Abstract:
Helicobacter pylori infection induces chronic gastric inflammation that can progress to cancer. In this process, the virulence factor cytotoxin-associated gene A (CagA) plays a central role by directly altering epithelial cell signaling and inducing a strong Th1 immune response, which contributes to carcinogenesis. It is still barely understood how the bacterium evades clearance despite this solid immune response and persists lifelong. Dendritic cells (DCs) play a major role in determining the adaptive immune response toward H. pylori, and high levels of regulatory T cells have been detected infiltrating the gastric mucosa of H. pylori-infected patients, which contribute to bacterial persistence. Although murine studies indicate that H. pylori induces tolerization of DCs and impairs DC maturation, the virulence determinants involved are still controversial. Moreover, the signaling cascades engaged in human DC tolerization upon H. pylori infection remain unknown. In the current study, we analyzed the effect of H. pylori infection on human DC maturation and function, focusing on the virulence factors implicated and signaling pathways involved. Our results reveal that CagA is crucial for DC tolerization by modulating IL-10 secretion and, in turn, STAT3 phosphorylation, favoring a regulatory T cell immune response. Our findings help to unravel the
paradox why CagA-positive strains, although eliciting a stronger inflammatory response, have overcome evolutionary pressure and persisted in their human host.