REVIEW

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Ligand-independent activity of the B cell antigen receptor in physiology and pathology

Daniel Corcos

The Babraham Institute, Babraham, Cambridge, UK

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Abstract

The B cell receptor (BCR) is required for stimulation of B cells by antigen, and is also involved in the negative selection of autoreactive B cells. In the past few years, a constitutive ligand-independent signaling activity of the BCR has been demonstrated. In this paper, the various findings are summarized and their interpretation and their significance, both in pathology and in physiology discussed. The constitutive activity of the BCR may be important for tumor formation, at least in the case of heavy-chain diseases, neoplastic proliferations developed from B cells. A large body of evidence suggests that this activity could be required for B cell survival and would play a role in B cell development as a process monitoring BCR functionality. A model explaining signaling in the absence of antigen as a function of dimer formation is proposed. The putative constitutive activity of the pre-BCR is also discussed.

Key words: B cell receptor, signaling, oncogenic growth factors, heavy-chain diseases, B cell development.

Corresponding author: Daniel Corcos, The Babraham Institute, Babraham, Cambridge CB22 3AT 4AT, UK, tel.: +44 1223 496304, fax: +44 1223 496023, e-mail: daniel.corcos@bbsrc.ac.uk

INTRODUCTION

It has been known for decades that the adaptive response of B cells requires specific recognition of pathogens by B cell surface immunoglobulins. The idea that antigen recognition triggers a signal originating from the B cell receptor (BCR) was substantiated by the discovery of membrane depolarization and calcium fluxes upon BCR crosslinking [9] and then definitively confirmed by the identification of the signal transduction apparatus, including the Igα/Igβ heterodimer and tyrosine kinases [45]. More recently, an antigen-independent signaling activity has been demonstrated for abnormal [12] and normal BCRs [54], which raises the question of its role in physiology and pathology.

STRUCTURE OF THE BCR

The BCR consists of a membrane immunoglobulin (comprising two heavy chains and two light chains) non-covalently associated to a disulfide-linked heterodimer of the signaling molecules Igα and Igβ (reviewed in [21]). These signaling molecules are transmembrane proteins which each contain one immunoreceptor tyrosine-based activation motif within their cytoplasmic tail (Fig. 1). Anti-IgM-induced aggregation of the BCRs results in the phosphorylation of multiple proteins, including Igα and Igβ, by protein tyrosine-kinases (PTKs). The structure of the pre-BCR, expressed in pre-B cells, is close to that of the BCR, except for the presence of surrogate light chains, formed by the associ-

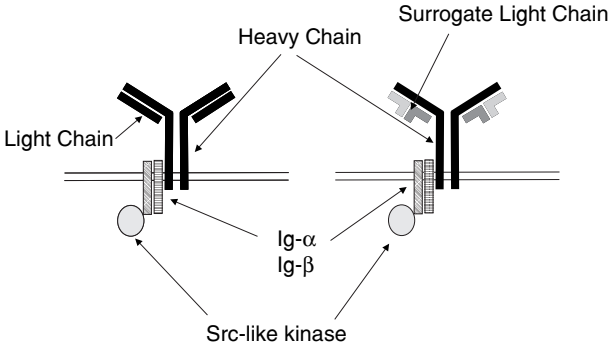

Fig. 1. The BCR is shown, comprising a surface immunoglobulin and a signal transduction apparatus. In the pre-BCR, the light chain is replaced by a surrogate light chain, formed by the λ-like and V-preB molecules. The pre-BCR tends to be present in an aggregated form [42].

ation of Vpre-B and λ-like (λ5 in the mouse) rather than light chains [32, 39]. Tyrosine phosphorylation of substrate proteins has been observed in pre-B cell lines in the absence of antibody-induced aggregation [3].

