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Th17 related cytokines in acute myeloid leukemia

Peng Li[1], Min Ji[1,3], Jino Park[3], Kevin D. Bunting[2], Chunyan Ji[1], William Tse[3]

[1]Department of Hematology, Qilu Hospital, Shandong University, Jinan, Shandong, P. R. China, [2]Aflac Cancer Center of Children's Heathcare of Atlanta and Emory University Department of Pediatrics, Atlanta, GA 30345, [3]Mary Babb Randolph Cancer Center, West Virginia University Health Science Center, Morgantown, WV 26506

TABLE OF CONTENTS

1. ABSTRACT

Acute myeloid leukemia (AML) is the most common hematological malignancy in adults, characterized by distorted proliferation and development of myeloid cells and their precursors in blood and bone marrow. Impressive biologic advances have increased our understanding of leukemogenesis, however, little is known about the pathogenic events which lead to the initiation and progression of AML. T helper type 17 (Th17) cells are a unique subset of CD4+ T cells. They play important roles in the pathogenesis of many diseases, including inflammatory diseases, autoimmune diseases, and cancers. A range of cytokines, such as interleukin (IL)-23, transforming growth factor-beta (TGF-beta), IL-1beta, IL-6, IL-17, IL-22, and IL-21, have been shown related to Th17 cells. Some researchers have reported that the levels of Th17 and its related cytokines were different between normal cells and malignant AML cells, suggesting that Th17 might be involved in AML pathogenesis. In this review, we summarize current progress in the mechanisms of Th17 related cytokines in AML pathogenesis.

2. INTRODUCTION

Th17 cells, which are described as IL-17-producing CD4+ helper T cells, are considered as a novel and early subset of effector CD4+ T cells produced directly from naive CD4+ T cells (1, 2). Classically, the known universe of CD4+ helper T cells can be separated into Th1 and Th2 due to secretion of different cytokine patterns and immune regulatory function (Figure 1) (3, 4). Th1 cells, which mediate cellular immunity, develop in response to IL-12 and produce interferon-gamma (IFN-gamma). Th2 cells, which evolve to enhance humoral immunity and allergic responses, develop in response to IL-4 and produce IL-4, IL-5 and IL-13 (5-7). In 2005, two reports in Nature Immunology challenged the idea of a shared developmental pathway for Th17 and Th1/Th2 cells. Instead they provided convincing evidence that Th17 cells are a completely separate and early lineage of effector CD4+ T cells produced directly from naive CD4+ T cells, which is a giant step toward understanding the role of Th cells in disease and health (8). It is well known that Th17 cells participate in inflammation and autoimmune diseases (10-

