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Distinct upstream role of type I IFN signaling in hematopoietic stem cell-derived and epithelial resident cells for concerted recruitment of Ly-6C^{hi} monocytes and NK cells *via* CCL2-CCL3 cascade

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Type I interferon (IFN-I)-dependent orchestrated mobilization of innate cells in inflamed tissues is believed to play a critical role in controlling replication and CNS-invasion of herpes simplex virus (HSV). However, the crucial regulators and cell populations that are affected by IFN-I to establish the early environment of innate cells in HSV-infected mucosal tissues are largely unknown. Here, we found that IFN-I signaling promoted the differentiation of CCL2-producing Ly-6C^{hi} monocytes and IFN-γ/granzyme B-producing NK cells, whereas deficiency of IFN-I signaling induced Ly-6C^{lo} monocytes producing CXCL1 and CXCL2. More interestingly, recruitment of Ly-6C^{hi} monocytes preceded that of NK cells with the levels peaked at 24 h post-infection in IFN-I–dependent manner, which was kinetically associated with the CCL2-CCL3 cascade response. Early Ly-6C^{hi} monocyte recruitment was governed by CCL2 produced from hematopoietic stem cell (HSC)-derived leukocytes, whereas NK cell recruitment predominantly depended on CC chemokines produced by resident epithelial cells. Also, IFN-I signaling in HSC-derived leukocytes appeared to suppress Ly-6Ghi neutrophil recruitment to ameliorate immunopathology. Finally, tissue resident CD11b^{hi}F4/80^{hi} macrophages and CD11c^{hi}EpCAM^{+} dendritic cells appeared to produce initial CCL2 for migration-based self-amplification of early infiltrated Ly-6C^{hi} monocytes upon stimulation by IFN-I produced from infected epithelial cells. Ultimately, these results decipher a detailed IFN-I–dependent pathway that establishes orchestrated mobilization of Ly-6C^{hi} monocytes and NK cells through CCL2-CCL3 cascade response of HSC-derived leukocytes and epithelium-resident cells. Therefore, this cascade response of resident to-hematopoietic–to-resident cells that drives cytokine–to-chemokine–to-cytokine production to recruit orchestrated innate cells is critical for attenuation of HSV replication in inflamed tissues.

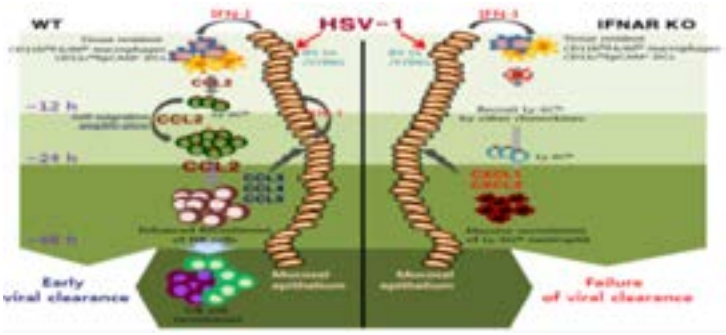

Figure : IFN-I–dependent cascade pathway for concerted recruitment of CD11b^{+}Ly-6C^{hi} monocytes and NK cells in mucosal tissues following HSV-1 infection. At the very initial phase of infection, CCL2 is initially produced from tissue resident CD11b^{hi}F4/80^{hi} macrophages and CD11c^{hi}EpCAM^{+} DCs through stimulation with IFN-I proteins produced from mucosal epithelium via the action of IFI-16 and STING in response to vaginal infection with HSV-1, thereby recruiting very early CD11b^{+}Ly-6C^{hi} monocytes within 12 h pi. Subsequently, the early infiltrated CD11b^{+}Ly-6C^{hi} monocytes contribute to migration-based self-amplification through the supply of higher levels of CCL2 at around 24 h pi. Delayed production of other CC chemokines (CCL3, CCL4, CCL5) from infected and uninfected epithelial cells, together with CCL2 provided by monocytes, then contributes to the recruitment of late-comer NK cells at 48 h pi. The lack of an initial CCL2 supply in *IFNAR KO* mice results in reduced recruitment of CD11b^{+}Ly-6C^{hi} monocytes; instead, CXC chemokines (CXCL1, CXCL2) primarily produced from resident cells and CD11b^{+}Ly-6C^{lo} monocytes probably induce massive recruitment of CD11b^{+}Ly-6G^{+} neutrophils.

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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