LIGAND-INDEPENDENT ACTIVITY OF TRUNCATED BCRs: THE CASE OF HEAVY-CHAIN DISEASES

A ligand-independent signaling activity by surface receptors was first described for oncogenic mutant forms of growth factor receptors (GFR) with PTK activity (reviewed in [6]). The ligand-independent activity can be evidenced by the ability of the mutant GFR to support the growth of cells in the absence of the cognate growth factor. In some cases, this constitutive activation is brought about by the loss of the ligand-binding domain of the receptor. This mechanism was demonstrated for the first time in the case of a mutant form of the epidermal GFR [38], and has been extended to other receptors, some of which do not belong to this class of receptors with PTK activity (for instance the prolactin receptor [37]). The mechanism by which the ligand-binding domain exerts a negative control on signaling might involve spontaneous dimerization in the absence of ligand [4, 40], but the absence of receptor down-regulation has been reported as an alternative mechanism [27].

Heavy-chain diseases (HCD) are B cell malignancies that are characterized by the production of monoclonal truncated immunoglobulin heavy (H) chains without associated light (L) chains by the malignant B cells [48]. Since the alteration occurs on the H-chain gene, it results also in the production of an abnormal BCR without antigen-binding capacity. Cells with this abnormal receptor are specifically selected by the carcinogenetic process, since these clonal proliferations are associated with clinically specific entities (this is particularly true for αHCD). While a specific advantage for the cells could in theory be the consequence of the loss of a negative (tolerogenic) signal triggered by antigen binding, this hypothesis is very unlikely because point mutations induced by somatic hypermutation in the CDRs would be sufficient to prevent binding and would be expected to be much more frequent than large deletions, as seen in HCD. Therefore, truncation of the BCR was hypothesized to confer a growth or survival advantage to the cells in a manner similar to that of oncogenic growth factors, by providing an aberrant constitutive signal [10]. In the absence of a B cell line whose growth would be supported by the cognate antigen, it is not possible to directly demonstrate such an activity. Transgenic mice expressing a membrane mu HCD protein (a V-less μ similar to the monoclonal protein found in two patients) have been created. The ΔVμ HCD protein leads to "allelic" exclusion with inhibition of endogenous H-chain gene rearrangement and allows the development of pre-B cells in the absence of surrogate light chains [14, 12]. A similar result is obtained with another truncated form of μ H-chain [49]. Since both the μ chain and the surrogate L-chain (the latter bearing the putative ligand-binding site) are required for pre-B cell development [32], this indicates that truncated H-chain-bearing pre-BCRs deliver a constitutive or ligand-independent signal, which has been interpreted by several groups as evidence for the absence of pre-BCR ligand. However, this latter interpretation remains a controversial and unresolved issue, as will be discussed further.

LIGAND-INDEPENDENT ACTIVITY OF NORMAL BCR

Experiments by Wienands et al. [54] have shown that assembly of the BCR on the cell surface is associated with biochemical activity, in the absence of external stimulation. When B cells are treated with tyrosine phosphatase inhibitors, tyrosine phosphorylation of substrate proteins occurs only when surface Ig are produced.

A requirement for a normal BCR in B cell development or survival could have been suspected from the absence of B cells devoid of BCR in the periphery, even though the random processes of VDJ rearrangement and somatic hypermutation might jeopardize BCR generation. The requirement for BCR signaling in B cell survival has been elegantly established by a series of experiments of BCR ablation using the cre-lox technology [33, 36]. However, although the most likely interpretation of these results is that a constitutive signal delivered by the BCR in the absence of antigen is required for survival of "naive" conventional B cells, it may also be interpreted as evidence for the requirement of continuous stimulation by self antigens involved in positive selection, as is the case for B1 cells and marginal-zone B cells [25]. In one transgenic system, there is clear evidence that the presence of self antigen is associated with increased conventional B cell numbers [20].

