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Colonel Bruton’s Kinase Defined the Molecular Basis of X-Linked Agammaglobulinemia, the First Primary Immunodeficiency

Wasif N. Khan

The importance of pathogen-specific humoral immunity was recognized from the early days of immunology. However, that integrity of humoral immunity is essential to protect against life-threatening infections was established with the discovery of the first primary immunodeficiency disease (PID). In the spring of 1952, Colonel Ogden C. Bruton (1) reported an 8-y-old boy with extreme susceptibility to infections. He had suffered from ≥19 episodes of clinical pneumococcal sepsis within the past 4 y. Electrophoretic analysis revealed a lack of gammaglobulins (IgG) in the patient’s serum. Remarkably, furnishing IgG controlled the life-threatening infections. This was the first description of a PID and its IgG replacement therapy (1). Janeway and colleagues’ observations with an additional five males corroborated Bruton’s findings (2). Based on the X-linked pattern of inheritance, the disease later became known as X-linked agammaglobulinemia (XLA), and IgG replacement remains an effective treatment for XLA today. XLA, a prototype for B cell developmental defects and Ab deficiency, is the most frequent PID and is responsible for disease in 85% of early-onset Ab-deficient patients (3).

The XLA defect is primarily characterized by a failure to clear infections, particularly those involving encapsulated bacteria. This defect is accompanied by a severe reduction in the basal serum IgGs, as well as a failure to produce Ag-induced Ab responses against infectious agents or immunizations (3, 4). Thus, XLA is a selective Ab defect that leaves cellular immunity relatively intact. This phenotype suggested that the immune system is composed of specialized compartments for humoral and cellular immune responses. These insights were highly significant, because, at this time, the basis for cellular and humoral immunity was not known. The selective Ab defect in XLA contributed to the concept of specialized lymphocyte lineages and the discovery by Cooper et al. (5, 6) that the B cell lineage was the source of IgGs and that T cells regulated delayed-type hypersensitivity and graft rejection.

Cellular characterization of peripheral blood revealed that XLA patients have very few or virtually no circulating B cells (3, 7). The peripheral B cell deficiency was found to be due to a developmental block at the pre-B (CD19+cytoplasmic μ+) cell stage in the bone marrow (7–11). However, this defect is leaky, yielding a few IgM+immature B cells, which fail to develop into fully mature B lymphocytes (3, 4). Together, these studies traced the Ig deficiency to B cell developmental defects in the bone marrow (pre-B) and in immature B cells in the periphery. These cellular defects suggested that the protein encoded by the XLA gene was expressed and critical for B cell differentiation at multiple stages, from pre-B to plasma cells.

The observation that XLA exclusively affected males indicated that the defective gene was localized to the X chromosome and that the hemizygosity of the X chromosome in males resulted in expression of the disease phenotype. Because of the random nature of X-chromosome inactivation in females, X-linked genes display mosaic expression. The X-linked nature of the defect was confirmed by X-chromosome inactivation in XLA patients; only B cells displayed a nonrandom X inactivation (12). Refined gene mapping localized the XLA genetic defect to the Xq22 region (13–15). Finally, the Bentley group (16), taking advantage of technical advances in positional cloning, identified genomic clones spanning the XLA locus and analyzed the corresponding transcripts for mutations and disease association. The DXS178 polymorphic DNA marker was found to be closely linked, and a clone spanning this marker yielded a transcript that corresponded to a region altered in all members of an XLA family. The transcript encoded a novel cytoplasmic tyrosine kinase and was termed Ark (16). The Witte group, while searching for novel tyrosine kinases involved in B cell development, identified a cDNA clone that also mapped close to the DXS178 marker. This clone encoded a tyrosine kinase and was termed bpk (17).

The findings of the two groups were later reconciled, and the causative gene for XLA was named Bruton’s agammaglobulinemia tyrosine kinase (BTK). The seminal research articles by Vetrie et. al. (16) and Tsukada et. al. (17) describing the underlying genetic defect in XLA are selected for the Pillars of Immunology series for this issue of The Journal of Immunology.

Within 1 y of BTK’s discovery, the Xid locus in the CBA/N mouse strain was mapped to the Btk gene (18, 19). A naturally occurring mutation (R28C) was found in the pleckstrin homology (PH) domain (see below) of the Btk gene.

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Abbreviations used in this article: PH, pleckstrin homology; PID, primary immunodeficiency disease; PLC, phospholipase C; TI, T cell independent; XLA, X-linked agammaglobulinemia.

