UPR-induced modulation of DC functions involved in T cell-mediated immunity during T. gondii infection.

The intracellular parasite Toxoplasma gondii (Tg) is one of the most common zoonotic pathogens in humans. In immune-competent individuals, Tg can persist in cysts in the central nervous system leading to severe neuropathologies. The control of chronic toxoplasmosis relies on dendritic cell (DCs) functions that activate the IL12-induced T cell IFNγ-derived response. Recent work highlighted the role of the Unfolded Protein Response (UPR) in the modulation of DC and macrophage functions. So far, nothing is known about the impact of Tg infection on the UPR response. We hypothesize that Tg induction of the UPR could modulate the antigenic presentation ability and cytokine secretion of DCs, thereby impacting parasite virulence, dissemination and persistence.
Using both, a transgenic mutant strain of Tg impaired in the secretion of key virulent factors and Bone-Marrow-Derived DC depleted for the ER sensors IRE1α, XBP1 and CHOP, we examined the modulation of the UPR during infection by RTqPCR, ELISA and WB. In vivo, a genetic mouse model defective for the IRE1α branch of the UPR was used to determine the impact of this pathway on DC-mediated T cell immunity and Tg virulence by RTqPCR and flow cytometry.
In vitro, our results demonstrated that Tg modulates the MyD88-mediated activation of the UPR in BMDCs to promote its survival. We also found that the UPR controls a unique set of secreted pro-inflammatory cytokines during infection. In vivo, the IRE1α-Xbp1 pathway is specifically activated in CD8α+ DCs of infected mice and regulates T cell responses. In addition, IRE1α-Xbp1ΔDC mice do not survive infection revealing an essential protective role of this pathway in DC during toxoplasmosis.

Keywords : Dendritic cells, Toxoplasma gondii, UPR response, immune response
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