Toxoplasma gondii: manipulation of host cell machinery in the journey from intestine to brain

ABSTRACT

Question: From previous work, this group had discovered that infection of dendritic cells (DC) caused by the intracellular parasite (Toxoplasma gondii) induced a hyper-migratory state in DC which was a possible mechanism of the protozoan dissemination. For this study, their question was whether ϒ-aminobutyric acid (GABA) signaling was the possible mechanism underlying the control to the migratory properties of the infected DC.

Methods: To affirm the hypothesis, a series of complimentary experiments were conducted using both animal and human DC, also in vitro and in vivo.

Main results: The main results of the experiments were as follows:

First, murine and human DC produced GABA upon T. gondii infection. By quantitatively measuring GABA in the supernatant by enzyme-linked immunosorbent assay (ELISA), they found that live Toxoplasma infection of mouse DC, from the three predominant genotypes, increased GABA and the secretion occurred rapidly following infection. In addition, the fluorescence-activated cell sorting (FACS) of infected DC populations demonstrated that GABA production happened mainly in green fluorescent protein (GFP) + DC.

Second, functional GABAA receptors were expressed in mouse and human DC. The GABAA receptors of a3, ß3, and r1 subunit expression was determined with quantitative reverse transcription polymerase reaction (RT-qPCR). Subsequent immune-cytochemical stainings indicated expression of the ß3 subunit in both infected and non infected DC. These receptors were proved to be functional in the electrophysiology tests as membrane currents were induced in T. gondii-infected DC.

Third, transmigration of infected DC in vitro was reduced by targeting GABA synthesis and transport. Addition of inhibitors of GABA system such as glutamic acid decarboxylase (GAD) inhibitor (SC) and gamma-aminobutyric acid transporter 4 (GAT4) inhibitor (SNAP) to the infected DC had significantly decreased the secretion of GABA and also the transmigration of infected DC.

Fourth, the motility and chemotaxis of infected DC in vitro was modulated by GABAergic signaling in vitro. In a chemotaxis chamber system which consisted of chemokine CCL19 concentration gradient, Toxoplasma-infected DC demonstrated an increased random directional motility and velocity even in absence of chemokine compared to non-infected DC.

Finally, up-regulation of CCR7 in human and mouse DC were observed upon T. gondii infection in vitro. Furthermore, the dissemination of T. gondii in vivo was reduced by GABAergic inhibition in adoptively transferred infected DC as shown in the bioluminescence imaging (BLI) studies. Photonic emissions were also observed ex vivo in different organs, and the authors noted significant differences in the emissions on days 1–2 in the brain parenchyma.

Conclusion: The authors concluded that GABAergic signaling modulated the transmigration of DC and that the intracellular pathogen Toxoplasma gondii seizes the GABAergic signaling of DC like a trojan horse mechanism to assure dissemination.

Keyword: Toxoplasmosis; Host-pathogen interactions; Central nervous system diseases