

THE ROLE OF INNATE IMMUNE RECEPTORS IN RESISTANCE OR SUSCEPTIBILITY TO *Brucella abortus* INFECTION

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The innate immune system is the first line of defensive mechanisms that protect hosts from invading *Brucella*. TLRs recognize *Brucella* spp. and bacterial components and initiate mononuclear phagocyte responses that influence both innate and adaptive immunity. Recently TLR2, TLR4 and TLR9 have been implicated in host interactions with *Brucella*. However, our group has determined that TLR9 has the most prominent role in resistance to *B. abortus* infection. Furthermore, MyD88-dependent signaling pathways are involved in *Brucella* activation of innate immune cells through TLRs. More recently, our group has determined that MyD88 KO mice are susceptible to *Brucella* infection. This susceptibility involves impairment on DC maturation and absence of IL-12 and TNF- α production. IL-12 was critical to this susceptibility since the treatment with rIL-12 enhances MyD88 KO resistance to *Brucella*. In addition to the MyD88-dependent pathway, NF- κ B is activated by the TRIF-dependent pathway. We observed that TRIF KO mice do not show enhanced susceptibility to infection as observed in MyD88-deficient animals. Stimulated to recent studies that have revealed the intracellular signaling cascades involved in immune response of bacteria infection dependent on IFN- $\alpha\beta$ R signaling pathway, we decided to also elucidate the role of type I interferon system activation in the innate immune response against *B. abortus*. Firstly, we determined that *B. abortus* induced IFN- α and IFN- β production, being IFN- β more prominent. To access the role of IFN- $\alpha\beta$ R signaling, IFN- $\alpha\beta$ R^{-/-} mice were infected and the number of viable bacteria recovery from spleen showed to be lower when compared to wild type mice. IFN- $\alpha\beta$ R^{-/-} showed a greater increase in IFN- γ and NO level in culture cells when stimulated with *B. abortus* and a lower apoptotic index in spleen from these mice. Related to this phenotype, TRAIL expression showed to be decreased in BMM ϕ s from IFN- $\alpha\beta$ R^{-/-} mice and lack of STAT1-Tyr701 phosphorylation was demonstrated in these cells. To understand the type I interferon activation by *B. abortus*, the IFN- β expression was measured in BMM ϕ s from TLR2^{-/-}, TLR4^{-/-}, TLR9^{-/-} or TRIF^{-/-}. It was demonstrated that IFN- β expression shows no difference in these mice when compared to control mouse cells. However, IFN- β expression requires MyD88-signaling. Finally, *Brucella* induced IFN- β and IFN- $\alpha\beta$ R signaling triggers host cell apoptosis and bacterial spread leading to enhanced susceptibility to *B. abortus* infection.