TNF MEDIATES DIFFERENTIAL MAST CELL TRAFFICKING IN NEUROGENIC CYSTITIS

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INTRODUCTION AND OBJECTIVE: Interstitial cystitis is considered a form of neurogenic inflammation in which abnormal release of neuropeptides from bladder sensory afferents induce mast cell (MC) degranulation and subsequent inflammation of urothelium. We have demonstrated previously that mast cells induce urothelial inflammatory responses in culture through the release of tumor necrosis factor (TNF). We have developed a mouse model of neurogenic cystitis to characterize the role of MCs and TNF signaling in vivo.
METHODS: Female wild type C57BL/6 mice (WT) and B6.129S mice deficient in TNFR1/2 (TNFR1/2 KO) were inoculated with Bartha's strain of pseudorabies virus (PRV) in the tail-base muscle to induce neurogenic cystitis. Mice were sacrificed at post infection day 3 (PID 3), and bladders were removed and prepared for histology. Inflammation was characterized by examining H&E sections. Mast cells were visualized by toludine blue staining. Bladder mast cell populations were identified within 4 layers of the bladder: urothelium, lamina propria, proximal detrusor, and distal detrusor.
RESULTS: Inoculation with PRV induced cystitis in WT mice, but TNFR1/2 KO mice did not develop cystitis by PID 3. MCs were distributed among the lamina propria, proximal and distal detrusor layers in mock-infected mice at PID 3. In contrast, MCs were increased 5.6-fold in the lamina propria of PRV-infected mice relative to mock ($p<0.0019$), and these MCs appeared to traffic from the proximal detrusor layer. No such MC trafficking was observed in TNFR1/2 KO mice ($p=0.57$).
CONCLUSIONS: These data indicate that TNF signaling is required for the development of cystitis and MC trafficking in the PRV-induced neurogenic cystitis model. Furthermore, the trafficking of MCs from the proximal detrusor indicates differential responses among distinct pools of mast cells.

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