B Cell Antigen Receptor Signaling: Roles in Cell Development and Disease

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Signals propagated through the B cell antigen receptor (BCR) are vital for the development and survival of B lymphocytes in both the bone marrow and the periphery. These signals not only guide maturation and activation but also affect the removal of potentially self-reactive B lymphocytes. Interestingly, these signals are known to be either ligand-independent ("tonic" signals) or induced by ligand (antigen) binding to the BCR. We focus on the problems that occur in B cell development due to defects in signals emanating from the BCR. In addition, we present the B Cell Antigen Receptor Pathway, an STKE Connections Map that illustrates the events involved in B cell signaling.

The signals propagated through the B cell antigen receptor (BCR) are central to B cell development and the response to antigen. Defective BCR signaling can result not only in impaired B cell development and immunodeficiencies but also in a predisposition to autoimmunity. *Science*'s Signal Transduction Knowledge Environment (STKE) Connections Maps are host to the B Cell Antigen Receptor Pathway (http://stke.sciencemag.org/cgi/cm/CMP_6909), which depicts and details the general, or canonical, mechanisms in B cell signaling (*1*).

The BCR is a multiprotein structure containing an antigen-binding component membrane immunoglobulin (mIg), which is produced from the rearrangement of immunoglobulin heavy and light chain genes, noncovalently associated with disulfide-linked signal transducing elements Ig-α (CD79a) and Ig-β (CD79b) (*2*). BCR signaling is initiated upon binding of antigen to mIg, which induces receptor aggregation and subsequent phosphorylation of the immunoreceptor tyrosine-based activation motifs (ITAMs) of Ig-α and Ig-β. Both Ig-α and Ig-β contain a single ITAM motif composed of two tyrosine residues with surrounding consensus sequences (*3*, *4*). Phosphorylation of these tyrosine residues by the Src family kinases Lyn, Fyn, or Blk results in the recruitment of another tyrosine kinase, Syk, through interactions with phosphotyrosine-binding Src homology 2 (SH2) domains (*5*). Syk recruitment to Ig-α/β facilitates its phosphorylation, activation, and initiation of downstream signaling cascades (Fig. 1) (*6*).

A number of molecules that interact at or near the receptor play essential roles in B cell development and function. B cells require the expression of a surface BCR for development and survival. The BCR can come in the form of functionally rearranged heavy and light chain Ig molecules as found on mature B cells or, in the case of pro– and pre–B cells, as nascent heavy chains coupled to surrogate light-chain partners (such as λ5 and VpreB) (*7*). Expression of Ig-α and Ig-β is essential for BCR transport and surface expression (*8*, *9*); however, these molecules also function in signal transduction, which can affect B cell development. Mutation of both tyrosine residues in the ITAM of Ig-α blocks B cell development at the pro– to pre–B cell transition. In mice unable to express a mature BCR on their cell surfaces ($RAG^{-/-}$), membrane targeting of the cytoplasmic domains of Ig-α and Ig-β alone is sufficient to promote B cell development (*10*, *11*). Thus, signals transduced by Ig-α, and presumably Ig-β, appear to be essential for the early stages of B cell development (*10*, *12*).

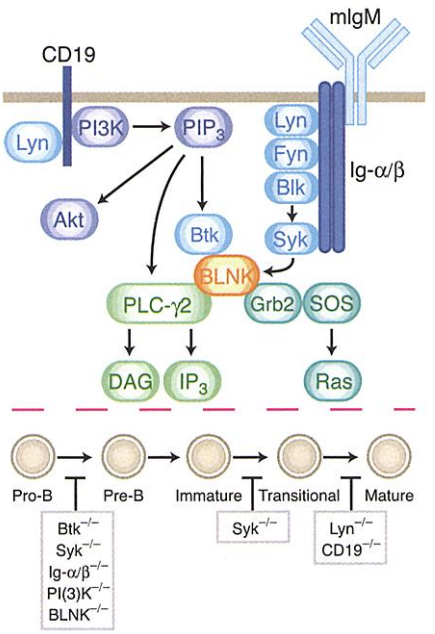

Fig. 1. B cell signaling and B cell development. (Upper panel) A simplified account of known signaling pathways activated after BCR activation. Arrows indicate physical interactions and/or activation steps. Abbreviations are as follows (for molecules not mentioned in the text): Akt, a protein kinase; BLNK, B cell linker protein, an adaptor protein; Grb2, an adaptor protein; PLC-γ2, phospholipase C–γ2, a phospholipase; DAG, diacylglycerol; IP_3, inositol trisphosphate; SOS, Son of Sevenless, a Ras exchange factor; Ras, a small guanosine triphosphate–binding protein. (Lower panel) Signals that influence stages of B cell development.

Many protein tyrosine kinases have vital roles in directing B cell development. The tyrosine kinase Lyn, for example, phosphorylates ITAM tyrosine residues after BCR aggregation but also negatively regulates B cell signaling (*13*). $Lyn^{-/-}$ mice display normal bone marrow B cell development but have difficulty in sustaining a mature peripheral B cell population (*14*). B cells that do progress to the mature B cell stage exhibit a predilection for autoreactivity (*15*, *16*). This phenotype may be due in part to Lyn's additional role in phosphorylation of the immunoreceptor tyrosine-based inhibitory motif domains (ITIMs) of inhibitory coreceptors, such as CD22 (*17*). Thus, although Lyn's absence does impede the progression of signals through the BCR and may contribute to impaired survival of mature B cells, it appears to have a nonredundant function in inhibitory pathways that are important for the maintenance of tolerance (*18*).

