Author's response to Journal Club by Bravo-Caparros and Nieto

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We thank the authors for their excellent review of our paper on the roles of CD8+ T cells and IL-10 in the resolution of paclitaxel-induced neuropathic pain (Krukowski et al., 2016). They provided an outstanding overview of our study in relation to the existing literature and raise an interesting point when comparing our results with a study by Liu et al. The comparison prompted us to further develop our working model. The journal club paper points out that there is an apparent discrepancy between our work and that of Liu et al. (2014), who showed in WT mice that intrathecal administration of anti-CD8 antibody reduces paclitaxel-induced neuropathy while intrathecal injection of CD8 T cells aggravated the response.

In our studies, we showed that severity or onset of neuropathy in response to paclitaxel was not different between WT and Rag1$^{-/-}$ mice that do not have mature T or B cells, but resolution of the pain response was delayed in these mice. Our finding that systemic administration of CD8 T cells or a mixture of CD4^{+} and CD8^{+} T cells to Rag1$^{-/-}$ mice normalized resolution, seems to be at odds with the findings in the Liu paper. In their Journal Club, Bravo-Caparros and Nieto suggest that the difference in route of administration of the cells (intrathecal in the Liu study and intravenous in our study) may be responsible for the differences. We think this is an interesting suggestion that leads to the hypothesis that the CD8 T cells may promote resolution of neuropathy outside the peripheral nervous system by "educating" monocytes/macrophages in secondary lymphoid organs to infiltrate into the DRG or nerve. This hypothesis is supported by our earlier work showing that antibody-mediated depletion of WT mice from circulating and non-resident monocytes/macrophages delays resolution of inflammatory pain (Willemen et al., 2014). In that study, we also presented evidence that the monocytes/macrophages that promote resolution of inflammatory pain need to be capable of producing IL-10. Collectively our findings would lead to a working model in which CD8 T cells promote education of monocytes/macrophages that produce IL-10 by interacting with these cells outside the nervous system. These "educated" monocytes/macrophages could then infiltrate into the spinal cord and release the IL-10 required for resolution of CIPN. We fully agree with Bravo-Caparros and Nieto that further studies are needed to identify the mechanism via which CD8 T cells and IL-10 signaling promote resolution of CIPN and experiments to solve this puzzle are ongoing in our laboratory.

Krukowski K, Eijkelkamp N, Laumet G, Hack CE, Li Y, Dougherty PM, Heijnen CJ, Kavelaars A. CD8+ T Cells and Endogenous IL-10 Are Required for Resolution of Chemotherapy-Induced Neuropathic Pain. The Journal of Neuroscience 2016;36(43):11074-83.

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