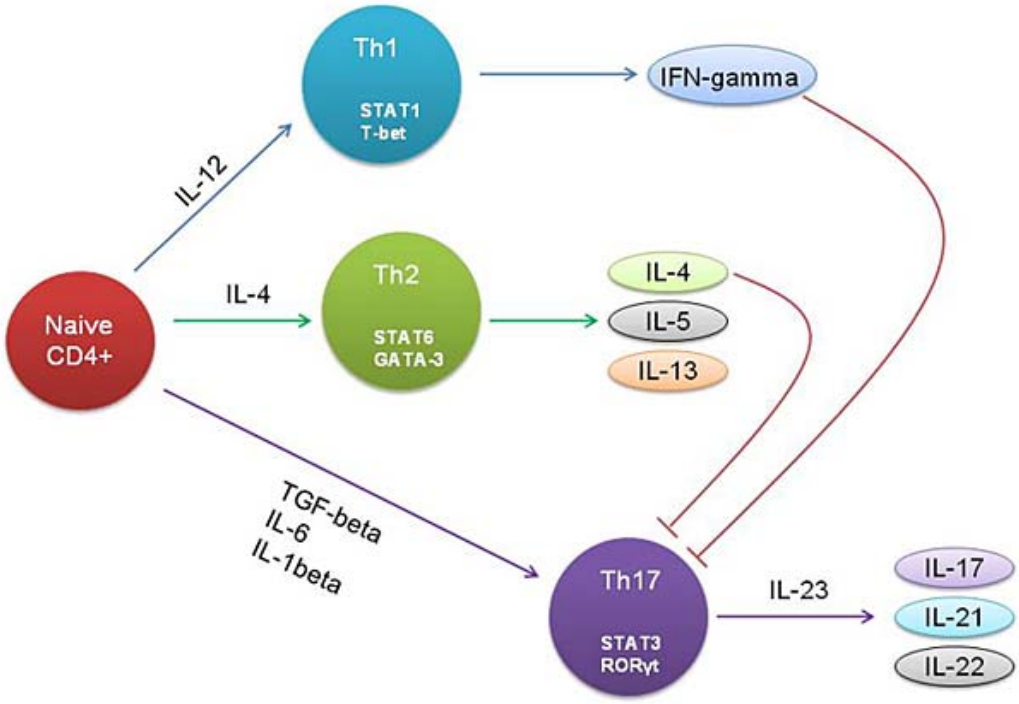

Figure 1. Naive CD4+ T cells can differentiate into one of three lineages of Th cells: Th1, Th2 or Th17 cells. These cells produce different cytokines and have distinct immunoregulatory functions. Th1 cells, which mediate cellular immunity, develop in response to IL-12 and produce IFN-gamma. Th2 cells, which evolve to enhance humoral immunity and allergic responses, develop in response to IL-4 and produce IL-4, IL-5 and IL-13. For human Th17 differentiation, TGF-beta, IL-23, IL-1beta and IL-6 are all essential. These cells express IL-17, IL-21 and IL-22 and play important roles in the pathogenesis of many diseases, including inflammatory diseases, autoimmune diseases and cancers.

14). Th17 cells are also detected in tumors, such as ovarian cancer, gastric cancer, and hepatocellular carcinoma (15-18). In addition to important immunoregulatory functions, Th17 cells and IL-17 also have a regulatory role in normal hematopoiesis (9).

AML is a life-threatening hematopoietic stem cell neoplasm characterized by an increase in the number of myeloid cells in the marrow and an arrest in their maturation, frequently resulting in fatal infection, bleeding, or organ infiltration, with or without leukocytosis (19-21). Biologic advances have increased our understanding of leukemogenesis, however, we still know little about the pathogenic events leading to the initiation and progression of this disease (22). Recently, Wu *et al* indicated that Th17 cell frequencies were increased significantly in peripheral blood samples with AML (23). Other reports suggest that Th17 related cytokines play an important role in AML. Here we will discuss the roles of Th17 cell and its related cytokines in AML.

3. TH17 RELATED CYTOKINES

Since the identification of Th17 cells, ongoing research efforts have been made to characterize the factors regulating their differentiation and function. Several cytokines drive the generation of Th17 cells and Th17 cells perform their biological function by secreting cytokines.

3.1. Cytokines participate in the generation of Th17 cells

Early reports indicated that IL-23 was essential for the differentiation of Th17 cells (13, 14). Aggarwal *et al* found that murine IL-23, which acted on memory T cells (a distinct CD4+ T cell activation state), resulted in elevated IL-17 secretion. IL-4 and IFN-gamma can inhibit the development of Th17 cells from naive precursor cells, and later negatively regulate T helper cell production of IL-17 in the effector phase (1, 2). In the absence of IFN-gamma and IL-4, IL-23 induces naive precursor cells to differentiate into Th17 cells independently of the transcription factors STAT1, T-bet, STAT4, and STAT6 (1). Later, it was shown that IL-23 maintained the effector function of Th17 cells, such as the secretion of large amounts of IL-17 (25), but did not affect differentiation of Th17 cells (26, 27).

TGF-beta can suppress IFN-gamma expression in some CD4+ T cells (28, 29). As a cytokine critical for commitment to Th17 development, TGF-beta acts to up-regulate IL-23R expression, thereby conferring responsiveness to IL-23 (30). Studies in mice have demonstrated that IL-6 and TGF-beta drive the differentiation of pathogenic Th17 cells from naive T cells (27). As a key transcription factor, the orphan nuclear receptor RORγt orchestrates the differentiation of mouse Th17 cells in response to IL-6 and TGF-beta (31). In

addition to TGF-beta and IL-6, IL-1beta can increase the production of IL-23, which induces IL-17 and OX40 expression in splenic CD4+ T cells of IL-1Ra–/– mice (32). Blocking IL-23 with anti-p19 Ab abolishes the IL-17 production induced by IL-1 in mouse splenocyte cultures (32). It is believed that for human Th17 differentiation, TGF-beta, IL-23 and proinflammatory cytokines (IL-1beta and IL-6) are all essential (33). However, Acosta-Rodriguez *et al* found that for human naive CD4+ T cells, RORγt expression and Th17 polarization were induced by IL-1beta and enhanced by IL-6 but were suppressed by TGF-beta (34). In addition, whereas in mice IL-6 is required for Th17 differentiation and IL-1beta exerts an enhancing effect, in humans it seems that IL-1beta has a chief function and IL-6 enhances IL-1beta-induced Th17 differentiation (34).