LIGAND-INDEPENDENT ACTIVITY OF THE PRE-BCR

It has also been proposed, on the basis of the activity of truncated pre-BCR, that pre-B cell development involves a signaling activity by the pre-BCR which is ligand independent [5, 49]. However, since mutant molecules could have an abnormal behavior, it is difficult to draw a firm conclusion from these experiments. While there is strong evidence that pre-BCR signaling activity can be induced in a cell autonomous fashion, it is not clear whether a ligand is necessary or not. Proposed ligands are galectin-1 [22] and heparan sulfate [7] and could be produced by stromal cells and pre-B cells themselves. Alternatively, pre-BCR signaling activity might be ligand independent and mediated by interac-

tion of two neighboring λ5, leading to homo-dimerization of pre-BCR [42]. It must be noted that there is an alternative pathway for pre-B cell development which does not require surrogate light chains, but requires membrane μ H-chain. It has been proposed that this alternative pathway involves conventional light chains [43, 44], but recent results rather suggest that light chains produced from rearranged genes are not required for this alternative pathway [19, 47, 50], which may instead require some form of μ H-chain [11, 47].

MECHANISM OF LIGAND-INDEPENDENT ACTIVITY

The first structural model of the BCR, with two Igα/Igβ heterodimers for one surface Ig [26], suggested the possibility that the assembly of the BCR in a signaling complex could bring into contact the two heterodimers. However, with the actual stoichiometry [46] (one heterodimer for one surface Ig), other mechanisms should be considered. Firstly, binding of surface Ig might modify the heterodimer in order to allow its phosphorylation. However, there is evidence that signaling activity can be induced in the absence of surface Ig when cytoplasmic domains of Igα and Igβ are targeted to the membrane [17]. From these data it has been proposed that a ligand-independent signal is generated when the Igα/Igβ heterodimers reach the cell surface with the assistance of the H-chain. Instead, it has been clearly shown that heterodimers are present on the cell surface of progenitor B cells of Rag-deficient mice (which cannot proceed through pre-B cell development), and that antibody-mediated crosslinking of Igβ on pro-B cells elicits differentiation signals analogous to those delivered by the pre-BCR in normal B cell development [41]. In addition, expression of a normal, signaling, pre-BCR is associated with aggregation and down-regulation [42], while mutant forms that do not aggregate are not associated with signaling or down-regulation. From these data one can conclude that pre-BCR aggregation is physiologically required for pre-B cell development, and that high levels of surface Igα/Igβ heterodimers can also promote development, in the absence of large heterodimer aggregates or preferential association to lipid rafts [17, 18]. One possibility is that the effective signaling complexes are dimeric forms of Igα/Igβ heterodimers whose levels are determined both by spontaneous, density-dependent dimerization and by externally induced dimerization.

It has been proposed that the ligand-independent activity of BCR generates a basal or "tonic" signal, as opposed to the signals induced by BCR ligation [16]. However, if both processes involve receptor dimerization, then one must consider rather that the difference between ligand-independent signaling and chronic BCR ligation, as it might occur in the course of antigen-induced tolerance, is merely quantitative.

ROLE OF LIGAND-INDEPENDENT ACTIVITY

Although there is clear evidence for ligand-independent activity of the BCR at the biochemical level, whether the effects observed *in vivo*, when pre-B cells develop in the absence of pre-BCR, or in the case of BCR ablation are related to a ligand independent activity is more difficult to ascertain, because these effects could conceivably be due to the absence of ligand binding. However, a reasonable assumption is that BCR ligand-independent activity allows mature B cell survival. This activity might be necessary because loss of BCR, and consequently of B cell function, might be generated during the processes of receptor editing and somatic hypermutation. Therefore, control of survival by the BCR would allow removal of useless B cells, which could be targets for oncogenic transformation. But in addition to these two extreme situations, presence or absence of the BCR, one should consider the problem of the level of expression, which may be determined both by H- and L-chain pairing and by down-regulation of the receptor.

