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Neuroimmune crosstalk in neuropathic and visceral pain: HMGB1 and ATP as key mediators

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A neuroimmune crosstalk participates in diverse neuronal diseases including pathological pain. We have been studying the role of innate immunity involving DAMPs, such as HMGB1, a nuclear protein, and ATP in the development of chemotherapy-induced peripheral neuropathy (CIPN) and cystitis-related bladder pain. Intraplantar administration of HMGB1 causes long-lasting allodynia in rodents. Macrophage ($M\phi$)-derived HMGB1 is involved in the development of CIPN following paclitaxel treatment. Paclitaxel directly causes HMGB1 release from $M\phi$, which is promoted by ATP released from neurons stimulated with paclitaxel. Similarly, $M\phi$ -derived HMGB1 is involved in bladder pain accompanying cyclophosphamide (CPA)-induced cystitis in mice. Acrolein, a hepatic metabolite of CPA, triggers release of ATP from the urothelial cells, which in turn causes HMGB1 release from $M\phi$. The extracellular HMGB1 induces NK- κ B-dependent upregulation of cystathionine- γ -lyase, an H_2S -generating enzyme, in the urothelium by activating RAGE, and the generated H_2S enhances the activity of $Ca_v3.2$ T-type calcium channels expressed in nociceptors, resulting in bladder pain. Together, a neuroimmune cross talk mediated by DAMPs including HMGB1 and ATP appears to play a critical role in the development of CIPN and cystitis-related bladder pain.