3.2. Cytokines secreted by Th17 cells

IL-17, now denoted as IL-17A, is the hallmark cytokine of Th17 cells (1, 2, 8). Th17 cells also express IL-22, an IL-10 family member, at substantially higher amounts than Th1 or Th2 cells (35). Similar to IL-17, IL-22 expression is initiated by TGF-beta signaling, IL-6 and other proinflammatory cytokines (35, 36). IL-21, an IL-2 cytokine family member, is another cytokine highly expressed by mouse Th17 cells, which is induced by IL-6 in activated T cells dependent on STAT3 but not RORγ (37). IL-21 may play an essential autocrine regulatory role in the generation of inflammatory T cells (38, 39). In the absence of IL-6, IL-21 cooperates with TGF-beta to induce Th17 cell differentiation (38). IL-21 and IL-23 induce the orphan nuclear receptor RORγt, which in synergy with STAT3 promotes IL-17 expression (39).

4. TH17 RELATED CYTOKINES IN ACUTE MYELOID LEUKEMIA

Our understanding of the role of T cells in human disease is undergoing revision as a result of the discovery of Th17 cells (10). In hematopoietic and blood system diseases, Ma *et al* have measured the plasma concentration of three Th17 associated cytokines (IL-17, TGF-beta, IL-6) in 29 adults with chronic ITP and 38 adult healthy volunteers. No significant differences were observed between the two groups (40). Later, their group found that the levels of IL-21, another Th17 related cytokine, were significantly elevated in ITP patients compared to controls, and that blockade of IL-21 may be a reasonable therapeutic strategy for ITP especially those with active disease (41). In hematopoietic and blood system malignancies, bone marrow from patients with myeloma contained a higher proportion of Th17 cells compared with the marrow in preneoplastic gammopathy (monoclonal gammopathy of undetermined significance (MGUS)) (42). In biopsy specimens from patients with B-cell non-Hodgkin's lymphoma, a significantly lower frequency of Th17 cells was observed, including 23% samples with no detectable amount of Th17 cells present in the tumor microenvironment (43). In AML, the frequencies of Th17 cells (CD3+CD8- T cells) in PBMCs from untreated patients were higher than controls (3.22 +/- 0.26% versus 0.88 +/- 0.16%; $p < 0.01$) (23). Also, increased Th17 cell frequencies decreased when patients achieved complete remission after chemotherapy, suggesting that measurement of Th17 cells may be valuable in the evaluation of therapeutic effect (23). However, another report showed that the relative levels of circulating Th17 cells, defined by the phenotype CD3+ CD8- IL-17A-, did not differ between healthy controls and AML patients with untreated disease, treatment-induced cytopenia and regeneration after chemotherapy (44). Th17 cells unfold their biological function by related cytokines, and many researchers have reported the difference and the role of those cytokines in AML.

4.1. IL-23

IL-23 is a pro-inflammatory cytokine belonging to the IL-12 family. Secreted by activated dendritic cells, IL-23 is composed of a specific polypeptide p19 and the p40 subunit of IL-12 (45). In addition to its effects on Th17 cells, IL-23 also has potent effects on cells of the innate immune system, inducing the production of inflammatory cytokines, such as IL-1, IL-6, and TNF-alpha, by monocytes and macrophages (46). The IL-23 receptor is composed of the IL-12 receptor chain IL-12Rβ1 and the unique IL-23R, which is critical for signal transduction (47).

