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Title: Understanding the role of NF-kB in innate and adaptive immunity to infection
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T. gondii is an opportunistic pathogen in patients with acquired and primary deficiencies in cell mediated immunity. Resistance to this pathogen is based on the production of IL-12 which is required for NK and T cell production of IFN-g, the major mediator of resistance to *T. gondii*. The NF-kB family of proteins are associated with many of the events that lead to the production of IFN-g required for resistance to *T. gondii*. For example, NF-kB is associated with the production of IL-12, and the ability of IL-12 to stimulate the production of IFN-g is dependent on co-factors, such as IL-18 and CD28, which activate NF-kB. Thus, NF-kB is likely to be involved in resistance to *T. gondii*. Our studies have shown that infection with *T. gondii* leads to activation of NF-kB and that two members of this family, c-Rel and RelB, are required for optimal production of IFN-g whereas NF-kB_2 has an important role in the maintenance. However, these findings do not distinguish between the role of these family members in accessory or lymphocyte functions. Therefore, transgenic mice in which activation of NF-kB in T and NK cells is specifically inhibited, were used to assess the role of NF-kB in these cells during toxoplasmosis. These mice were highly susceptible to *T. gondii* and had defective T and NK responses and these findings supports a direct role for NF-kB in the development of protective IFN-g responses. However, our studies indicate that c-Rel has a lineage and stimulus specific role in the production of IL-12. Specifically, c-Rel is required for Toll2/4 induced production of IL-12 by macrophages but other stimuli such as CpG and CD40L induce IL-12 independently of c-Rel. Moreover, the ability of dendritic cells to make IL-12 in response to all these stimuli was independent of c-Rel. Together, these studies provide us with a better picture of the role of NF-kB in the regulation of immune responses associated with resistance to intracellular pathogens.