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

Atsufumi Kawabata

Lab. Pharmacol. Pathophysiol., Fac. Pharm., Kindai Univ.

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 (Mϕ)-derived HMGB1 is involved in the development of CIPN following paclitaxel treatment. Paclitaxel directly causes HMGB1 release from Mϕ, which is promoted by ATP released from neurons stimulated with paclitaxel. Similarly, Mϕ-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 Mϕ. The extracellular HMGB1 induces NK-κB-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.