The tyrosine kinase Syk is also critical for proper B cell development (*19*–*21*). Mice deficient in Syk exhibit an early block in B cell development, with cells accumulating at the late pro–B cell stage (*22*, *23*). Unlike B cells of $RAG^{-/-}$ mice, which arrest at a similar point, B cells of $Syk^{-/-}$ animals are capable of initiating Ig heavy-chain rearrangement but progress no further, which suggests that Syk is essential for signaling through the BCR at this point in development.

The Tec family kinase member Bruton's tyrosine kinase (Btk) is involved in B cell development, and its dysfunction leads to often severe immunodeficiencies. Naturally occurring mutations to Btk are responsible for X-linked agammaglobulinemia (XLA) in humans and a related deficiency in mice, *xid*.

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XLA results in an enlargement of the pro–B cell population and inefficient development of pre–B cells in the bone marrow, resulting in very few mature peripheral B cells (1% of normal) and severe hypogammaglobulinemia of all immunoglobulin isotypes (*24*, *25*). The *xid* (and XLA) phenotype is the result of a point mutation in the pleckstrin homology (PH) domain of Btk. However, *Xid* mice have a less dramatic decrease in the number of peripheral B cells than do XLA patients, but many of these peripheral cells appear immature in nature. *Xid* mice have relatively normal serum concentrations of IgG1, IgG2a, and IgG2b but markedly reduced serum concentrations of IgM (*26*, *27*). Mice with a targeted deletion of Btk (*28*, *29*) show similar characteristics. The differences in severity of phenotypes observed between humans (XLA) and mice (*xid*) might be due to the presence in the latter of the molecule Tec, which may partially compensate for defective Btk activity (*30*).

CD19 is a B cell coreceptor that augments signals delivered through the BCR by lowering the signaling threshold for B cell activation. Although CD19 is expressed throughout B cell development, no absolute requirement for this molecule is evident until the mature B cell stage, where lack of CD19 causes a substantial decrease in the number of mature splenic B cells (*31*). In contrast, transgenic mice in which CD19 is overexpressed exhibit a hyperresponsive B cell phenotype with a predisposition for autoimmunity (*31*, *32*).

Another key pathway activated after BCR activation involves phosphoinositide 3-kinase (PI3K), a lipid kinase that mediates production of phosphatidylinositol 3,4,5-trisphosphate [$PI(3,4,5)P_3$] from phosphatidylinositol 4,5-bisphosphate [$PI(4,5)P_2$]. Disruption of PI3K expression by genetic deletion (*33*, *34*) results in impaired B cell development, vastly decreased numbers of pre–B cells and mature peripheral B cells, and reduced serum Ig concentrations. The observed defects are reminiscent of those found in *xid* mice. This is consistent with the requirement for $PI(3,4,5)P_3$ generation in BCR-mediated activation of Btk (*35*).

Further elucidation of the signaling cascades initiated by BCR aggregation will aid our understanding of both immunodeficiency and autoimmune disorders resulting from aberrant BCR signaling.

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VIEWPOINT

Connections and Regulation of the Human Estrogen Receptor

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Estrogen regulates a plethora of functionally dissimilar processes in a broad range of tissues. Recent progress in the study of the molecular mechanism of action of estrogen(s) has revealed why different cells can respond to the same hormone in a different manner. Three of these findings are of particular importance: (i) There are two genetically and functionally distinct estrogen receptors that have distinct expression patterns in vivo; (ii) the positive and negative transcriptional activities of these receptors require them to engage transcription cofactors (coactivators or corepressors) in target cells; and (iii) not all cofactors are functionally equivalent, nor are they expressed in the same manner in all cells. Thus, although the estrogen receptor is required for a cell to respond to an estrogenic stimulus, the nature and extent of that response are determined by the proteins, pathways, and processes with which the receptor interacts.

The ovarian steroid hormone estrogen has a primary role in the establishment and maintenance of reproductive function. However, the widespread use of estrogen-containing medicines as contraceptives and as components of hormone replacement therapies in postmenopausal women has highlighted additional functions for estrogens in the skeleton, the cardiovascular system, and the nonreproductive centers of the brain (*1*). In addition to these normal homeostatic functions, inappropriate responses to the mitogenic actions of estrogens occur in the majority of malignant breast tumors. Hence, it is not surprising that there is intense interest in defining the molecular mechanism(s) of action of this hormone, so as to clarify how it can participate in a wide variety of seemingly unlinked biological processes.

The biological actions of estrogens are manifest only in cells expressing a specific high-affinity estrogen receptor (ER) (*2*). The ER is in fact a ligand-dependent transcription factor, which accounts for the latency of most estrogenic responses in target tissues (*3*). Recent genetic, biochemical, and pharmacological dissection of the estrogen signal transduction pathway has led to the identification of numerous proteins and processes that impinge on ER function, revealing an unexpect-

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