

Interferon- γ promotes abortion due to *Brucella* infection in pregnant mice.

Masahisa Watarai

Faculty of Agriculture, Yamaguchi University, Japan

The mechanisms of abortion induced by bacterial infection are largely unknown. We investigated abortion induced by *Brucella abortus* in a mouse model. High rates of abortion were observed for bacterial infection on day 4.5 of gestation, but not for other days. There was a higher degree of bacterial colonization in the placenta than in other organs and many bacteria were detected in trophoblast giant (TG) cells in the placenta. Intracellular growth-defective *virB4* mutant and attenuated vaccine strain S19 did not induce abortion. In the case of abortion, around day 7.5 of gestation (period of placental development), transient induction of IFN- γ production was observed for infection by the wild type strain, but not by the *virB4* mutant and S19. We also found that production of regulated upon activation normal T-cell expressed and secreted (RANTES) due to *B. abortus* infection contributes to abortion in pregnant mice. *B. abortus* infected pregnant IFN- γ knockout mice died within 15 days of infection, but non-pregnant IFN- γ knockout mice were still alive. With infection by wild type *B. abortus*, a large amount of RANTES production was observed in pregnant IFN- γ knockout mice, and induction of RANTES was also observed in normal pregnant mice infected with the wild type, but not in those infected with *virB4* mutant. Production of RANTES and IFN- γ were inhibited in mice inoculated with the respective RANTES or IFN- γ antibody. Neutralization of IFN- γ and RANTES, induced by *B. abortus* infection, served to prevent abortion. These results indicate that the production and function of RANTES are correlated with IFN- γ in pregnant mice infected with *B. abortus*. We investigated the role of heme oxygenase (HO)-1 in abortion induced by *B. abortus* infection in the pregnant mouse. Expression of HO-1 in the placenta was decreased by *B. abortus* infection and treatment with cobalt-protoporphyrin (Co-PP) inhibited abortion due to the bacterial infection. In TG cells, treatment with Co-PP was shown to up-regulate HO-1, whereas its expression was decreased by *B. abortus* infection. Such down-regulation of HO-1 in the TG cells was enhanced by IFN- γ treatment. HO-1 down-regulation in TG cells due to knockdown or IFN- γ treatment served to induce cell death caused by *B. abortus* infection. These results suggest that down-regulation of HO-1 in TG cells due to *B. abortus* infection is an important event in infectious abortion.