Allogeneic hematopoietic stem cell transplantation (HSCT), using hematopoietic progenitor cells from a related HLA-identical donor, is the most common form of effective adoptive immunotherapy, permitting the cure of malignant diseases of the marrow included acute myeloid leukemia (48). The graft-versus-leukemia (GVL) effect mediated by the allogeneic graft, compared with graft-versus-host disease (GVHD), is the major cause of morbidity and mortality after HSCT (49). The selective protection of the colon that occurs as a consequence of blockade of IL-23 signaling reduces GVHD, but without loss of the GVL effect (50). IL-23 receptor (IL-23R) polymorphism in oneself or donors might be beneficial to children with HSCT. Gruhn *et al* analyzed the 1142 G>A single-nucleotide polymorphism (SNP) in the IL-23R gene in a cohort of 231 children who underwent allogeneic stem cell transplantation and their respective donors (51). The incidence of acute GVHD (aGVHD) grade II-IV was significantly reduced in patients who were transplanted from a donor with the IL-23R polymorphism (5.0% versus 33.3%; $p = 0.009$). No case of aGVHD was grade III-IV when this polymorphism occurred in the donor.

Recently a study showed that IL-23 may direct anti-tumor activity in pediatric B-acute lymphoblastic leukemia (B-ALL) cells (52). IL-23R is up-regulated in primary B-ALL cells as compared to normal early B lymphocytes, and IL-23 dampens directly tumor growth *in vitro* and *in vivo* through inhibition of tumor cell proliferation and induction of apoptosis. IL-23 induced up-regulation of miR-15a expression and the consequent down-regulation of BCL-2 protein expression in pediatric B-ALL cells. In the AML cell line K562, at least four spliced isoforms of IL-23R (IL-23R1-4) were detected by RT-PCR (53). Nonetheless, the role of IL-23 in AML patients remains unsubstantiated.

4.2. TGF-beta

TGF-beta signaling controls a diverse set of cellular fuctions, including cell proliferation, recognition, differentiation, apoptosis, tumorigenesis and specification of developmental fate, during embryogenesis as well as in mature tissues (54). The three major cell surface receptors for TGF-beta are termed types I, II, and III (TβRI, II, and III, respectively). TβRI and TβRII are the signaling receptors, while TβRIII appears to promote ligand binding to TβRI and TβRII (55). The TGF-beta pathway involves TGF-beta binding to the TβRII and the recruitment of TβRI, leading to assembly of the heterodimeric receptor complex (56). TβRI then phosphorylates receptor-activated Smads (R-Smads), which are composed of Smad2 and Smad3 (56). R-Smads are released from the receptor complex upon phosphorylation and form a heterodimeric complex with Smad4 (Co-Smad), which then translocates into the nucleus (56). In the nucleus, Smad proteins bind to their cognate DNA binding sites, where they interact with transcriptional coactivators or transcription repressors (56).

In the erythroleukemia TF1 cell line, the aberrant expression of Smad5beta is likely to alter the erythroid differentiation response to TGF-beta/BMP ligands (57). Two distinct mutations (a missense mutation in the MH1 domain (P102L) and a frameshift mutation resulting in termination in the MH2 domain (Delta (483 - 552))) in Smad4 resulted in disruption of TGF-beta signaling, and thus led to AML (58). AML1-ETO, an AML-associated fusion protein, cooperates with Smads, blocking the response to TGF-beta1 (59), and inducing the expression of C-KIT gene mutation (60). Production and secretion of an active form of TGF-beta and stimulation of collagen synthesis in a paracrine manner results in bone marrow fibroblasts, which is often associated with acute megakaryoblastic leukemia (AMKBL) (61). The concentration of plasma TGF-beta is also found higher in AMLs than in controls (51.37 +/- 11.30 versus 14.35 +/- 4.00 ng/ml, $p < 0.01$) (23).

More and more evidence supports deregulated TGF-beta signalling in leukemogenesis, especially in acute promyelocytic leukemia (APL). APL, caused by the clonal expansion of tumor cells with promyelocytic morphological characteristics, is a distinct subtype of acute myeloid leukemia (the AML-M3 subtype according to the French-American-British classification) that accounts for more than 10% of all AMLs (62). APL blasts harbor-specific reciprocal chromosomal translocations which always involve the retinoic acid receptor alpha (RARα) locus on chromosome 17. In most APL patients, the translocation observed is t(15;17)(q22;q11-12), encoding a fusion protein between the RARα and a myeloid gene product called promyelocytic leukemia (PML) (63). Combined treatment with TGF-beta and 1,25-dihydroxyvitamin D3 (D3) can cause terminal monocytic maturation in human monocytic (U-937) and promyelocytic (HL-60 and AML-193) leukemic cell lines (64). While APL blasts are poorly responsive to TGF-beta, treatment with all-trans retinoid acid (ATRA) induces degradation of PML-RARα and resensitizes leukemic cells to TGF-beta-induced growth inhibition (65). PML-null primary cells have impaired phosphorylation and nuclear translocation of Smad2 and Smad3, as well as impaired induction of TGF-beta target genes (65). Cytoplasmic PML (cPML), which is induced by TGF-beta, is required for association of Smad2/3 with SARA and for the accumulation of SARA and TGF-beta receptor in the early endosome (65). The PML-RARα oncoprotein of APL can antagonize cPML function and defect in TGF-beta signalling similar to those observed in PML-null primary cells (65).