When a functional L-chain is synthesized, the intracellular H-chain may be released from interaction with the BiP chaperone [24], which should allow the production of surface Ig. In the absence of L-chain production, B cells are not or poorly exported in the periphery [55].

It is likely that pairing of the L-chain with the H-chain is required to stop L-chain gene rearrangements [2]. However, whether this is mediated by ligand-independent activity of a conventional BCR, disruption of a residual pre-BCR activity, or by a different and unknown mechanism is not clear. If L-chain pairing is insufficient, rearrangements continue and the same is true when the BCR is cross-linked by a self antigen [51]. Continuing rearrangement allows cells to get rid of unsuitable kappa proteins, but whether the cell senses differently the lack of efficient pairing and signals from autoreactive receptors is not known. Cross-linking of the BCR is followed by down-regulation of its surface expression. The concept of constitutive signaling raises the possibility that, in addition to making the receptor unavailable for the antigen, this process also decreases ligand-independent signaling. This suggests that there is a feedback mechanism between surface expression and constitutive signaling, where spontaneous dimerization is the signaling event and down-regulation is the control mechanism (Fig. 2). An alternative view to the hypothesis of down-regulation of ligand-independent signaling is that during internalization of the BCR, remaining surface Igα/Igβ heterodimers mediate tonic signaling [34].

The possibility that down-regulation of basal signaling is the direct cause of L-chain editing has been suggested following experiments showing that cre-mediated Ig-H-chain deletion is followed by L-chain editing [52]. However, this hypothesis does not explain why immature B cells in ΔVμ mice have both high levels of L-chain gene rearrangement and high levels of truncated BCR [13]. Therefore, one is led to consider either that strong

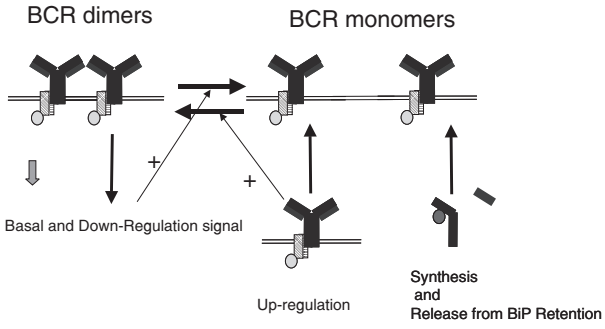

Fig. 2. A model for the generation of tonic, ligand-independent BCR signaling. In this model, dimers of BCR are formed in the absence of ligand and are in equilibrium with monomers. As for antigen-dependent signaling, only dimers are generating signals. The level of antigen-independent signaling is therefore dependent on the numbers of dimers present on the surface and could be affected negatively by down-regulation (which might be a way of feedback regulation) and BiP retention, and positively by up-regulation, synthesis, and BiP displacement by light chains. Vertical black arrows indicate moves of BCR between the surface and the inside of the cell.

signaling and insufficient signaling both induce L-chain gene rearrangement, or that the effect of cre-mediated Ig-H-chain deletion is the consequence of the disruption of a residual but strong pre-BCR activity.

