P036 TLR-independent Type I interferon induction in response to an extracellular bacteria is based on an intracellular receptor.

M. Charrel-Dennis, Severa M., Goutagny N, Fitzgerald KA, Kasper DL and Golenbock DG

Harvard Medical School Boston MA, University of Massachusetts, Worcester, MA

We have studied and characterized the pathway leading to type I interferons production in mouse macrophages infected with an extracellular bacteria: *Streptococcus agalactiae*. Beta interferon (IFNβ), critical member of the Type I interferon's family, is produced by bone-marrow derived macrophages when stimulated with live GBS. We have used a highly interferon-inducible gene, *viperin,* as a read out for IFNβ production. Based on experiments using chemical inhibitors, we showed that the induction of type I interferon upon GBS encounter by macrophages relied on the phagocytosis and degradation of GBS by the macrophage. The use of genetic mutants allowed us to identify the critical role of the transcription factor interferon-regulatory factor 3 (IRF3) binding to the IFNβ promoter during GBS infection. Moreover, we identified the serine-threonine kinase TNFR-associated NF-KB kinase (TANK)-binding kinase a (TBK1) as the main kinase necessary in the phosphorylation of IRF3 during GBS infection. These events eventually lead to the upregulation of a large number of interferon-inducible genes such as *IRF7* and *viperin*. We have also identified that the activation of this pathway is MyD88 and Trif independent. The data presented above suggest that the phagocytosis and degradation of GBS by macrophages lead to the release of molecule binding to an intracellular receptor other than TLR with the ability to activated the TBK1/IKKepsilon kinases. This event eventually leads to the production of type I interferon and Interferon-inducible genes.