate evaluations of DenV-infected and uninfected bystander DCs, infected DCs showed impaired maturation accompanied with TLR2-dependent production of inflammatory cytokines, by which uninfected bystander DCs showed increased expression of co-stimulatory molecules. Differential phosphorylation of MAPK and STAT3 was also detected between DenV-infected and uninfected DCs. Furthermore, DenV infection stimulated Th2-polarized humoral and cellular immunity against foreign and DenV Ag *via* TLR2/MyD88 pathway, and DenV-infected DCs were revealed to facilitate Th2-biased immune responses in TLR2-dependent manner. TLR2/MyD88-mediated Th2-biased Ab responses to primary DenV infection increased the infectivity of secondary homotypic or heterotypic DenV *via* ADE. Collectively, these results indicate that TLR2/MyD88 pathway in DC-priming receptors can drive Th2-biased immune responses during primary DenV infection, which could favor secondary DenV infection to DHF/DSS *via* ADE.

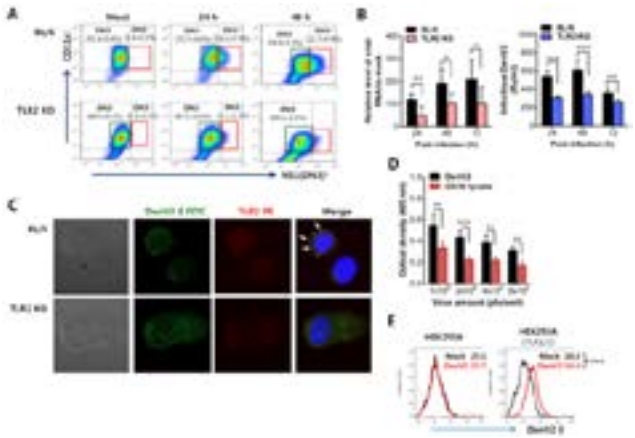

Figure : TLR2 molecule facilitates infection of DenV in DCs. (A) Infection frequency of BMDCs derived from BL/6 and TLR2 KO mice. (B) Multiplication of DenV2 in BMDCs derived from BL/6 and TLR2 KO mice. (C) Confocal microscopy of DenV2 Ag and TLR2 molecules in BL/6 and TLR KO BMDCs following DenV infection. (D) Binding of DenV2 virion to TLR2 molecule. (E) Cell-binding assay of DenV2 to TLR2-expressing cells.

Recent Publications

1. Katzelnick L C, Coloma J, Harris E (2017) Dengue: Knowledge gaps, unmet needs, and research priorities. The Lancet Infect. Dis. 17(3): e88-e100.
2. Modhiran N, Watterson D, Muller D A, Panetta A K, Sester D P et al. (2015) Dengue virus NS1 protein activates cells *via* Toll-like receptor 4 and disrupts endothelial cell monolayer integrity. Sci. Transl. Med. 7: 304ra142.
3. Chen J, Ng M M, Chu J J (2015) Activation of TLR2 and TLR6 by dengue NS1 protein and its implications in the immunopathogenesis of dengue virus infection. PLoS Pathog. 11(7): e1005053.

Biography

Seong Kug Eo in his lab, has focused on unveiling how hosts response to pathogen infection. They have used various infectious models to prove host responses upon pathogenic infection. His lab has recently found the detailed pathway that IFN-I signal pathway orchestrated environments to provide effective protection against mucosal viral infection. Moreover, his lab is expert on viral acute encephalitis caused by flavivirus infection.

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