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## Viruses in female breast cancer

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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. 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 pathway was associated with an increased frequency of IFN-II-producing NK and CD4<sup>+</sup> Th1 cells as well as increased infiltration of mature Ly-6C<sup>hi</sup> 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. Blocking the 4-1BB signaling pathway ameliorates JE via divergent enhancement of IFN-II-producing NK and CD4<sup>+</sup> Th1 cells and mature Ly-6C<sup>hi</sup> monocyte infiltration, as well as an IFN-I innate response of myeloid-derived cells. Therefore, regulation of the 4-1BB signaling pathway with antibodies or inhibitors could be a valuable therapeutic strategy for the treatment of JE.

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