Regulation of Bruton's tyrosine kinase through phosphorylation

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Bruton's tyrosine kinase is a member of the Tec/Btk non-receptor tyrosine kinase family and these kinases are important for hematopoietic cell development and function. Although Tec/Btk family kinases share similarity of domain structure with Src and Abl kinases, the detailed regulatory mechanism is still not fully understood.

Mutations in Bruton's tyrosine kinase (Btk) have been shown to cause human X-linked agammaglobulinemia (XLA) and murine x-linked immunodeficiency (xid). Btk is expressed in multiple lineages of hematopoietic cell including all stages of B cell except plasma cell, mast cell and myeloid cells. However, defects in Btk have a dramatic effect only on B cell maturation and activation. Recent studies also demonstrated that Btk is a weak tumor suppressor in pre-B cell stage. Phosphorylation of Btk at various sites, including transphosphorylation at Y551 by Src family kinase Lyn, autophosphorylation at Y223 and phosphorylation at S180 by PKCβ, has been demonstrated to be critical ways of Btk regulation.

To look for more potential phosphorylation sites in Btk, we conducted mass spectrometry analysis of his-tagged Btk. Multiple phosphorylation sites were revealed when Btk was co-expressed with Lyn and a cluster of tyrosine/serine/threonine phosphorylation sites were found in the C-terminal of the kinase domain. Mutagenesis study showed that one of the potential tyrosine phosphorylation sites (Y617) is required for Btk-mediated calcium response. The effect of this potential phosphorylation on B cell development and function will also be investigated. This study will extend our understanding of the regulation of Btk and may provide insight into new therapeutic targets for Btk.