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Soon thereafter, gene-targeted mice with a \textit{Btk}-null mutation unequivocally demonstrated that \textit{Xid} is caused by a defect in the \textit{Btk} gene (20–22). The \textit{Xid} mouse strain has been a model for B cell and Ab immunodeficiency in mice since 1975 (23). Although \textit{Xid} mice display a much milder phenotype than do XLA patients, perhaps due to a compensatory effect of the Tec kinase (24), they do display B cell developmental defects at the pro- to pre-B and the immature to mature B cell stages (22, 23, 25, 26). \textit{Xid} mice also displayed a severely defective response to T cell-independent (TI) type 2 and a reduced response to TI type 1 polysaccharide Ags (22, 23, 25, 26). This observation strongly suggests that Btk function is required for TI immune responses in the mouse. Furthermore, this defect is reminiscent of the unusual susceptibility of XLA patients to encapsulated bacterial infections and suggests that this kinase is a critical signaling molecule in the regulation of TI Ab responses both in mouse and man. It remains to be investigated whether the lack of mature B cells in XLA or the lack of functional BTK in mature B cells is responsible for the TI Ab response defect. A failure to produce TI Ab responses is dangerous, because Abs facilitate complement-mediated lysis of bacteria and eliminate pathogens more rapidly than does a delayed T cell-mediated immune response.

After the discovery that defects in the \textit{BTK} gene caused XLA, it was expected that it would be possible to correlate gene mutations with the severity of disease phenotype, which would allow a better understanding of the functional significance of the BTK protein domains. More than 800 mutations have been identified that are scattered throughout the \textit{BTK} gene and include missense, nonsense, and insertion/deletion mutations; however, no straightforward structure–function correlation has been found (http://bioinf.uta.fi/BTKbase). This is due, in part, to variability of the phenotype among XLA patients, even those bearing the same mutation. Further, different mutations differentially affect the stability of the BTK protein, and studies in mice suggest that Btk protein levels are critical for its function at distinct B cell developmental stages and during activation processes (27, 28).

Studies of BTK revealed that it belongs to a unique family of cytoplasmic tyrosine kinases, termed the Tec family, and plays a role in BCR signaling distinct from the Src family kinase Lyn and the spleen tyrosine kinase Syk (29). The Tec kinases have unique features, including a PH domain (mutated in Xid) at the N terminus. Two of the Tec kinases, Tec and Itk, were known at the time of BTK discovery. However, discovery of the significance of BTK in a human disease brought this family of kinases to the attention of the wider scientific community. In addition to the PH domain, BTK contains a Tec homology domain followed by SH3, SH2, and kinase domains. BTK activation and function are intertwined with lipid metabolism and calcium signaling (30). In response to BCR engagement, BTK activation requires phosphorylation by the Src kinase Lyn in the catalytic domain and membrane recruitment by interaction of the PH domain with phosphatidylinositol 3,4,5-triphosphate, a PI3K product. Active BTK auto phosphorylates its SH3 domain and ignites downstream pathways by directly phosphorylating phospholipase C (PLC)-\(\gamma\)2. Active PLC-\(\gamma\)2 hydrolyzes phosphatidylinositol-4,5-bisphosphate into inositol triphosphate and diacylglycerol, mobilizing intracellular \(\text{Ca}^{2+}\) and activating protein kinase C and RasGRP (24, 31). BTK activation of PLC-\(\gamma\)2 provided a missing link between BCR and the generation of lipid second messengers. Consistently, BTK-deficient B cells are impaired in activating the protein kinase C- and \(\text{Ca}^{2+}\)-regulated transcription factors NF-\(\kappa\)B and NFAT (31–35).

Recent studies demonstrate an involvement of BTK function in many signaling pathways in addition to that downstream of the BCR. These include pathways induced by stimulation of cytokine receptors, G protein–coupled receptors, receptors of the TNFR family, and most TLRs (31, 36–38). Recent studies also suggest that TLR and BAFF receptors play an important role in regulating TI Ab responses. It remains to be explored whether defective BTK signaling in the TLR and BAFF receptor pathways contributes to the defective TI immune responses in XLA and Xid. A role for BTK in these signaling pathways is also relevant for immune tolerance and autoimmunity. Recently, a novel function of BTK in the full activation of TLR signaling was described in which it forms a complex with nonconventional endosomal MHC class II, CD40, and MyD88 (39). This type of signaling in B cells can enhance B cell survival and activation and can play a role in TLR7/9-dependent development of autoimmunity. The physiological significance of these newly discovered BTK signaling mechanisms in B cell development, survival, and immune responses both in health and autoimmune disease remains to be explored.

The identification of BTK has allowed detection of female carriers of the defective \textit{XLA} allele and corroboration of clinical diagnosis of XLA patients with specific mutations in the \textit{BTK} gene. The discovery of BTK also has implications for prenatal screening for the PIDs. Given that XLA is the most common monogenetic immunodeficiency in humans, the potential for gene replacement and correction therapy needs to be explored. Indeed, \textit{Btk} gene replacement has been successful in mouse models; thus, human XLA gene therapy remains a potential goal (40, 41). A successful human XLA gene therapy may require precise genetic manipulations, such as targeting the endogenous \textit{BTK} locus in stem cells. The origins of the clinical usefulness and potential for \textit{Btk} gene therapy lie in the discovery of XLA and the underlying defect in the gene encoding Colonel Bruton’s kinase.

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Disclosures

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References


