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Indispensable role of TLR2 and TLR9 in regulating protection against mucosal infection with herpes virus through maturation of Ly-6Chi monocytes and NK cells

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The importance of TLR2 and TLR9 in the recognition of infection with herpes simplex virus (HSV) and HSV-caused diseases has been described, but some discrepancies remain concerning the benefits of these responses. Moreover, the impact of TLR2/9 on innate and adaptive immune responses within relevant mucosal tissues has not been elucidated using natural mucosal infection model of HSV. Here, we demonstrate that dual TLR2/9 recognition is essential to provide resistance against mucosal infection with HSV via an intravaginal route. Dual TLR2/9 ablation resulted in the highly enhanced mortality with exacerbated symptoms of encephalitis compared to TLR2 or TLR9 deficiency alone, coinciding with highly increased viral load in CNS tissues. TLR2 appeared to play a minor role in providing resistance against mucosal infection with HSV, since TLR2-ablated mice showed higher survival rate compared with TLR9-ablated mice. Also, the high mortality in dual TLR2/9-ablated mice was closely associated with the reduction in early Ly-6Chi monocyte and NK cell infiltration in the vaginal tract, which was likely to correlate with low expression of cytokines and CCR2 ligands (CCL2, CCL7). More interestingly, our data revealed that dual TLR2/9 recognition of HSV infection plays an important role in the functional maturation of TNF- and iNOS-producing dendritic cells (Tip-DCs) from Ly-6Chi monocytes as well as NK cell activation in vaginal tract. TLR2/9-dependent maturation of Tip-DCs from Ly-6Chi monocytes appeared to specifically present cognate Ag, which effectively provided functional effector CD4⁺ and CD8⁺ T cells specific for HSV Ag in vaginal tract and its draining lymph nodes. TLR2/9 expressed in Ly-6Chi monocytes was likely to directly facilitate Tip-DC-like features after HSV infection. Also, dual TLR2/9 recognition of HSV infection directly activated NK cells without the aid of DCs through activation of p38 MAPK pathway. Taken together, these results indicate that dual TLR2/9 recognition plays a critical role in providing resistance against mucosal infection with HSV, which may involve a direct regulation of Tip-DCs and NK cells in vaginal tract. Therefore, our data provide a more detailed understanding of TLR2/9 role in conferring antiviral immunity within relevant mucosal tissues after mucosal infection with HSV.

Biography

Seong Kug Eo's lab has focused on unveiling how hosts response to pathogen infection. They have used various infectious models to prove host responses upon pathogenic infection. In recent, EO's lab has 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 flaviviral infection.

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