4.3. IL-1beta

IL-1 family consists of three structurally related members: IL-1alpha, IL-1beta and IL-1 receptor antagonist (IL-1Ra). IL-1alpha and IL-1beta are the product of separate genes having different amino acid sequences but which are structurally related and act through the same cell-surface receptors to exert their biologic activities (66). IL-1Ra, a specific inhibitor of IL-1, acts by blocking the binding of IL-1 to its cell-surface receptors (67). All three proteins are produced as precursors, of which pro-IL-1alpha and pro-IL-1Ra possess biological activity, however, pro-IL-1beta requires cleavage by caspase-1 (IL-1beta converting enzyme, ICE) to become biologically active (68). There are two IL-1 receptors: the type I IL-1 receptor (IL-1RI) and the type II IL-1 receptor (IL-1RII). Of the two receptors that bind IL-1, IL-1RI is known to mediate signaling activity, whereas IL-1RII serves as a decoy receptor as it binds all IL-1 ligands but lacks an intracellular domain and does not transduce a signal (69).

Increasing evidence demonstrates that IL-1 is a growth factor for AML cells. IL-1beta is not expressed in peripheral-blood cells or bone marrow aspirates from normal subjects, but it can be detected in cells from patients with AML (70, 71). Preisler *et al* found that steady state levels of IL-1beta were expressed, and that a strong inverse relationship between remission duration and IL-1beta expression existed (72). IL-1 can maintain the autocrine synthesis of colony-stimulating factors (CSFs) and thus sustains leukemic growth (71). Culture supernatants of AML cells which contain IL-1 can induce the expression of both the granulocyte macrophage CSF (GM-CSF) and granulocyte CSF (G-CSF) genes in human endothelial cells *in vitro* (73). When incubated with the IL-1Ra, a reduction or disappearance of GM-CSF was observed in 8 of 10 cases, whereas spontaneous IL-1 production was reduced in 4 of 7 cases (71). By Northern hybridization, IL-1beta gene transcripts were shown in 20 of 23 AML cases, whereas IL-1Ra-specific messenger RNA was present in only two of the patients studied (71). Soluble IL-1 receptors (sIL-1R), anti-IL-1beta neutralizing antibodies and IL-1Ra can inhibit blast colony-forming cell replication in a dose-dependent fashion and their inhibitory effect was partially reversed by IL-1beta (74). Those observations implicate IL-1 in AML blast proliferation and suggest the potential benefits of using IL-1-inhibitory molecules in future therapies for AML (74). One approach to reduce the action of IL-1 in myeloid leukemia would therefore be to prevent proteolytic cleavage of the IL-1beta precursor, because the IL-1-specific precursor-converting enzyme is found in large quantity in myeloid leukemia cells (75). Meyers *et al* proved that both the levels of the circulating IL-1 and IL-1Ra were elevated highly in patients with AML/MDS

compared with normal controls, and patients who obtained a complete response tended to have better fine motor control at baseline and lower circulating IL-1 levels (76). Those results suggest that anti-IL-1 therapy may be useful to restrict the growth of the leukemia cells and strengthen the susceptibility to chemotherapy drugs.

4.4. IL-6

IL-6 is produced by a variety of cells including T cells, B cells, fibroblasts, endothelial cells, monocytes, keratinocytes, mesangium cells, and some tumor cells (77, 78). IL-6 signals through a cell-surface type I cytokine receptor complex consisting of the ligand-binding IL-6R chain and the signal-transducing component gp130 (79). As IL-6 interacts with its receptor, it triggers the gp130 and IL-6R proteins to form a complex, thus activating the receptor. These complexes bring together the intracellular regions of gp130 to initiate a signal transduction cascade through certain transcription factors, Janus kinases (JAKs) and Signal Transducers and Activators of Transcription (STATs) (80).

