

IL-21: An Executor of B Cell Fate¹

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IL-21 is a type I cytokine that shares the common receptor γ -chain with IL-2, IL-4, IL-7, IL-9, and IL-15. B cells are one of the lymphoid cell types whose development and function are regulated by IL-21. Depending on the interplay with costimulatory signals and on the developmental stage of a B cell, IL-21 can induce proliferation, differentiation into Ig-producing plasma cells, or apoptosis in both mice and humans. Alone and in combination with Th cell-derived cytokines IL-21 can regulate class switch recombination to IgG, IgA, or IgE isotypes, indicating its important role in shaping the effector function of B cells. This review highlights the role of IL-21 in B cell development, function, and disease and provides some perspectives on the future studies in this area. *The Journal of Immunology*, 2009, 182: 1781–1787.

Interleukin-21 is a member of the family of common receptor γ -chain (γ)³-dependent cytokines. Its structure is related to the four-helix bundle type I cytokine and shows significant homology to IL-2, IL-4, and IL-15 (1). IL-21 was originally identified in the culture supernatants of activated human CD3⁺ T cells (1). Further studies established that Th17, T follicular helper (Tfh), and NKT cells also secrete IL-21 (2–5). IL-21 exerts pleiotropic actions on the immune system. Its functional receptor, IL-21R, consisting of the IL-21R α / γ c complex, is expressed on various hematopoietic cells. The effects of IL-21 on T, NK, and dendritic cells (DCs) have been reviewed elsewhere and will not be discussed here (reviewed in Refs. 6–8). This review focuses on the influence of IL-21 in B cell biology.

IL-21R expression and signaling

In mice, the cell surface levels of IL-21R progressively increase as B cells develop from progenitors in the bone marrow to mature B cells in the peripheral lymphoid tissues (9). Transitional 1 (T1) B cells, which represent the most immature B cell population in the periphery, and marginal zone (MZ) B cells ex-

press similarly low levels of IL-21R (10). As T1 B cells mature to the T2 stage, the expression of IL-21R increases to levels comparable to that found on follicular B cells (10). IL-21R is also present on human naive and germinal center (GC) B cells, but not on memory B cells and plasma cells (PCs) (11). The surface levels of IL-21R increase on murine naive B cells when they get activated either through the TLR or CD40, and on human memory B cells after stimulation through CD40 (9, 11). Development- and activation-dependent regulation of IL-21R expression on the surface of B cells suggests that IL-21 has important functions late in B cell development and in the immune response.

Like other γ c-dependent cytokines, IL-21 activates the Janus family tyrosine kinases, Jak1 and Jak3, which, in turn, activate STAT1 and STAT3 and to a lesser extent STAT5. In vitro results obtained from activated murine splenocytes, EBV-infected human B cell lines, human chronic lymphocytic leukemia (CLL) B cells, and multiple myeloma lines indicate that IL-21:IL-21R binding leads to strong STAT3 activation (12–15). In EBV-infected B cells, activated STAT3 is observed as early as 5 min after binding and persists to up to 6 days (12). Activation of STAT1 is weaker, whereas activation of STAT5 is transient (<60 min) and is observed only in some cells, such as CLL B cells and activated murine splenocytes (12–14). Working with EBV-infected human B cell lines we found that inhibition of IL-21-induced JAK/STAT signaling did not interfere with the initial increase in proliferation of EBV-infected B cell lines. By contrast, intact JAK/STAT signaling was required for the subsequent differentiation into late plasmablasts/early PCs (12). Biochemical studies of murine IL-21R α showed that simultaneous mutation of all six tyrosine residues in the IL-21R α cytoplasmic domain greatly reduced IL-21-mediated proliferation of murine T cells, whereas retention of tyrosine 510 (Y510) only was sufficient for the full proliferative response. Y510 mediated IL-21-induced activation of STAT1 and STAT3, but not STAT5, in T cells (14). The precise role of Y510 and the other tyrosine residues in IL-21R signaling in B cells has not yet been determined. Similarly, it is of interest to determine

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Received for publication November 17, 2008. Accepted for publication December 24, 2008.

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¹ This work was supported by the grants from the National Cancer Institute of Canada and by the Canadian Institutes of Health Research (CIHR) Grant 9862. N.S. is the recipient of a graduate student scholarship from the CIHR.

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³ Abbreviations used in this paper: γ c, common receptor γ -chain; AID, activation-induced cytidine deaminase; BAFF, B cell-activating factor (TNF family); CB, cord blood; CD40L, CD40 ligand; CSR, class switch recombination; CLL, chronic lymphocytic leukemia; DC, dendritic cell; GC, germinal center; MZ, marginal zone; MZA, MZ analog; PB, peripheral blood; PC, plasma cell; RA, rheumatoid arthritis; SHM, somatic hypermutation; SLE, systemic lupus erythematosus; Tfh, T follicular helper cell; WT, wild type.

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whether certain IL-21R tyrosine residues can recruit phosphatases or other proteins that inhibit STAT activation and help terminate IL-21 signaling.

It will also be important to investigate whether the balance between IL-21-induced STAT1 and STAT3 signals influences different B cell fates. Generally, STAT1 has been implicated in cell cycle arrest and apoptotic cell death (16). By contrast, STAT3 mostly functions as an antiapoptotic or growth factor, especially in numerous malignancies where it is constitutively active (17–19). The consequence of STAT activation depends on the expression of STAT target genes that are regulated directly or indirectly. Granzyme A, Jak3, and IL-17R are among the genes activated by IL-21 in a STAT3-dependent fashion (20). We showed that intact JAK/STAT signal is required for IL-21-induced c-myc repression and subsequent differentiation of EBV-infected B cell lines into late plasmablasts/early PCs (12).

In addition to the JAK/STAT pathway, two other signaling regulators activated by γ c-dependent cytokines are the PI3K/Akt and RAS/MAPK (21, 22). Three members of the MAPK family, ERK1/2, p54 (JNK), and p38 participate in the control of cell proliferation and survival downstream of IL-2 and IL-4 receptors (23–25). Because IL-21R α shows the highest homology to IL-2R β and IL-4R α (22), it is likely that the MAPK pathway could also contribute to IL-21-mediated proliferation of B cells. IL-21-induced ERK1/2 phosphorylation was shown in multiple myeloma cell lines (15). In murine T cells it was shown that IL-21 slightly induced phosphorylation of Shc (SRC homology 2 domain containing) and Akt, whose inhibition partially prevented IL-21-induced proliferation of T cells (14). It remains to be determined how the MAPK and PI3K pathways contribute to IL-21-regulated proliferative, survival, or differentiation signals in B cells.

IL-21 regulates proliferation and survival of B cells

Cytokines influence B cell development and homeostasis by regulating their proliferation and survival. Critical insights into the role of IL-21 in murine B cell proliferation and survival come from experiments in which IL-21 is overexpressed *in vivo*. This was achieved using either transgenic methods or by hydrodynamic transfection of IL-21 cDNA into wild-type (WT) mice. In both cases, increased numbers of immature transitional B cells, isotype-switched memory B cells, and PCs were observed. In addition, total serum IgG and IgM were found to be increased in these animals (26). Of the tested splenic B cell populations, the follicular B cell subset was significantly lower, whereas the percentage of splenic MZ B cells was normal, although MZ B cells were found to be relocated outside the MZ area (26, 27).

In vitro experiments show that IL-21 can have both positive and negative effects on B lineage cells depending on the presence or absence of other signals. For example, the addition of IL-21 increased the proliferation of murine splenic B cells that had been stimulated by a combination of anti-IgM, which mimics a BCR-mediated signal, and anti-CD40, which mimics a signal provided by Th cells. By contrast, proliferation induced by anti-IgM and IL-4 was inhibited by IL-21, although this effect could be reversed when anti-CD40 was added, resulting in increased proliferation (26). In the presence of strong innate signals such as LPS or CpG DNA, the addition of IL-21 alone or in combination with IL-4 was shown to inhibit proliferation

and increase the cell death of murine follicular, MZ, and total splenic B cells (9). In human *in vitro* systems, IL-2, IL-4, IL-10, and IL-13, known for their key roles in B cell function, had notably lower effects on proliferation of anti-CD40-stimulated B cells compared with IL-21 (11, 27, 28). Similarly as for murine B cells, anti-CD40 stimulation protected anti-IgM-activated human B cells from IL-21-mediated death (27).

The ability of IL-21 to induce apoptosis sets it apart from other members of the γ c-dependent family of cytokines, most of which activate prosurvival and proliferation signals. Complete protection from IL-21-mediated apoptosis was observed when murine B cells were pretreated for 6 h with anti-CD40 Ab and then cultured with IL-21 for 24 h. In this case, it was found that anti-CD40 induced gene and protein expression of a prosurvival factor, Bcl-x_L (29). IL-21-mediated apoptosis was not blocked in FAS ligand or TNFR1- or TNFR2-transgenic mice, but it was blocked in Bcl-2 transgenic mice (9). Functional studies demonstrated that IL-21 substantially inhibited proliferation and induced Bim-dependent apoptosis of LPS or CpG DNA-activated murine B cells (9). Collectively, these results suggest that the mitochondrial death pathway plays a role in IL-21-induced apoptosis of murine B cells. In contrast to murine B cells, Bim did not seem to play a role in IL-21-induced cell death in human B cells, as its expression did not change when B cells were stimulated with anti-IgM and IL-21 (30).

Genetic background also influences the response of murine B cells to IL21. For example, in BALB/c mice, IL-21 stimulated the proliferation of B cells activated with anti-CD40. This effect was not observed in C57BL/6 mice treated in the same way. In addition, B cells from C57BL/6 mice were more susceptible to IL-21-mediated cell death after stimulation with LPS, CpG DNA, or anti-CD40 than B cells from BALB/c mice (9).

The capacity of IL-21 to regulate survival and proliferation of B cells demonstrates its importance in controlling the fate of activated B cells. Taken together, current data suggest that IL-21 promotes survival and proliferation of appropriately activated B cells that respond to Ag and receive cognate T cell help. By contrast, IL-21 inhibits proliferation and/or initiates apoptosis of B cells that receive a nonspecific signal via BCR only or that receive a strong signal via TLR.

IL-21 induces activation-induced cytidine deaminase (AID) and regulates class switch recombination (CSR) to IgG and IgA

Ab diversity is critical to eliciting an efficient immune response against a plethora of different pathogens. Two mechanisms involved in creating such diversity are somatic hypermutation (SHM) and CSR. Both processes require the AID enzyme, which converts cytosines in switch and Ig V regions to uracils by deamination (31, 32). IL-21 stimulation of mouse and human naive B cells has been shown to induce the expression of AID when used in combination with CD40- and IgM-specific Abs (28, 33). Interestingly, although AID catalyzes both CSR and SHM, only CSR was induced in naive human B cells after treatment with IL-21 and anti-CD40 (28). The discovery that the C-terminal 10 aa of AID were required for CSR but not for SHM could explain this observation (34, 35). It has been hypothesized that IL-21 induces activity of AID, but only at the C terminus (28).

Multiple studies have shown that IL-21 causes CSR of CD40-stimulated human naive splenic IgM⁺ B cells to IgG1 and IgG3 and that of CD40-stimulated cord blood (CB) B cells

to IgA (36, 37). The addition of IL-4 to these cultures prevents class switching to IgA (37, 38). There is no evidence that IL-21 alone activates CSR to the IgE isotype. In the absence of IL-4, IL-21 does not induce CSR of human CD40-activated naive B cells to IgE (39, 40). Furthermore, IL-21 does not affect anti-CD40 mAb- and IL-4-induced C ϵ promoter activation or germline C ϵ mRNA expression in purified human spleen or peripheral blood B cells (39, 40). Overall, the studies discussed here show that IL-21 regulates CSR of naive B cells to IgG- and IgA- expressing B cells, thereby contributing to the diversity of Ig function. It remains to be determined how other cytokines that regulate B cell differentiation, such as IL-2, IL-6, and TGF- β , can affect the outcome of IL-21-mediated CSR.

IL-21 regulates differentiation of B cells to Ig-secreting PCs

Studies of IL-21R knockout mice. PCs represent the end point of B cell lineage differentiation and are essential for protective immunity. IL-21R^{-/-} mice provide important insights into the role of IL-21 in the differentiation of B cells to the PC stage. Steady-state serum levels of IgG2a, IgG3, and IgM were normal in naive IL-21R^{-/-} mice, but the amounts of IgG1 and IgG2b were lower compared with WT controls (41). By contrast, steady-state serum levels of IgE were higher in IL-21R^{-/-} mice (41). T cell-dependent Ag immunization of IL-21R^{-/-} mice with OVA or keyhole limpet hemocyanin resulted in a severe defect in the production of both total serum and Ag-specific IgG1. Moreover, Ag-specific IgG2b and IgG3 responses were also impaired in immunized IL-21R^{-/-} mice, although the total serum levels of IgG2b and IgG3 as well as IgM and IgA remained normal. Serum concentrations of IgE, an isotype whose production is usually associated with IL-4, were variable although distinctly higher in IL-21R^{-/-} mice (41, 42). Augmented IgE response was also observed in IL-21R^{-/-} mice infected with *Toxoplasma gondii*, a parasite that is not normally associated with the induction of an IgE response (43). Altogether, these results clearly show that IL-21 plays an essential role in the generation of Ig-secreting B cells, both at steady state and during the immune response.

In vitro studies of T cell-B cell interactions. Most PCs develop from B cells that have passed through the GC reaction (44). In GC, Tfh cells provide help to GC B cells in the form of CD40 ligand (CD40L) and cytokines, thereby promoting the differentiation of Ag-selected, high-affinity B cells into PCs or memory B cells (45). Both murine and human Tfh cells were shown to produce IL-21 (5, 38, 46). Coculture experiments of human B cells and T cells have addressed the contribution of T cell-secreted IL-21 in the differentiation of B cells. These experiments showed that anti-CD3-activated CD4⁺ peripheral blood (PB) and tonsillar T cells, and activated tonsillar Tfh cells can induce proliferation and differentiation of autologous naive B cells in an IL-21-dependent manner (5, 38, 47). In this system, the production of IgM, IgG, and IgA by naive B cells was almost exclusively dependent on IL-21 (47). In comparison, the ability of memory B cells to secrete IgM in response to activated T cells was only marginally affected by blocking IL-21, whereas IgG production from memory B cells required IL-21 (47). It will be of interest to determine whether IL-21 produced by other cells, such as Th17 and NKT cells, plays a similar role in B cell differentiation to PCs.

Effects of IL-21 on differentiation of human B cell subsets. In vitro studies revealed that the effects of IL-21 on the differentiation to

Ig-secreting PCs vary between the different subsets of human B cells (28, 30, 37, 38). IL-21 induced PC differentiation and Ig production when used in combination with anti-CD40 or with anti-IgM and anti-CD40 in human naive and memory B cells from PB, tonsil, and spleen, as well as in CB B cells (11, 28, 37, 38). However, IgM⁺ and isotype-switched memory B cells were much more sensitive to CD40L/IL-21 than naive B cells, which was reflected in a greater rate of differentiation to Ig-secreting PCs (38). Also, >50% of PCs resulting from IgM memory B cells were secreting IgG and IgA, in addition to IgM. By contrast, most PCs produced from naive B cells secreted IgM, with low frequencies of IgG and IgA (38). This result reflects a greater ability of IgM memory B cells to undergo CSR compared with naive B cells.

Some B cell subsets do not require BCR- and CD40-mediated stimulation to differentiate to PCs in response to IL-21. For instance, Ettinger et al. (30) isolated novel MZ analog (MZA) B cell populations from human spleen, which consisted of both IgG⁺ and IgM⁺ memory B cells that expressed a unique set of markers (CD27^{high}CD21^{high}CD23⁻CD38^{int}; where "int" is "intermediate"). In this population, IL-21 and B cell-activating factor (BAFF; belonging to the TNF family) costimulation alone was sufficient to induce PC differentiation and the production of large amounts of IgG (30). This suggests that IL-21 and BAFF could participate in the Ag-independent replenishment of serologic memory by inducing differentiation of MZA B cell to PCs.

IL-21 and other Th-secreted cytokines in B cell differentiation. IL-21 is not only a potent inducer of PC differentiation by all types of human B cells, but its effects also greatly exceed those of other cytokines such as IL-2, IL-10, and IL-4. For example, IL-21 and CD40 stimulation of human PB naive B cells caused secretion of IgG that was up to 10-fold higher than that induced by IL-4 or IL-2 in combination with CD40 stimulation (11, 27, 28). IL-21 increased the frequency of Ig-secreting cells generated in cultures of human CB, GC, naive, and memory B cells by 5- to 20-fold compared with that induced by CD40L alone or the combination of CD40L and IL-10 (38).

The outcome of IL-21-mediated Ig secretion depends on the presence of other cytokines. For example, IL-10 has been shown to synergize with IL-21 to induce the secretion of IgA by CD40L-stimulated human B cells, whereas IL-4 diminished it (37). Most studies have focused on the interplay between IL-21 and IL-4 in differentiation of B cells to IgE-secreting PCs. As mentioned above, the inhibitory effect of IL-21 on IgE production was first reported in IL-21R^{-/-} mice, which produced larger quantities of IgE than WT mice. In agreement with this observation, the administration of IL-21 in WT mice or the addition of IL-21 to cultures of murine splenic B cells stimulated with LPS and IL-4 prevented the production of Ag-specific IgE (48). Generation of mice deficient for both IL-4 and IL-21R revealed that IL-4 was needed for the production of IgE in IL-21R^{-/-} mice, as IL-4^{-/-}IL-21R^{-/-} mice, similarly as IL-4^{-/-} mice, did not make IgE. IL-21 has also been shown to inhibit the IL-4-driven production of IgE in cultured human PBMC or total splenocytes. This inhibition was not the result of a direct effect of IL-21 on B cells but was dependent on the presence of IFN- γ (39, 40). By contrast, when purified naive and memory B cells from PB or spleen were used, IL-21 enhanced the production of IgE (39, 40). The reasons for the opposite in vitro effects of IL-21 on IgE secretion observed in

Table I. *Modulation of IL-21 for therapy*

Potential Benefits of IL-21 Administration and Reduction/Neutralization (with references)
Potential benefits of IL-21 administration:
Treatment of allergy (4, 56–58)
Treatment of cancer (direct cytotoxicity)
Chronic lymphocytic leukemia (15)
Diffuse large B cell lymphoma (67)
Cancer immunotherapy (69–71)
Treatment of immunodeficiency (39)
Vaccine development (29, 32)
Potential benefits of IL-21 reduction/neutralization:
Treatment of autoimmunity
SLE (59–61)
RA (62)
Treatment of cancer
Multiple myeloma (17)
Burkitt's lymphoma (67)
Hodgkin's lymphoma (68)

mouse vs human purified B cells are not clear. It was suggested that the impact of IL-21 and IL-4 on IgE secretion depends on B cell density. When IL-4- and CD40-stimulated murine splenic B cells as well as human tonsillar B cells were cultured at low cell density, the secretion of IgE was increased by the addition of IL-21. By contrast, the production of IgE was diminished when the murine B cells were plated at high density (49). At low cell density IL-21 increased the rate of cell division, which was suggested to be a mechanism to enhance IL-4-mediated switching to IgE (49). This hypothesis is supported by the demonstration that B cell division is required for isotype switching. For example, in mouse cells, isotype switching to IgG and IgE required a minimum of three or five divisions, respectively (50, 51).

IL-21 regulates expression of PC fate-determining transcription factors. IL-21-mediated induction of PCs is driven by the expression of multiple transcription factors. Induction of Blimp1, Irf4, Xbp1s, and Bcl6 with a parallel decrease in Pax5 could explain how IL-21 regulates the maturation of both murine and human B cells into both PCs and isotype-switched memory B cells (26, 38, 47, 52). It is hypothesized that an IL-21-mediated increase in Blimp1 leads to differentiation to PC, whereas induction of Bcl6 may be important for the differentiation of GC B cells into isotype-switched memory B cells (53). The IL-21-mediated decrease of Pax5 may bias responses toward PC differentiation, as Pax5 is known to inhibit this process (38, 52).

IL-21 in disease

The discovery that IL-21 controls B cell maturation and function prompted multiple studies into its involvement in those diseases that have a major B cell component. (Table I). Some insight into the role of IL-21 in allergic responses came from studies showing that exposure to IL-21 resulted in decreased IgE production in an OVA-induced mouse model of allergic rhinitis and in a mouse food allergy model (54, 55). In humans, diminution of IgE production has been reported following vaccination with *Mycobacterium bovis* bacillus Calmette Guerin, BCG (56). This effect has been attributed to the apoptosis of IgE-producing B cells caused by the IL-21 secreted by NKT cells (4). Collectively, these studies suggest that IL-21 modulation of IgE production may have potential therapeutic applications in the treatment of IgE-mediated diseases such as allergy.

In addition, based on results from experimental animal models, there is a growing body of evidence that links IL-21 to the regulation of B cell responses in autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel disease. For example, it was shown that IL-21 has a pathogenic role in the MRL-Fas(lpr) murine model of SLE by impacting B cell function and regulating the production of pathogenic autoantibodies (57). In this model, extrafollicular Th cells governed the high-affinity, isotype-switched autoantibody production via IL-21 and CD40 (58). Higher serum levels of IL-21 were also detected in the BSXB-Yaa SLE mouse model, and neutralization of IL-21 in late disease improved animal survival, presumably by dampening the humoral components of lupus (59). In the collagen-induced and adjuvant murine model of arthritis, blockade of IL-21 with the IL-21R-Fc fusion protein reversed clinical disease severity (60). In humans, a higher percentage of IL-21R positive cells was detected in the blood and synovial fluid of patients with RA (61). It remains to be determined whether IL-21 affects the generation or function of autoreactive B cells in RA. Multiple studies have demonstrated that Th17 cells are implicated in the pathogenesis of SLE and RA (62, 63). As Th17 cells also represent a rich source of IL-21 (64), it will be of interest to determine whether Th17-produced IL-21 contributes to aberrant B cell responses in these diseases.

Apart from its involvement in autoimmunity, there is evidence that IL-21 can be an important factor in the regulation of growth and survival of various B cell malignancies. Exposure to IL-21 induces apoptosis of CLL B cells and diffuse large B cell lymphoma cells (13, 65). Targeted delivery of IL-21 may be beneficial for the therapy of these types of cancers. By contrast, IL-21 increases the proliferation of Burkitt's lymphoma and multiple myeloma cells in vitro (13, 15, 65). Hodgkin Reed-Sternberg cells from Hodgkin's lymphoma were shown to both secrete and respond to IL-21. IL-21 protects Hodgkin Reed-Sternberg cells, which are thought to be crippled B cells, from CD95 death receptor-induced apoptosis (66). Therefore, limiting IL-21 may be beneficial for treatment of Burkitt's lymphoma, multiple myeloma, and Hodgkin's lymphoma.

IL-21 has been used in cancer immunotherapy primarily to elicit protective T cell responses. However, there exists some evidence that the function of IL-21 in the differentiation of B cells to Ab-producing PCs is critical for mounting antitumor humoral responses. Administration of IL-21-transduced glioma cells resulted in Ab responses to glioma Ags, predominantly IgG2a and IgG2b isotypes, which mediated complement- or cell-dependent glioma cell lysis in immunocompetent mice. This protocol failed in syngeneic μ MT B cell-deficient mice (67). In a different model, IL-21 gene transfer promoted the production of tumor-specific IgG in mice bearing s.c. head and neck squamous cell carcinomas (68). Injection of IL-21 and IL-2 as adjuvants to a T cell transfer caused an effective regression of established pulmonary metastatic tumors and s.c. tumors in mice. Tumor-specific IgG2b from the sera of treated animals mediated tumor cell lysis in the presence of complement. Use of B cell-deficient μ MT mice provided direct evidence that humoral responses contributed to antitumor immunity (69). Importantly, IL-21 is being tested in clinical trials for advanced melanoma, renal cell carcinoma, as well as in clinical trials for CD20⁺ B cell non-Hodgkin's lymphoma in combination with rituximab (70, 71).

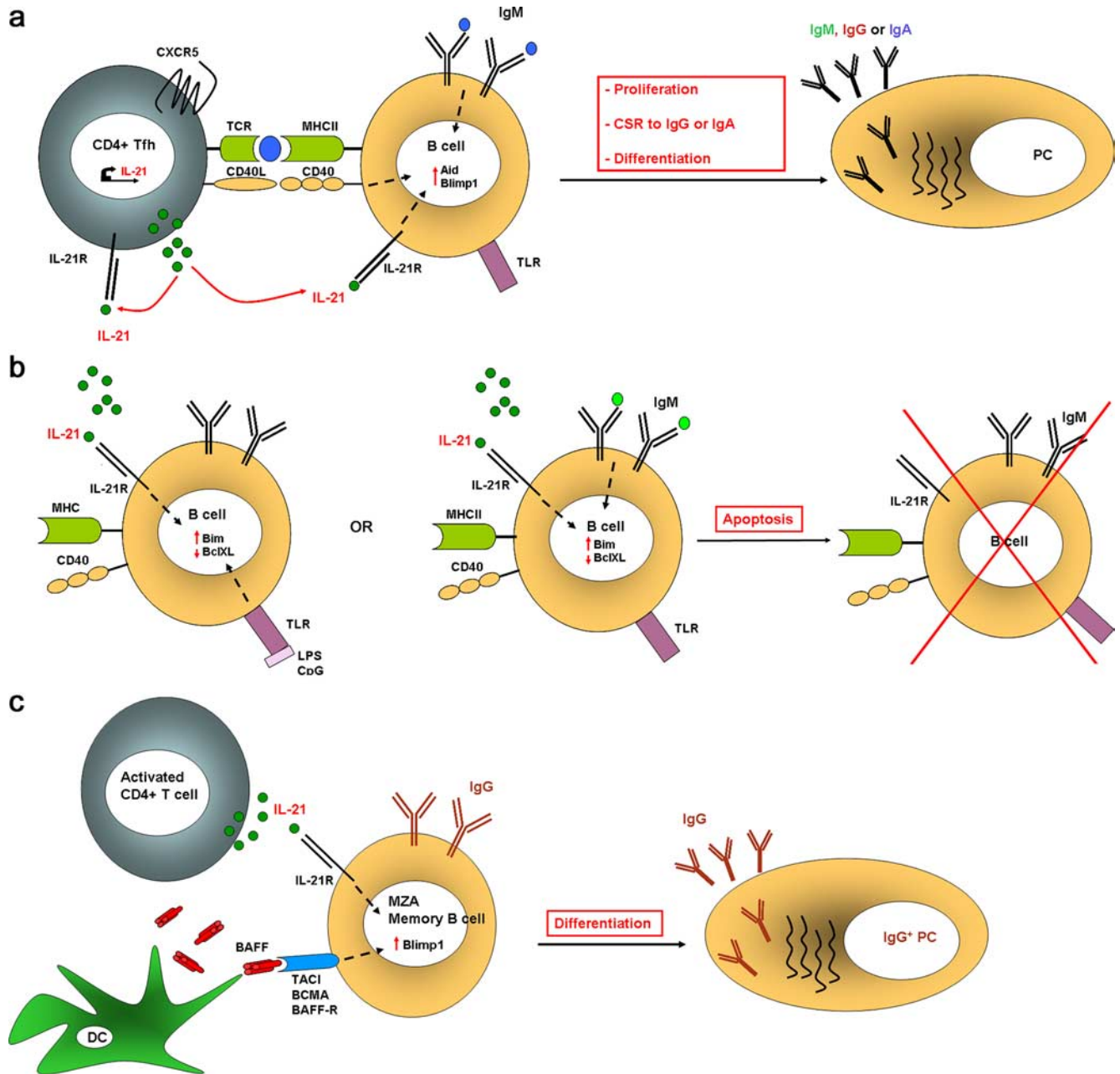


FIGURE 1. Functional outcomes of IL-21 signaling in B cells. *a*, In GCs, B cells that have undergone somatic hypermutation pass through checkpoints where they get tested for their ability to bind Ag presented in the form of immune complexes on the surface of follicular DCs. If B cells recognize an Ag via BCR, they can process and present it to Tfh cells and elicit their help via CD40L-mediated and IL-21-mediated signals. This results in survival, proliferation, CSR, and differentiation of B cells to IgM-, IgG-, or IgA-secreting PCs. Other cytokines, such as IL-4 and IL-10, can modulate IL-21 effects on CSRs to certain Ig isotypes. In vivo results suggest an inhibitory role for IL-21 in differentiation to IgE-secreting PCs, but in vitro results are conflicting. *b*, IL-21 costimulation causes Bim-mediated apoptosis in murine naive B cells that receive strong signals via TLR or via BCR in the absence of adequate T cell help. *c*, In human spleen, MZA IgG⁺ memory B cells respond to T cell-produced IL-21 and DC-produced BAFF by differentiating to IgG-secreting PCs. BCMA, B cell maturation Ag; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor.

Conclusions

The effects of IL-21 on normal and malignant B cells vary (Fig. 1). In B cells that recognize Ag and receive T cell help, IL-21 induces survival, proliferation, isotype switching, and differentiation to Ig-secreting PCs (Fig. 1*a*). In those B cells receiving a strong signal via BCR alone, as can be the case for some autoantigens, or via TLR, IL-21 costimulation causes death (Fig. 1*b*). Signals via CD40L or BAFF, provided by bystander T cell help or DCs, respectively, can promote differentiation of human B cells in an Ag-independent manner when costimulated with

IL-21 (Fig. 1*c*). Balance between proliferation/survival and apoptosis signals is necessary to maintain B cell homeostasis, mount effective immune responses, and prevent the development of autoimmunity or cancer. Future studies should focus on understanding the complete signaling cascades and downstream changes in the patterns of gene and protein expression in B cells in response to IL-21 alone or in combination with other Th-produced cytokines such as IL-2, IL-4, IL-10, IL-6, and IL-12. This knowledge may help us predict the functional outcomes of IL-21 signaling in different B cell backgrounds, which will be

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