Seong Kug Eo et al., J Infec Dis Treat 2018, Volume 4
DOI: 10.21767/2472-1093-C1-003

Blocking 4-1BB signal ameliorates the progression of Japanese encephalitis via divergent type I innate responses

Seong Kug Eo, Seong Bum Kim, Jin Young Choi, Jin Hyoung Kim and **Erdenebelig Uyangaa**
Chonbuk National University, South Korea

Japanese encephalitis (JE), a neuroinflammation caused by zoonotic JE virus, is the major cause of viral encephalitis worldwide and poses an increasing threat to global health and welfare. To date, however, there has been no report describing the regulation of JE progression using immunomodulatory tools for developing therapeutic strategies. We tested whether blocking the 4-1BB signaling pathway would regulate JE progression using murine JE model. Infected wild-type and 4-1BB-knockout (KO) mice were examined daily for mortality and clinical signs and neuroinflammation in the CNS was evaluated by infiltration of inflammatory leukocytes and cytokine expression. In addition, viral burden, JEV-specific T cell and type I/II IFN (IFN-I/II) innate responses were analyzed. Blocking the 4-1BB signaling pathway significantly increased resistance to JE and reduced viral burden in extraneural tissues and the CNS, rather than causing a detrimental effect. In addition, treatment with 4-1BB agonistic antibody exacerbated JE. Furthermore, JE amelioration and reduction of viral burden by blocking the 4-1BB signaling pathways were associated with an increased frequency of IFN-II-producing NK and $CD4^+$ Th1 cells as well as increased infiltration of mature Ly-6Chi monocytes in the inflamed CNS. More interestingly, DCs and macrophages derived from 4-1BB KO mice showed potent and rapid IFN-I innate immune responses upon JEV infection, which was coupled to strong induction of PRRs (RIG-I, MDA5), transcription factors (IRF7) and antiviral ISG genes (ISG49, ISG54, ISG56). Further, the ablation of 4-1BB signaling enhanced IFN-I innate responses in neuron cells, which likely regulated viral spread in the CNS. Finally, we confirmed that blocking the 4-1BB signaling pathway in myeloid cells derived from hematopoietic stem cells (HSCs) played a dominant role in ameliorating JE. In support of this finding, HSC-derived leukocytes played a dominant role in generating the IFN-I innate responses in the host.

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.

vetvirus@chonbuk.ac.kr

Notes: