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BAFF, APRIL, and their receptors: physiological role and involvement in the pathogenesis of chronic lymphocytic leukemia

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Abstract

Chronic lymphocytic leukemia (CLL) is hematopoietic malignancy involving clonal proliferation and accumulation of morphologically mature yet functionally incompetent B-lymphocytes in blood, lymphoid tissue and, less commonly, extralymphatic organs. Despite significant advances in molecular characterization of CLL, the pathogenesis of the disease remains incompletely understood. Besides disturbed apoptosis considered to be the main molecular defect responsible for the development of CLL, some role is also attributed to activation of BCR receptor, triggering of PI3K and MEK/ERK signaling pathways, and activation of nuclear transcription factor κB (NF-κB) which result in increased proliferation of leukemic cells. Intracellular activation pathways may also be triggered by other proteins, including proteins of the TNF family. B cell activating factor (BAFF) and its homolog A proliferation inducing ligand (APRIL) are cytokines of the tumor necrosis factor (TNF) family considered to play the key role in regulation of biological function of B-lymphocytes. Interactions of both molecules with their receptors (BAFF-R, TACI, BCMA) promote survival of normal B-lymphocytes while also affecting their differentiation, maturation, chemotaxis, class switching and antibody production. According to current knowledge, malignant B-lymphocytes responsible for CLL are characterized by upregulation of these proteins and receptors which translates into deregulation of apoptosis and proliferation of cells, higher stage of the disease, and poorer prognosis. This article summarizes current knowledge on the characteristics and physiological importance of BAFF, APRIL and their receptors as well as on the established role of these proteins

in the pathogenesis of chronic lymphocytic leukemia including deregulation of leukemic B-lymphocytes together with the potential for BAFF and APRIL proteins being used as prognostic markers in clinical medicine.

Key words: TNF family proteins, BAFF, APRIL, chronic lymphocytic leukemia

1. Introduction

Chronic lymphocytic leukemia (CLL) is hematopoietic malignancy involving clonal proliferation and accumulation of morphologically mature yet functionally incompetent B-lymphocytes in blood, lymphoid tissue and, less commonly, extralymphatic organs [1]. CLL is the most common type of leukemia in the overall adult population of the Western countries, with its morbidity rates continuously increasing [2]. The median age at CLL onset is in the range of 67-72 years, with more than 70% of patients being over the age of 70 at the time of diagnosis [1,3]. Despite the disease being chronic by definition, it is characterized by significant heterogeneity of natural history. While some patients present with slow disease development and long times to disease progression, others require treatment immediately or shortly after being diagnosed, their disease following a very aggressive course [4,5]. Leukemic cells have the phenotype of small, mature B-lymphocytes characterized by expression of CD19, CD20, CD23, or CD5 surface markers. The majority of these cells are arrested at the G0 stage of the cell cycle [2]. At the same time, part of cells within the bone marrow and peripheral lymphatic organs present with potential for proliferation contributing to the pool of leukemic B-lymphocytes in the course of the disease. Disturbed apoptosis was generally considered to be the main molecular defect responsible for the accumulation of B-lymphocytes and the development of CLL, with survival of lymphatic cells being attributed to disruption of apoptotic pathways as well as increased responsiveness to pro-survival factors [6]. In recent years, an additional factor which determines the dynamics of the disease was identified, consisting in the cells' active proliferation ability triggered by activation of the BCR receptor by a hitherto unknown endo- or exogenous factors [1]. Despite significant advances in characterization of molecular defects responsible for CLL, the pathogenesis of the disease remains incompletely understood. In recent years, proteins of the tumor necrosis factor (TNF) family became the object of research interest in the context of their physiological role as well as their involvement in deregulation of B-lymphocytes in the course of CLL, other lymphoproliferative diseases, and humoral immunity deficiencies. B cell activating factor (BAFF) and its homolog a proliferation inducing ligand (APRIL) are cytokines of the tumor necrosis factor (TNF) family which, by interacting with their specific receptors, regulate the biological function of B-lymphocytes in physiological conditions [7]. As shown in studies published to date, the expression of these proteins on the surface of CLL B-cells is significantly higher than on the physiological B-cells in healthy subjects, contributing to the increased survival and proliferation potential of the leukemic cells. This article summarizes current reports on the involvement of BAFF, APRIL and their receptors in the mechanisms responsible for of leukemic B-lymphocytes and their impact on the development of chronic lymphocytic leukemia.

2. Objective, materials, and methods

The aim of this study was to summarize current knowledge on BAFF, APRIL, and their receptors with respect to their physiological role as well as their involvement in the pathogenesis of chronic lymphocytic leukemia. Included in the review are the reports on protein structure characterization, molecular effects of ligand-receptor interactions, the role of these interactions in deregulation of leukemic B-lymphocytes, and potential future clinical applications of the collected knowledge. Literature search was carried out by means of a PubMed database query.

3. Discussion

3.1. Pathogenesis of chronic lymphocytic leukemia (CLL)

As mentioned before, chronic lymphocytic leukemia (CLL) is a malignancy of the lymphoid system associated with clonal proliferation of morphologically mature yet functionally incompetent B-lymphocytes; in the course of the disease, these cells are found within blood, bone marrow, peripheral lymphatic organs and lymphoid tissue (lymph nodes and nodules) and, less commonly, extralymphatic organ infiltrates. According to 2008 WHO classification, CLL is a malignancy of the lymphatic system originating from peripheral B-lymphocytes [1]. In general, leukemic B-lymphocytes phenotypically correspond to mature peripheral B-lymphocytes as evidenced by the set of surface antigens including CD19, CD20, and CD23; they are also

characterized by low expression of surface immunoglobulins [2]. At the same time, leukemic cells are characterized by expression of CD5; this antigen is present only in a small subpopulation of physiological B-lymphocytes (B1 cells). Over the last several years, the origin of the leukemic cells in the course of CLL has been widely discussed. Gene expression profiling suggests high similarity between CLL B-cells and CD5+ cells of healthy adults; it appears that leukemic B-cells with no mutations within the immunoglobulin heavy chain variable region gene (IgVH) originate from CD5+CD27− (classical memory cells) with the same IgVH mutation status whereas B-cells with mutations within the IgVH gene originate from the less studied subpopulation of CD5+CD27+ cells featuring IgVH mutations. It is estimated that a vast majority (ca. 95-97%) of leukemic cells are arrested at the G0/G1 stage of the cell cycle which is responsible for the relative resistance of CLL to standard cytostatic drugs as observed in numerous cases [6]. According to the traditional explanation, the main factor responsible for CLL pathogenesis was considered to consist in disturbed apoptotic pathways. Leukemic B-lymphocytes present with overexpression of B-cell lymphoma 2 (Bcl-2) protein and aryl hydrocarbon receptor-interacting protein (AIP) along with reduced levels of proapoptotic Bcl-2-associated X (BAX) and Bcl-2 antagonist/killer (BAK) proteins, resulting in reduced permeability of mitochondrial membranes and reduced secretion of cytochrome c, ultimately inhibiting mitochondrial apoptosis [8]. In recent years, involvement of excessive proliferation of B-lymphocytes within the lymph nodes and bone marrow has also been highlighted; the process is dependent on the B-cell receptors (BCRs) and the microenvironment of lymphatic organs [9]. Stimulation of BCR activates Lck/Yes novel tyrosine kinase (LYN) and spleen tyrosine kinase (SYK) which phosphorylate immune-receptor tyrosine-based activatory motifs (ITAMs) within BCR-bound CD79a and CD79b proteins. Phosphorylated ITAMs recruit adaptor proteins such as Bruton tyrosine kinase (BTK) and phosphoinositol 3-kinase (PI3K) which in turn activate mammalian target of rapamycin (mTOR) kinase and protein kinase B (PKB, Akt) and ultimately nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) which triggers the transcription of genes responsible for cell activation and proliferation [10]. In about one half of patients, leukemic cells also express ZAP-70 (ζ-associated protein of 70 kDa) kinase which additionally promotes the recruitment of adaptor kinases to BCRs and facilitates transduction of signals to the interior of cells [11]. As the result of BCR activation, leukemic cell is provided not only with increased ability to proliferate, but also with increased expression of chemokines such as CCL3 and CCL4 which recruit other cells facilitating the survival of leukemic cells, such as regulatory T cells, into the microenvironment [12]. Besides lymphocytes T, proliferating leukemic cells remain in close contact with numerous cells within their immediate microenvironment in the lymphatic organs, including mesenchymal stem cells and monocyte/macrophage-derived cells (nurse-like cells) [10]. Interestingly, leukemic cells present with increased activation of not only BCRs, but also of TNF family receptors (TNF-R) such as B cell-activating factor receptor (BAFF-R), transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) and B cell maturation antigen (BCMA), with the aforementioned BAFF and APRIL proteins acting as ligands thereof [13].

3.2. Characterization of selected TNF superfamily proteins and their receptors

TNF superfamily is a complex group of cytokines which currently consists of 19 proteins with structural and functional analogies. These cytokines exert complex impact on survival, differentiation, and numerous functions of immune cells in the course of inflammatory processes or specific immune responses [14]. The members of the superfamily include molecules involved in positive regulation of cell apoptosis (FASL, TRAIL) or lysis (LTα, LTβ), pyrogens (TNFα), and stimulators of differentiation and proliferation of T-lymphocytes (CD27L, CD30L, 4-1BBL, OX40L) as well as B-lymphocytes (CD40L). The proteins of interest in this review, BAFF and APRIL, are TNF superfamily members which have been discovered only several years ago and which play a crucial role in regulation of B cell homeostasis.

B cell activator factor (BAFF), also known as B lymphocyte stimulator (BlyS), TNF and apoptosis ligand-related leukocyte-expressed ligand 1 (TALL-1), or CD257 is a 285-amino acid molecule which may be found in cell membrane-bound or soluble secreted form [7]. The membrane-bound form of BAFF consists of cytoplasmic, transmembrane, and extracellular domains; the latter domain contains sequences shared by all TNF superfamily members [15]. An unique feature of BAFF consists in its ability to assemble in trimeric but also up to 60-meric forms referred to as viral-like forms and characterized by higher receptor binding strengths [7,15]. Although BAFF is produced mainly in B cells follicular T helper (fTh) cells and myeloid-line cells, it is expressed in most cells of all types of tissues [6]. Thanks to its continuous expression BAFF facilitates constant positive regulation

of B cell survival and function; the expression is increased by the presence of inflammatory cytokines (IFNα, IFNγ, G-CSF, IL-10), stimulation of Toll-like receptor 3 (TLR3) or interactions between T and B cells mediated by CD40-CD40L molecules in the process of physiological B cell activation [16,17].

A member proliferation-inducing ligand (APRIL), also known as TALL-2 or CD256, is a 250-amino acid homolog of BAFF sharing about 30% of TNF superfamily-homologous sequences present within the extracellular domain of BAFF [7]. Notably, in the contrary to BAFF, APRIL contains the short alkaline amino acid sequence which facilitates binding of proteoglycans present within the cell microenvironment [7, 18]. APRIL is found mainly in the form of homotrimers; however, a heterotrimeric form (consisting of APRIL and BAFF molecules) is also known and encountered mainly in autoimmune diseases [19]. In contrast to BAFF, APRIL is rarely expressed on the cell membrane, being usually present either in soluble form or bound to the Golgi apparatus [20, 21]. APRIL is produced mainly by myeloid-line cells, B cells, epithelial cells, and osteoclasts. Particularly high expression of APRIL has been observed for dendritic cells exposed to interferons (IFN-α, IFN-γ) or interaction with CD40L [22].

The biological effects of BAFF and APRIL are triggered by their interactions with appropriate receptors. The best-studied receptors for the BAFF and APRIL ligands include the aforementioned BAFF-R, TACI, and BCMA. B cell-activating factor receptor (BAFF-R), also referred to as BAFF receptor 3 (BR3) or CD268, is a small membrane molecule of the TNF-R family found on the surface of B-lymphocytes as well as activated T-lymphocytes and regulatory T-lymphocytes [23,24]. Out of the entire population of human B cells, the highest expression of BAFF-R is observed on naive B cells and memory B cells; the receptor is absent only from the surface of plasma cells [24]. The structure of the receptor corresponds to that of most TNF-Rs with a certain difference consisting in a lower number of cysteine-rich domains (CDRs) within the extracellular domain, making BAFFF the preferred ligand for stable binding [25]. Interactions with ligands activates TNF-receptor associated factor 3 (TRAF-3) which in turn activates NF-κB along with its pro-cell survival, pro-proliferative, pro-cell activation and pro-differentiation effects [22, 24, 26].

Transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) is a membrane protein present mainly on the surface of memory B cells and macrophages [27, 28]. The effects exerted by TACI largely depend on the connected ligand. Binding of a BAFF molecule is known to downregulate the function of mature lymphocytes, reducing their ability to survive, proliferate, and produce antibodies [27]. On the other hand binding of an APRIL molecule results in a series of counteracting effects starting from increased cell survival, ability to antibody class switching and somatic hypermutations within the first days of antigen-dependent lymphocyte activation [29-31]. TACI binding affects activation of TRAF-2, TRAF-5, TRAF-6, c-jun N-terminal kinase (JNK) and, consequently, activation of NF- κB as well as nuclear factor of activated T-cells (NF-AT) and activator protein 1 (AP-1), featuring a survival regulating-function [29].

B-cell maturation antigen (BCMA) is a membrane receptor protein with a structure analogous to that of other TNF-R family receptors. The reports on the exact structure and function of BCMA are sparse. The molecule is known to undergo expression mainly on the surface of mature B lymphocytes. In a manner similar to BAFF-R and TACI, it is involved in regulation of survival and proliferation of these cells [32]. Biological effects are mediated by activation of TRAF-1, TRAF-2, and TRAF-3, activation of mitogen-activated protein kinase 8 (MAPK-8) and JNK, and activation of transcription factors NF-κB and Ets-like transcription factor 1 (Elk-1) [32].

3.3. The role of BAFF, APRIL, and their receptors in the homeostasis of B-lymphocytes

BAFF and APRIL are native, constitutively produced immune modulators required for the development of B lymphocytes within the bone marrow and for the maintenance of homeostasis of peripheral B lymphocytes at rest as well as during immune responses. Both BAFF and APRIL have high affinity towards TACI; BAFF is also capable of binding BAFF-R, and APRIL has high affinity towards BCMA [33]. Intracellular signaling triggered by interactions between BAFF/APRIL proteins and their receptors proceeds mainly via activation of TRAF proteins and NF-κB by canonical or non-canonical pathway [30,34]. NF-κB is a transcription factor known to play a key role in the expression of immunoglobulin genes as well as numerous genes responsible for survival, activation, differentiation, and proliferation of lymphocytes [35]. In physiological conditions, the development and functions of B cells are strictly regulated by numerous types of cells and factors secreted therefrom. As shown in studies conducted to date, molecules of the TNF family are involved in said regulation both during the

antigen-independent development of B lymphocytes within the bone marrow and during their proliferation and activation following antigen exposure. Interactions of BAFF/APRIL proteins with their specific receptors within the bone marrow enhances expression of paired box 5 (Pax5) transcription factor which, along with early B cell factor (EBF) is a key transcription factor responsible for lymphoid progenitor differentiation into B lymphocyte and involved in activation of plasma cells present within the bone marrow [36]. In addition, BAFF and APRIL facilitate survival of B cells in peripheral lymphatic organs. The expression of these proteins is constitutive and increases as the cells are stimulated with interferon, activation of TLR receptors or ligated by CD40 in the course of ongoing inflammation. This is an additional observation supporting the suggested importance of the proteins of interest in the immune response process. Particularly in the case of BAFF, it was demonstrated that once bound to the BAFF-R, the protein enhances the expression of a number of antiapoptotic proteins of the Bcl-2 family, including B-cell lymphoma extra large (Bcl-XL), Bcl-2-like protein 11 (Bim) and myeloid cell leukemia 1 (Mcl-1) proteins within B lymphocytes [23, 26]. Pro-proliferative and pro-survival effects of BAFF are also the result of protooncogene serine/threonine-protein kinase (Pim-1) and extracellular signal-regulated kinases (ERK) activation, the enzymes are involved in the transmission of stimulatory signals to the cell nucleus, as well as activation of molecules involved in cell cycle regulation such as cyclin D, p27Kip1, or c-myc proteins [23,26,37]. The soluble form of BAFF is considered to the crucial for proper development of B lymphocytes in the antigen-dependent phase, both within the lymph nodules and the marginal zone [38]. By means of the aforementioned signaling pathways, BAFF stimulates not only the proliferation of B cells, but also class switching and production of antibodies, thus overseeing the correct course of humoral immune response [39]. Biological activity of APRIL is somewhat less understood compared to that of BAFF; however, APRIL was shown to promote B cell survival at late development stages, stimulate proliferation of T and B cells, as well as enhance class switching and production of antibodies [40]. In addition, together with IL-6 and SCF (stem cell factor), APRIL is responsible for creating conditions promoting the survival of long-lived plasma cells within the bone marrow [26]. By means of PI3K/AKT and MAP kinase pathway activation, BAFF and APRIL are also involved in regulation of chemotaxis [41].

3.4. The role of BAFF, APRIL, and their receptors in the pathogenesis of CLL

The important role of BAFF and APRIL in the maintenance of survival and stimulation of proliferation of B-lymphocytes suggests that overexpression of these proteins may deeply disrupt the control of these functions and lead to carcinogenesis or autoimmune disorders [26]. The importance of these molecules for the regulation of B cell biology was shown in a murine model study where a BAFF-R gene mutation leading to complete lack of BAFF-R protein was demonstrated to be responsible for complete lack of B2 (CD5−) cells, which are the main systemic subpopulation of B-lymphocytes [38]. On the other hand, mice with artificially activated overexpression of APRIL gene were characterized by increased proliferation of B1 (CD5+) cells within the peritoneum resulting in progressive hyperplasia of Peyer's patches and mesenteric lymph nodes or even in B-cell infiltrations of parenchymal abdominal organs [42]. To date, numerous studies were initiated to assess the potential involvement of BAFF, APRIL and their receptors in the pathogenesis of chronic lymphocytic leukemia in humans. One of the main findings consisted of a significantly increased levels of BAFF and APRIL within the blood sera of patients diagnosed with CLL as compared to the control group consisting of healthy volunteers [33, 34]. The expression of BAFF and APRIL was also higher within the cell membranes as well as inside the B-lymphocytes in CLL patients compared to healthy controls [33]. Other reports highlighted elevated levels of the proteins of interest on the surface of monocyte-derived cells present in the microenvironment of peripheral lymph nodes (nurse-like cells) [34]. What's more, studies of CLL showed that leukemic cells are characterized not only by elevated levels of BAFF, APRIL and their receptors, but also by survival-stimulating signals being received via these molecules as demonstrated in *in vitro* models [6,43]. BAFF and APRIL produced within the microenvironment of lymphatic organs enhance the proliferation ability of leukemic cells by means of autocrine as well as paracrine mechanisms, and are thus considered to be, along with excess activation of BCRs, the key factor responsible for active proliferation and accumulation of leukemic cells within the lymphoid organs [44]. At the same time, literature data suggest that analogous increase is observed in patients diagnosed with CLL with regard to the levels BAFF-R, TACI, and BCMA receptors on the surface of B cells present within the blood and lymphatic tissue [6]. Interesting results were obtained in a study of intracellular expression of BAFF and APRIL in leukemic B cells and of the relationship between the levels of these proteins and certain clinical and

prognostic parameters [33]. The levels of BAFF and APRIL proteins as assessed by cytometry was significantly higher in CLL B-cells as compared to B cells of a healthy control and correlated with the presence of unfavorable prognostic factors ZAP-70 and CD38 (no correlation was observed for IgVH mutation status). The observed overexpression of BAFF and APRIL had negative impact on the overall survival (OS) in these patients. In addition, the same study showed that also the elevated soluble APRIL serum levels in patients with CLL determined by means of enzyme-linked immunosorbent assay (ELISA) is correlated with higher Rai stage and shorter overall survival [33]. The results are all the more interesting that they suggest the potential of intracellular BAFF and APRIL (determined by means of cytometry) as well as soluble APRIL (determined in the serum by means of ELISA) being useful as prognostic markers. The ease of the assays and the prognostic values of these proteins suggested in studies conducted to date warrants their use in CLL prognosis being considered in the future. On the other hand, considering the complex and strong impact of BAFF/APRIL on the cellular processes (apoptosis, cell cycle control, activation of intracellular signaling pathways, gene expression), the proteins may also be considered potential molecular targets for future therapy of chronic lymphocytic leukemia [45].

4. Summary

CLL is the most common type of leukemia in the overall adult population in Western countries and the morbidity rates of CLL are continually increasing. Despite numerous studies being undertaken to examine the molecular background of the disease, the pathogenesis of CLL remains incompletely understood and the disease remains incurable. Accumulation of leukemic cells is caused by disturbed apoptosis; however, uncontrolled activation and proliferation of cells secondary to BCR stimulation is equally important, and the original cause of this phenomenon is still a subject of studies. Proteins of the TNF cytokine family are a large group of molecules exerting complex impact on immune cell functions. By interaction with their specific receptors, two members of this family, BAFF and APRIL, impact on the survival, proliferation, and numerous biological functions of B cells. It was demonstrated that interactions between these proteins and their receptors trigger a number of molecular effects hitherto observed in leukemic cells, such as inhibition of apoptosis, activation of kinase pathways involved in immune cell activation, and increased numbers of transcription factors involved in the expression of genes responsible for survival and proliferation, suggesting their role in deregulation of B cells which accompanies malignant transformation and chronic lymphocytic leukemia. CLL studies conducted to date revealed significantly higher levels of BAFF, APRIL, TACI, BCMA, and BAFF-R on leukemic B cells compared to B cells of healthy controls. At the same time, elevated levels of these proteins were shown to be associated with higher clinical stage and unfavorable prognosis. Potential use of BAFF and APRIL or their receptors and CLL prognostic markers in routine clinical practice requires numerous further studies; however, considering the knowledge that has already been collected, the relatively simple methodology and low cost of respective assays, the perspective is very interesting.

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