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REVIEW

Activation-induced cell death in B lymphocytes

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ABSTRACT

Upon encountering the antigen (Ag), the immune system can either develop a specific immune response or enter a specific state of unresponsiveness, tolerance. The response of B cells to their specific Ag can be activation and proliferation, leading to the immune response, or anergy and activation-induced cell death (AICD), leading to tolerance. AICD in B lymphocytes is a highly regulated event initiated by crosslinking of the B cell receptor (BCR). BCR engagement initiates several signaling events such as activation of PLCγ, Ras, and PI3K, which generally speaking, lead to survival. However, in the absence of survival signals (CD40 or IL-4R engagement), BCR crosslinking can also promote apoptotic signal transduction pathways such as activation of effector caspases, expression of pro-apoptotic genes, and inhibition of pro-survival genes. The complex interplay between survival and death signals determines the B cell fate and, consequently, the immune response.

Key words: *B lymphocytes, activation-induced cell death, B cell receptor.*

INTRODUCTION

In order for the B cell to be activated and to proliferate, or to undergo AICD or

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anergy, it has to be signaled via its BCR. During the course of development, the immature B cell is the first stage at which the B cell expresses functional membrane immunoglobulin (mIg) that can recognize Ag and transmit signal. In general, crosslinking of mIgM results in apoptosis of immature B cells and in proliferation of mature B cells. There are four possible explanations for a negative response to Ag by immature B cells (reviewed in[1]): 1) developmentally regulated differences in Ig isotype expression; 2) lack of T cell help (co-stimulatory signal) in areas of hematopoiesis (such as bone marrow), or inability of immature B cells to receive a second signal from T cells; 3) negative autocrine factors secreted by BCR-stimulated immature B cells and/or lack of positive signals derived from mature B cells; and 4) intrinsic differences in the integration of signals generated and transduced by the BCR at the immature and mature stage of development (independent of isotype). Which of these models is closest to reality, or whether a combination of two or more is correct, is still a debate, and this area of research needs further experimental evidence that would explain why immature B cells are more sensitive to AICD. An enormous amount of data in this field comes from in vitro models for B cell tolerance using either human or murine B-lymphoma cells of immature phenotype. WEHI-231, CH31 and CH33 cells, for example, are prototypical of such immature murine B-lymphoma cells in which mIgM crosslinking results in G1 growth arrest[2],[3] and subsequent apoptosis[4],[5]. In this review, signal transduction pathways initiated by BCR crosslinking will be discussed. Additionally, the role of c-Myc oncoprotein, p27 ^{Kip1} cyclin kinase inhibitor (CKI), and caspases in mIgM-mediated growth arrest and apoptosis of B cells and B-lymphoma cells, will be presented.

BCR-mediated signal transduction pathway

One of the first steps in the signal transduction pathway triggered by BCR crosslinking is activation of the Src family members (Fig 1). The src family of kinases (reviewed in[6]) consists of several non-receptor protein tyrosine kinases such as Blk, Fgr, Fyn, Hck, Lck, Lyn, Src, and Yes. In B lineage cells, several members of the Src family are noncovalently coupled to an activated membrane Ig receptor complex, including p55^{Blk}, p59^{Fyn}, p53/p56^{Lyn}, and p56^{Lck} (reviewed in[7]). Using the antisense oligodeoxynucleotide approach, Yao et al.[8] showed that Blk kinase is implicated in anti-IgM-mediated growth arrest and apoptosis in murine B-lymphoma cells (reviewed in[9]). The BCR is a multimeric complex consisting of the ligand binding mIgM and two Ig α /Ig β heterodimers (reviewed in[10]). The cytoplasmic portion of Ig heavy chain is very short, and cytoplasmic portions of Igα/Igβ heterodimers are necessary for signal transduction. The cytoplasmic tails of Ig α and Ig β contain a consensus sequence termed immunoreceptor tyrosine-based activation motif (ITAM) which is required for the signal transduction and for anti-IgM-mediated growth arrest and apoptosis[11]. Selective point mutations of either one of the two conserved tyrosine residues within

ITAM (Y23 and Y34) completely abrogates the ability of this motif to mediate anti-IgM-induced death signal. Furthermore, chimeric receptors containing extracellular and transmembrane portions of CD8 and intracellular portion of either Ig α or Ig β can transduce growth arrest and death signal when crosslinked with anti-CD8 Ab[12]. In normal B cells, the N-terminus of Lyn and Fyn can bind unphosphorylated Iga and phosphorylate the first tyrosine residue of the ITAM. Phosphorylation of these residues then results in increased binding of proteins with Src-homology domain (SH), such as Src family members and the adapter protein Shc (Fig 1).

Events downstream from the initial activation of Blk in anti-IgM signaling in murine B-lymphoma cells are still largely unknown. In normal B cells, after initial tyrosine kinase activation, the BCR signaling pathway diverges into several different signaling cascades (reviewed in[13]). Activation of Src family kinases leads to activation of three different molecules that serve as transducers of the signal, namely phospholipase Cγ (PLCγ, Ras, and phosphatidylinositol-3 kinase (PI3K; see Fig 1).

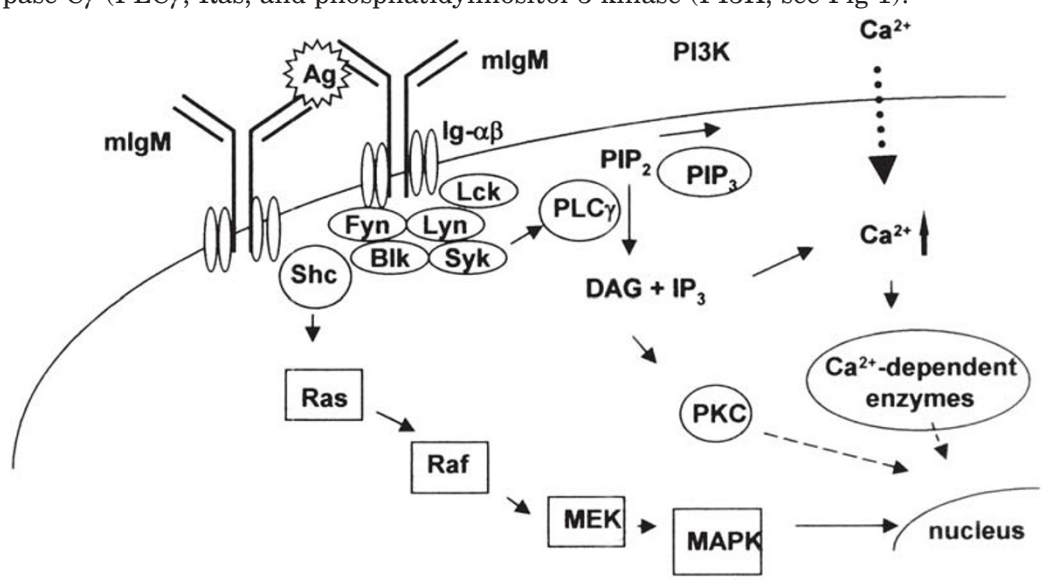

Fig 1. BCR-mediated signal transduction pathway
Crosslinking of mIgM activates Src family of non-receptor protein tyrosine kinases which phosphorylate conserved tyrosine residues in the ITAM motifs of Ig α and Ig β cytoplasmic tails. This then leads to recruitment of Src homology domain containing proteins such as the adapter protein Shc, resulting in Ras-GDP to Ras-GTP conversion and activation of MAPK signal transduction pathway. Active MAPK translocates into nucleus and induces transcription. Activation of Src family kinases also leads to activation of PLC γ, an enzyme that breaks down PIP2 into the second messengers DAG and IP_3. DAG mediates PKC activation, which in turn leads to activation of transcription factors AP-1 and NFkB. IP_3 mediates an increase in free cytoplasmic calcium, which in turn activates calcium dependent enzymes such as calcineurin. Calcineurin is a phosphatase that dephosphorylates cytoplasmic component of nuclear factor of activated T cells (NFATc) transcription factor, thereby enabling its translocation into nucleus. Finally, activation of Src family kinases leads to PI3K activation, which in turn phosphorylates PIP_2 leading to PIP_3 second messenger. Downstream target of PI3K is PKB/Akt, which acts upon $p70^{S6K}$, an enzyme implicated in mRNA translation.

The role of PLCr in BCR signaling

PLC γ activation by phosphorylation results in phospholipid hydrolysis yielding inositol 1, 4, 5-trisphosphate (IP_3) and diacylglycerol (DAG), Fig 1. These are the second messengers that mediate an increase of cytosolic free calcium (via activation of calcium release from the endoplasmic reticulum, as well as calcium influx) and activation of various protein kinase C (PKC; such as α , β , and δ isozymes), respectively (Fig 1). Indeed, for DNA synthesis to occur and for B cells to proliferate upon BCR crosslinking, there must be a small, but sustained increase in cytoplasmic free calcium [14]. Furthermore, B cell stimulation via BCR crosslinking can be successfully mimicked using calcium ionophores (such as ionomycin) to increase cytoplasmic free calcium, in combination with phorbol esters (such as PMA) to activate PKC[15]. Calcium mobilization, in turn, leads to activation of calcium calmodulin regulated enzymes as well as activation of calcineurin, a calcium-dependent phosphatase. PKC activation, on the other hand, leads to activation of AP-1 and NFakB transcription factors.

Anti-IgM treatment of WEHI-231, CH31, CH33, and ECH408 cells also leads to a rapid increase in cytosolic free calcium, as a result of both mobilization from internal stores and influx via calcium channels[16],[17]. Ionomycin also augments anti-IgM-induced growth arrest and apoptosis[18]. Furthermore, in several immature B-lymphoma cells such as in murine B-lymphoma cells WEHI-231[19] or BKS-2[18], in Burkitt's lymphoma cells[20], and in the human B-lymphoma cell line, B104[21], elevation of cytosolic free calcium seems to be sufficient to induce growth inhibition and apoptosis. In agreement with this notion, immunosuppressant cyclosporin A (CsA) that inhibits calcineurin (reviewed in[22]), protects some of these B-lymphoma cells from calcium-induced, as well as from anti-IgM-induced growth arrest and apoptosis [23]. However, the role of immunosuppressants in immature B-lymphoma cells is still controversial since several other groups reported that CsA, FK506 and rapamycin actually induce growth arrest and apoptosis in WEHI-231 cells[24], [25]. Recently, we reported that in WEHI-231 cells, an increase in cytoplasmic free calcium is necessary for anti-IgM-mediated accumulation of CKI $p27^{Kip}1$[26]. As expected, CsA prevents anti-IgM-induced $p27^{Kip}1$ up-regulation in these cells.

The role of PKC in BCR signaling in immature B-lymphoma cells is still controversial. Activation of PKC is generally thought to result from the translocation of inactive cytosolic enzyme to activation sites in the cell membrane, which does not happen upon mIgM crosslinking of WEHI-231 cells[27]. In agreement with this, phorbol ester PMA was shown to rescue cells from ionomycin- or anti-IgM-induced growth arrest and apoptosis[16], [23],[28]. However, Kuwahara et al.[29] more recently reported that PKC (a and β isozymes) can translocate from the cytosolic to the membrane compartment in WEHI-231 cells. In agreement with this, PMA was reported to actually induce growth arrest in WEHI-231 cells[30]. In conclusion, the role of PKC in BCR signaling in immature B-lymphoma cells is still controversial and needs further studies.

The role of Ras in BCR signaling

The second signal transduction cascade initiated by BCR crosslinking is mediated by Ras activation. src family kinase activation leads to recruitment of the SH domain containing proteins such as Shc. This, in turn, results in the conversion of inactive Ras-GDP into active Ras-GTP. Ras exerts its functions on nuclear events by stimulating a sequential phosphorylation cascade involving Raf-1, MAPK/Erk kinase (MEK) and mitogen-activated protein kinase (MAPK; Fig 1). The latter translocates into the nucleus to induce transcription. Crosslinking of mIgM, as well as treatment with ionomycin, induces delayed but sustained activation of MAPK in human B-lymphoma cell line B104. CsA inhibits MAPK activation and can protect B lymphoma cell lines from anti-IgM- or ionomycin-induced apoptosis, suggesting that stimulation of MAPK might be required for the induction of apoptosis[21], although it remains possible that CsA effect is simply due to the inhibition of the calcium signal which is responsible for the death.

The role of PI3K in BCR signaling

PI3K (reviewed in [31]) has been implicated in BCR signaling (reviewed in[32]), see Fig 1. An 85 kDa regulatory subunit of this kinase has SH3 and SH2 domains (reviewed in[33]) that enable it to associate with the BCR complex, thereby positioning the 110 kDa catalytic subunit near the membrane where it phosphorylates phosphatidylinositol 4, 5-bisphosphate (PIP_2) to the second messenger phosphatidylinositol 3, 4, 5-trisphosphate PIP3 (Fig 1). One of the important downstream targets of PI3K is PKB/Akt, a kinase that acts upon $p70^{S6K}$. Another downstream target of PKB has more recently been reported, albeit in T cells[34]. These authors showed that IL-2-induced T cell proliferation is a result of pRb hyperphosphorylation. This, in turn, is a consequence of IL-2-induced $p27^{Kip1}$ down-regulation and cyclin D3 (the most abundant D-type cyclin in T cells) up-regulation mediated via PI3/PKB pathway. IL-2-mediated $p27^{Kip1}$ down-regulation is prevented by immunosuppressant rapamycin, an inhibitor of $p70^{S6K}$ [35]. In anti-IgM-treated WEHI-231 cells, there is a sustained decrease in PIP3 levels bellow the baseline as early as 1 h after the treatment (Carey and Scott, in preparation). Anti-IgD treatment, on the other hand, also induces PI3K inactivation at the 1 h time point, but the PIP3 levels return to and remain at the baseline at 4-8 h after the treatment. Additionally, only anti-IgM, but not anti-IgD, induces sustained inactivation of $p70^{S6K}$, a downstream effector in PI3K signaling pathway. Finally, inhibition of PI3K pathway, using specific pharmacological inhibitors, induces G1 arrest and apoptosis, enhances anti-IgM-induced apoptosis, and converts anti-IgD into a death signal (Carey and Scott, in preparation). In conclusion, there is a correlation between BCR-mediated inactivation of PI3K/$p70^{S6K}$ pathway and BCR-mediated apoptosis in immature murine B-lymphoma cells.

The role of c-Myc in BCR-mediated G1 arrest and apoptosis

Mature B cells express low baseline levels of c-Myc. mIgM crosslinking of mature, resting B cells induces evanescent c-Myc up-regulation and cells enter the cell cycle [36]. However, extensive crosslinking of mIgM or mIgD can also lead to apoptosis of mature B cells, unless T cell help is provided either by IL-4 or by CD40L signaling[37]. Furthermore, anti-IgM-induced apoptosis of mature B cells can be prevented by c-myc antisense oligodeoxynucleotides, which prevent an anti-IgM-induced increase in c-Myc [36]. Together, these data suggest that BCR-induced apoptosis of mature B cells may be due to an overexpression of c-Myc in the absence of co-stimulatory signals provided by T helper cells.

In immature B-lymphoma cells, the situation is different. mIgM crosslinking in unsynchronized murine B-lymphoma cells (such as WEHI-231, CH31, and ECH408), leads to a transient increase in c-myc mRNA and protein within one to two hours, and a decrease to much below the baseline level at four to eight hours[38-40]. Human Burkitt's lymphoma cells also down-regulate c-Myc upon mIgM crosslinking[41]. IgD crosslinking, on the other hand, also leads to a transient increase in c-Myc, but the levels of mRNA and protein never drop below the baseline levels ([39]; Liu et al., in preparation).

Extensive evidence from Sonenshein and colleagues (reviewed in[42],[43]), as well as from Scott and coworkers (reviewed in[44]), suggest that down-regulation of c-Myc is necessary for anti-IgM-induced apoptosis. The strongest experimental evidence that supports this notion is that overexpression of exogenous c-Myc protects WEHI-231 cells from anti-IgM-induced apoptosis[45] and that stabilization of c-Myc levels by antisense c-myc oligodeoxynucleotides rescues WEHI-231 and CH31 cells from anti-IgM-induced apoptosis[40]. Conversely, inhibition of c-Myc expression using a serine/threonine protease inhibitor TPCK (N-tosyl-L-phenylalanine chloromethyl ketone) induces apoptosis in WEHI-231 cells[45]. Additionally, down-regulation of c-Myc (using a pharmacological inhibitor of c-Myc, FR901228), together with an increase in cytoplasmic free calcium results in accumulation of $p27^{Kip1}$, G1 arrest, and apoptosis in WEHI-231 and ECH408 cells.

There is one NFkB binding site in c-myc promoter and one upstream of the promoter (reviewed in[46]), and c-myc transcription in WEHI-231 cells seems to be regulated by NFkB[47]. Consequently, inhibition of NFκB using the drug TPCK, (a serine/threonine protease inhibitor that inhibits IκB degradation, thereby inactivating NFκB), or microinjection of IkB induces apoptosis in WEHI-231 cells via c-Myc down-regulation[48]. NFκB (reviewed in[49]) binds to DNA as a dimer that can be composed of the following subunits: RelA (p65), RelB, c-Rel, p50, and p52. In WEHI-231 cells, the major NF κ B species is p50/c-Rel heterodimer, but minor amounts of p50/RelA are also present.

In conclusion, resting, mature B cells express low basal levels of c-Myc and up-regulate it upon BCR stimulation, leading to either proliferation (in the presence of a

co-stimulatory signal) or apoptosis (in the absence of T cell help). Immature, B-lymphoma cells, on the other hand, express high levels of c-Myc and profoundly down-regulate it upon stimulation, leading to growth arrest and apoptosis. Very recently however, Tsubata and colleagues[50] reported that inducible over-expression of c-Myc results in apoptosis of WEHI-231 cells, suggesting that either profound down-regulation, or over-expression of c-myc oncogene, is lethal for these cells.

The role of T cell help in BCR-mediated G1 arrest and apoptosis

For the sustained proliferation upon the engagement of the BCR, resting, mature, splenic B cells need a second co-stimulatory signal that is provided by T helper cells in vivo, and can be provided in vitro by co-culturing cells with IL-4 or with CD40L (or anti-CD40 Ab, see Fig 2). In the case of immature murine B-lymphoma cells, growth arrest and cell death induced via BCR engagement can be prevented by either IL-4 or CD40L. Addition of recombinant IL-4 in culture[51], or co-culture with activated Th2 clone that produces IL-4[52], rescues WEHI-231, CH33, and CH31 cells from anti-IgM-induced growth arrest (reviewed in[53]). Engagement of CD40 expressed on the surface of B cells, with its ligand (CD40L) expressed on the surface of T cells (Fig 2), protects

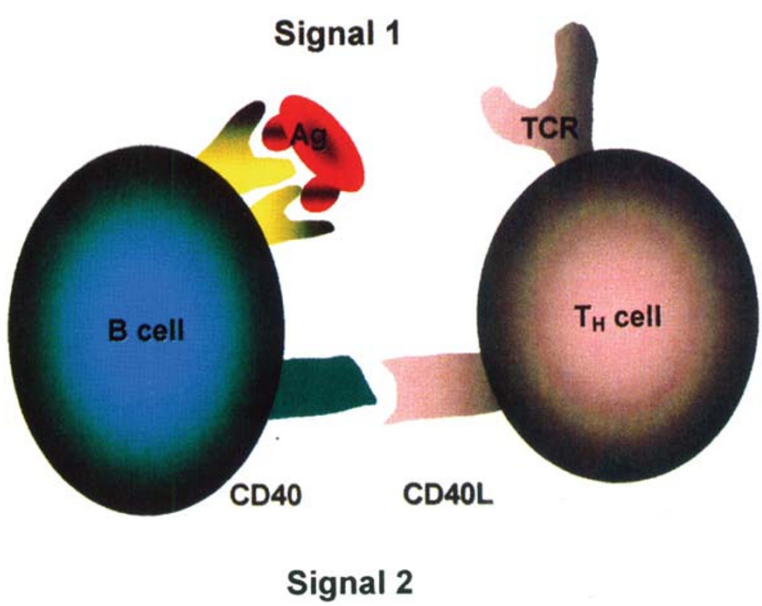

Fig 2. The two signal model for B cell activation
Activation of resting B cells requires two signals. The first signal is generated by antigen-mediated BCR crosslinking and the second is provided by T cell help, via CD40/CD40L engagement. Signal one in the absence of signal two leads to abortive activation, anergy, or deletion, resulting in tolerance to the activation antigen. In the presence of signal two, signal one leads to B cell activation, proliferation and/or differentiation.

immature human[54] as well as murine[55] B-lymphoma cells from anti-IgM-induced apoptosis and growth arrest. A 17 amino acid domain within the cytoplasmic portion of CD40L called TIM (TRAF family member interacting motif) that binds TNFR associated factor (TRAF) family members is necessary and sufficient for the protective effect of CD40L[56]. CD40L prevents anti-IgM-induced c-Myc down-regulation via maintaining NFκB activity in WEHI-231 cells[57]. It seems that CD40L maintains NFκB activity by inducing a sustained decrease in IkBa and a transient decrease in IkBβ. As expected, microinjection of IkBa into the nuclei of WEHI-231 cells ablates protection mediated by CD40L[58].

An important effect of signaling via CD40/CD40L engagement on WEHI-231 cells is maintenance of high c-Myc levels via maintaining NFκB activity. In addition, signaling by CD40 has another important effect, which is induction of anti-apoptotic Bcl-xL protein[59-61]. Indeed, overexpression of Bcl-xL rescues WEHI-231 cells from anti-IgM-mediated apoptosis[62], while having no effect on G1 growth arrest. These results suggest that the Bcl-x_L-inhibitable event is either downstream of growth arrest, or on a separate signal transduction pathway. Bcl-2 overexpressing cells are not only resistant to apoptosis mediated by BCR crosslinking, but also to apoptosis following serum deprivation,γ-irradiation, exposure to ceramides or compounds that increase the intracellular level of oxidants[63]. Furthermore, immunosuppressants (such as rapamycin, FK506, and CsA) have been shown to induce growth arrest and apoptosis in immature B-lymphoma cells[24],[25] and Bcl-xL protects WEHI-231 cells from apoptosis induced by these compounds. Again, Bcl-xL has no effect on the G1 arrest mediated by these immunosuppressants[24].

The role of cell cycle proteins in BCR-mediated G1 arrest and apoptosis

Mature, resting B cells express very low basal levels of Cdk2 and Cdk4 and high levels of CKI $p27^{Kip1}$. Upon complete stimulation with PMA and ionomycin, Cdk2, Cdk4, cyclin D2, and cyclin E protein levels increase[64]. Interestingly, complete stimulation of mature B cells (BCR crosslinking and CD40 engagement) also leads to CKI p21Cip1 accumulation[65]. If BCR crosslinking and IL-4 are used as a complete stimulus, in addition to Cdk2, Cdk4, cyclin D2, cyclin E, and $p21^{Cip1}$, mature B cells also increase expression of cyclin D3, cyclin A, and cyclin B as well as Cdk6, Cdc2 and CKI $p19^{INK4D}$ [66]. Furthermore, stimulation of resting B cells with anti-IgM and IL-4 causes very rapid down-regulation of $p27^{Kip1}$. However, this down-regulation is only transient, but can become permanent if CD40L is also added to the culture. As expected, addition of CD40L in the culture results in long-term B cell proliferation[66].

Crosslinking of BCR on the surface of immature B cells results in apoptosis as well as in growth arrest in late G1 phase of the cell cycle. Furthermore, cells are sensitive to anti-IgM treatment only when in early G1 phase[3]. As one would predict, in these

growth arrested cells (such as anti-IgM-treated WEHI-231 or CH31 cells), pRb is in its active, growth suppressive form, i.e. it is hypophosphorylated[67]. Additionally, BCR crosslinking also leads to hypophosphorylation of another pRb family member, p130 [68]. The appearance of the hypophosphorylated form of pRb family members correlates with inhibition of Cdk2 kinase activity. Since Cdk2/cyclin complexes are responsible for phosphorylation of pRb family members at G1 to S transition, inactivation of Cdk2 can explain why these cells are arrested in late G1 phase[69],[70]. However, anti-IgM-mediated reduction in Cdk2 kinase activity is not the result of decreased expression of Cdk2, cyclin A, or cyclin E since the levels of these proteins do not change upon the treatment[70]. It also does not appear to involve cyclin dependent kinase activating kinase (CAK) whose activity is not affected by BCR crosslinking[71]. How does anti-IgM treatment decrease Cdk2 activity? Immature murine B-lymphoma cells are proliferating cells and, as expected, have very low basal levels of CKI $p27^{Kip1}$. Inactivation of Cdk2 by anti-IgM correlates with an increased total amount of $p27^{Kip1}$ in the cells, and more importantly, it correlates with the amount of $p27^{Kip1}$ present in cyclin A[70] and Cdk2[71] complexes. Furthermore, the amount of $p27^{Kip1}$ in cyclin A complexes correlates with the percentage of the cells in G1 phase upon BCR crosslinking. Finally, CD40L, which rescues WEHI-231 cells from anti-IgM-induced apoptosis and growth arrest, also prevents $p27^{Kip1}$ accumulation upon BCR crosslinking[71], or upon co-treatment with ionomycin and FR901228[26]. One group reported that BCR crosslinking in WEHI-231 cells results in decreased protein levels of early G1 kinases Cdk4 and Cdk6 which can be prevented by CD40/CD40L engagement[60], but this has not been reproduced[70]. Finally, Sonenshein and coworkers reported that anti-IgM treatment increases p53 expression, and consequently $p21^{Cip1}$ expression ($p21^{Cip1}$ is under positive transcriptional control of p53)[72].

