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The gradual evolution of the immune system has allowed it to respond to various pathogens by different effector mechanisms. The potential range of immune responses that can be mounted against a given antigen is extensive and is characterized by the type of antigen and the cells of the immune system involved. Broadly classified, the vertebrate immune system consists of two components a) myeloid cells such as macrophages and neutrophils which form the major component of the innate immune system and b) lymphoid cells (B and T cells) which make up the adaptive immune system (Medzhithov, R. et al. 1998).

Innate immune recognition is mediated by a set of germline encoded non-clonal receptors which belong to several distinct protein families (Janeway, C.A. Jr 1992.; Medzhithov, R. et al. 1997a). These receptors recognize conserved molecular patterns associated with microbial pathogens (PAMPs for pathogen associated molecular patterns), and are therefore referred to as pattern recognition receptors (PRR) (Medzhithov, R. et al. 1997b). Toll-like receptors (TLRs) function as the PRRs in mammals and play an essential role in the recognition of microbial components. Since, PAMPs are present only in microbes and not in the host organism, their recognition by PRRs can signal the presence of pathogens. PAMP recognition can directly activate effector mechanisms of innate immunity, such as phagocytosis and induction of nitric oxide synthase in macrophages (Liu, Y. et al 1991.; Medzhithov, R. et al. 1997c). Additionally, PAMPs induce expression of a set of endogenous signals in the form of inflammatory and effector cytokines and chemokines. These signals control the recruitment of leukocytes to the sites of infection and regulate the activation of appropriate effector mechanisms.

Innate immunity was formerly thought to be a non-specific immune response characterized by engulfment and digestion of microorganisms and foreign substances by macrophages and leukocytes. However, innate immunity has considerable specificity and is capable of discriminating between pathogens and self. In addition, the activation of the innate immune response can be a prerequisite for the triggering of acquired immunity.
Adaptive immunity is influenced by the generation of helper T (T<sub>H</sub>) cell subsets and the consequent production of effector cytokines by these cells. Naive T<sub>H</sub> cells, when stimulated with cognate antigens by antigen-presenting cells (APCs) differentiate into two cell subsets: T<sub>H1</sub> and T<sub>H2</sub>. T<sub>H1</sub> cells secrete interferon-γ (IFN-γ) and promote mainly cellular immunity, whereas T<sub>H2</sub> cells produce interleukin 4 (IL-4), IL-5, IL-10 and IL-13 and primarily promote humoral immunity. The cytokine milieu is critically involved in this step. IL-12 drives T<sub>H1</sub> differentiation, whereas IL-4 induces T<sub>H2</sub> differentiation. These "conditional" (or instructive) cytokines are produced in the early phase of infection.

In addition to instructive cytokines, APCs use several costimulatory molecules, including CD80 and CD86, to signal T cells and to induce clonal expansion of antigen-specific T cells.

Signaling through PRRs involves signal transduction cascades comprising receptor associated and receptor non-associated protein tyrosine kinases. The Tec family of protein tyrosine kinases (PTKs) of which Bruton's tyrosine kinase (Btk) is a prototypical member are involved in a vast array of signaling pathways in cells of hematopoietic lineage. Btk is expressed in all hematopoietic cells except T lymphocytes and natural killer (NK) cells. It is critically important for B cell development as well as mature B cell activation and survival. It has also been shown to be important for IgE-mediated activation of mast cells resulting in allergic reactions. Btk kinase activity and tyrosine phosphorylation have both been shown to increase upon cross-linking or stimulation of the B cell receptor (BCR), the IgE receptor (FceRII), and a number of cytokine receptors such as those for IL-3, IL-5, IL-6 and IL-10, suggesting a general role for Btk in immune regulation. While the molecular mechanisms by which the BCR regulates B cell proliferation and survival are not well understood, Btk has recently been shown to lie downstream of the BCR on the pathway regulating activation of the key pro-inflammatory transcription factor NFκB.

There are some recent data about the role of Btk in macrophage functions. It has been shown that in Btk-deficient macrophages, induction of nitric oxide production
(NO) is severely inhibited, through inhibition of inducible nitric oxide synthase (iNOS) induction via interferon regulatory factor (IRF-1).

These data further raise questions, as to what is the role of Btk in other inducible macrophage effector functions. Additionally, whether Btk affects cell priming functions is also an issue. Answers to these questions would provide a conceptual framework to evaluate the role of Btk in inducing innate immune function and regulating it. Further, the role of Btk in transducing activation signals for other cells of the myeloid lineage also needs to be addressed.

The present study tries to address these questions by an analysis of signaling and functionality of these cell types in mice genetically deficient for Btk.