CONSTITUTIVE ACTIVITY OF THE BCR IN LYMPHOID NEOPLASIA

As the BCR is essential for growth and survival of normal B cells, a reasonable hypothesis is that alterations of BCR signaling will contribute to neoplasia. Alterations of the BCR are known to occur in HCD. Due to the absence of the antigen-binding region of the BCR, it is easy to conclude that the BCR signals in HCD are ligand independent [10]. How they confer a growth advantage to B cells is a different issue. ΔVμ mice (unlike ΔVTCRβ mice [28]) do not have an increased frequency of lymphoid malignancy. Instead, B cell development in these mice is reminiscent of transgenic immunoglobulin models where the cognate antigen is present and induces tolerance [13]. This indicates that ΔVμ signals are not sufficient and/or that they are not provided at the appropriate stage of development for a B cell proliferation to occur. One possibility is that, in HCD, the signal of the mutant receptor mimics that of antigen-induced signaling in a mature B cell, while the equivalent of T cell help is provided by other uncharacterized mutations. According to this view, signaling by the truncated BCR might involve BCR dimers in the same way as ligand-induced signals. In the absence of ligand, these dimers might be more easily formed with truncated BCR than with complete BCR. Several models can account for this different behavior: first, truncated heavy chains might be inherently more prone to spontaneous aggregation because they are misfolded in the absence of L-chain pairing, due to loss of control by the BiP chaperone. Evidence for enhanced aggregation has been obtained for mu HCD proteins in transgenic mice [12]. Moreover, in patient cells, the secreted forms of mu HCD tend to aggregate to form intracellular vacuoles [31]. Another possibility is that mutant molecules tend to aggregate because steric hindrance by laterally protruding V regions is a limiting factor of normal BCR dimer formation. A third possibility is that dimer formation is increased because of the loss of a down-regulation mechanism, as discussed above. This absence of down-regulation is also suggested by the observations in transgenic mice [13].

In most of the B cell diseases with an intact BCR antigen-binding domain, it is difficult to know what role BCR ligand-independent activity might play in carcinogenesis, for cellular growth or survival might be related to antigen binding. However, in chronic lymphoid leukemia (CLL), some BCR defects are found that are reminiscent of the pathophysiological model proposed for HCD. In this disease, which is much more frequent than μ HCD, but with similar clinical features, a down--regulation of the BCR is observed, together with glycosylation defects, misfolding, and intracellular aggregation of μ heavy chains [53]. Misfolding of heavy chains with increased propensity to self-aggregate might enhance constitutive signaling. Alternatively, the modifications that are observed might be the consequence of chronic exposure to a hitherto unknown antigen. Other abnormalities have been described for Igβ in CLL [23], but how they relate to the malignant process is unclear.

In a percentage of B cell-derived Hodgkin's diseases, the normal BCR is absent, which seems to indicate that these proliferations are not only antigen independent, but also BCR independent, and therefore would be out of our scope. However, the present knowledge of a BCR signal requirement for normal B cell survival raises the question of how these cells manage to survive [35]. As a possible explanation, a protein encoded by the Epstein-Barr virus (a prominent agent of B cell transformation), LMP2A, has been characterized as having the ability to provide a surrogate constitutive B cell--receptor signaling to the cell [1, 8]. Nevertheless, the story is more complex, because the signaling apparatus of malignant Hodgkin Sternberg Reed cells is apparently lost, suggesting that LMP2A is involved only at the initiation stage of the disease [35].

SLP-65-DEFICIENT MICE

SLP-65 is an adaptor protein controlling the activity of the BCR. In SLP-65-deficient mice, B cell development is partially impaired and the mice have a low incidence of pre-B cell leukemia [15]. It has been shown that leukemogenesis is dependent on signaling via the pre-BCR, which might be, as discussed earlier, ligand independent. Interest in this murine model rose when a drastic reduction of SLP-65 expression was found in

an important percentage of childhood pre-B acute lymphoblastic leukemia [29]. However, it is not clear yet whether these proliferations require pre-BCR signaling. A more detailed description of this model, with the putative role of BCR-associated proteins in signal transduction and tumorigenesis, has been presented recently by Jumaa et al. [30].

CONCLUSION

Due to the multiplicity of putative antigens of low affinity, it will remain extremely difficult to establish whether the effects of a BCR on B cell development, survival, or tumorigenesis are ligand independent, although *in vitro* experiments indicate clearly a constitutive biochemical activity. However, it seems reasonable to assume that most of the effects on conventional B cells after BCR loss are related to the absence of constitutive activity rather than loss of antigen binding. The question of a pre-BCR ligand is still open and will be definitively answered only in the case where a ligand would prove to be necessary for pre-B cell development. Finally, the mechanism of constitutive activity is an important issue, with general implications for the field of signal transduction.

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