In conclusion, while resting, mature B cells express high levels of $p27^{Kip1}$ and profoundly down-regulate it upon stimulation which leads to proliferation, in immature B-lymphoma cells the situation is the opposite. These cells are continuously proliferating and express very low basal levels of $p27^{Kip1}$, which is profoundly up-regulated upon stimulation that leads to G1 arrest and apoptosis.

The role of caspases in BCR-mediated G1 arrest and apoptosis

Caspases, a family of cysteine proteases, are crucial executors of apoptosis in mammalian cells. Indeed, as one might predict, BCR-mediated apoptosis also involves activation of caspases and can be inhibited by caspase inhibitors. For example, a broad spectrum inhibitor carbobenzoxy-Val-Ala-Asp-fluoromethyl ketone (Z-VAD-FMK) inhibits anti-IgM-induced apoptosis in WEHI-231[26],[73] and in CH31 [74] immature B-lymphoma cells. However, caspase inhibitors have no effect on anti-BCR-induced inhibition of Cdk2 kinase activity and induction of G1 growth arrest[73], nor on anti-BCR-induced c-Myc down-regulation and $p27^{Kip1}$ accumulation[26]. Together, these data

suggest that anti-IgM-induced down-regulation of c-Myc, accumulation of $p27^{Kip1}$, and growth arrest are either upstream or on a separate pathway(s) from caspase activation. Which caspases exactly are activated by BCR crosslinking? Anti-IgM treatment of WEHI-231 cells or extensive mIgM crosslinking in mature B cells leads to caspase 7 activation while caspase 2 and caspase 3 are not activated[73]. In CH31 cells, treated with anti-IgM, caspase 3-like activity is observed as shown by poly (ADP-ribose) polymerase (PARP) cleavage (PARP is a substrate of caspase 3 subfamily of caspases, i. e. caspase 2, 3, and 7), [74].

Finally, even though crosslinking of BCR in immature B cells, as well as in mature B cells (if the T cell help is not provided, or if crosslinking is extensive), can lead to apoptosis, it can also protect splenic cells[75] and A20 murine B-lymphoma cells[76] from CD95-induced apoptosis (reviewed in[77]). CD95 signaling activates caspase 8 in A20 cells and induces apoptosis. Both of these events can be prevented by BCR (mIgG in this case) crosslinking[76]. In this experimental system CD95 ligation also triggers Bcl-2 and Bcl-x_L down-regulation, which is prevented by BCR crosslinking as well as by caspase inhibitor acetyl-Tyr-Val-Ala-Asp-chloromethyl ketone (YVAD-CMK).

CONCLUSION

AICD is an essential property of the lymphocytes and plays an important role in the development of the immune repertoire, as well as in the regulation of the immune response. In recent years, we learned a lot about programmed cell death in mammalian cells, and this knowledge greatly enhanced our understanding of the molecular mechanisms of AICD in both B and T cells. Some signaling events that lead to AICD in lymphocytes seem to be universal (such as activation of effector caspases), while the others are specific for lymphocyte lineages (such as engagement of BCR or T cell receptor). Further elucidation of the molecular events that determine whether a B cell will proliferate, survive in growth arrested state (anergy), or die via AICD will provide a potential for a novel therapeutic approaches in the treatment of immune disorders where AICD is desirable (auto-immunity), as well as in disorders where AICD is detrimental (immuno-deficiency).

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