

"ISG15 regulates peritoneal macrophage functionality against viral infection"

Susana GUERRA, PhD

Abstract:

Upon viral infection, the production of type I interferon (IFN) and the subsequent upregulation of IFN stimulated genes (ISGs) generate an antiviral state with an important role in the activation of innate and adaptive host immune responses. The ubiquitin-like protein (UBL) ISG15 is a critical IFN-induced antiviral molecule that protects against several viral infections, but the mechanism by which ISG15 exerts its antiviral function is not completely understood. Here, we report that ISG15 plays an important role in the regulation of macrophage responses. ISG15^{-/-} macrophages display reduced activation, phagocytic capacity and programmed cell death activation in response to vaccinia virus (VACV) infection. Moreover, peritoneal macrophages from mice lacking ISG15 are neither able to phagocytose infected cells nor to block viral infection in co-culture experiments with VACV-infected murine embryonic fibroblast (MEFs). This phenotype is independent of cytokine production and secretion, but clearly correlates with impaired activation of the protein kinase AKT in ISG15 knock-out macrophages. Altogether, these results indicate an essential role of ISG15 in the cellular immune antiviral response and points out that a better understanding of the antiviral responses triggered by ISG15 may lead to the development of therapies against important human pathogens.