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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-6G^{hi} 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.

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 (PLoS Pathog., 2016). Moreover, EO's lab is expert on viral acute encephalitis caused by flaviviral infection. They have got many reports to unveil how immune system works on viral encephalitis caused by Japanese encephalitis virus (J. Neuroinflammation, 2014 and 2016).

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