In vitro, IL-6 production was paralleled by IL-1 production in the neoplastic cells from patients with AML. IL-6 production was found to be specific for cells from patients with AML with monocytic differentiation (M4 and M5 patients) (81). Moreover, it synergized with mast cell growth factor or GM-CSF in the stimulation of AML blast colony formation (82). The intracellular signaling pathways for IL-6 are distinct from those of known second messengers and involved protein phosphorylation, notably tyrosine phosphorylation of p160 protein, as an essential step in the immediate early activation of myeloid differentiation gene expression (83). Secreted with IL-6, IL-6 receptor protein was present at the AML cell surface (84). Whereas approximately 40% of AML blasts with autonomous growth have been reported to exhibit abnormalities of retinoblastoma (Rb) protein (transcriptional repressor of the IL-6 promoter) expression (85). In contrast with normal DC development, further advancement of monocyte-dendritic cell colony-forming unit (mono-DC-CFU) and terminal DC maturation from the AML cells ORL47 were dependent on the addition of IL-6 and it provided a new perspective to classify leukemias (86). Levels of the circulating IL-6 were highly elevated in patients with AML/MDS compared with normal controls, and higher IL-6 levels were associated with poorer executive function (76). Wu *et al* detected the concentration of plasma IL-6 of 42 untreated patients with AML and 36 healthy volunteers by ELISA. They also showed that the concentration in untreated patients was higher than controls (15.22 +/- 3.86 versus 1.44 +/- 0.48 pg/ml, $p < 0.01$) (23). Variant alleles of IL-6 (with the G allele in the IL-6 promoter at -174bp) could significantly increase susceptibility to infection with Gram-negative bacteria in children undergoing therapy for AML. This may be a useful standard in evaluating prognosis (87).

4.5. IL-17

IL-17 was originally described and cloned by Rouvier *et al* and termed cytotoxic T lymphocyte-associated antigen-8 (CTLA-8) (88). As a 32kD dimer, IL-17 induces the production of chemokines and antimicrobial peptides by tissue cells, leading to the recruitment of neutrophils into sites of inflammation (89). The JAK/STAT pathway is recognized as an integral and widespread mediator by which cytokine receptors transduce intracellular signals (90). This signaling pathway influences normal cell survival and growth mechanisms and may contribute to oncogenic transformation (91). In human U937 monocytic leukemia cells, IL-17 triggered tyrosine phosphorylation of several members of the JAK and STAT proteins (such as JAK 1, 2 and 3, Tyk 2 and STAT 1, 2, 3 and 4) (92). Evi27, which shows homology to the IL-17 receptor, is up-regulated as a result of retroviral integration in BXH2 murine myeloid leukemia (93).

In clinical patients, Wu *et al* detected the concentration of plasma IL-17 of 42 untreated patients with AML and 36 healthy volunteers by ELISA. They showed that the concentration in untreated patients was higher than controls (18.65 +/- 3.19 versus 10.52 +/- 1.69 pg/ml, $p < 0.05$) (23). Ersvaer *et al* examined levels of IL-17 in culture supernatants when T cells among leukemic and normal PBMC were activated with anti-CD3 plus anti-CD28, considering the different T cell concentrations in the cultures. IL-17 levels were actually higher for untreated patients than for the controls (44). IL-17 released by polyclonal T cells of AML patients with chemotherapy-induced cytopenia was undetectable or at low levels, and it increased significantly after stimulation with anti-CD3+anti-CD28 and anti-CD3+anti-CD28+IL-2 (94). PEP005, a selective small-molecule activator of protein kinase C, can significantly enhance anti-CD3+anti-CD28+IL-2 stimulated IL-17 secretion (94, 95). Wrobel *et al* measured IL-17 levels by ELISA in plasma samples taken from 68 adult patients with AML before chemotherapy was administered; in addition, 20 out of 68 patients were reanalyzed after achieving complete remission (CR) and 10 samples from healthy volunteers were evaluated as the control (96). However, no statistical differences in IL-17 levels between groups of AML patients (at diagnosis and CR) and controls were demonstrated (96). These different findings may result from the investigation of relatively low sample numbers and thus, larger scale case-control studies should be implemented.

4.6. IL-21

The mature IL-21 polypeptide has a predicted molecular weight of 15kD and consists of a 131 amino acid four-helix bundle cytokine domain with highest sequence and structural homology to IL-15 and IL-2 (97). IL-21 has a role in the proliferation and maturation of natural killer (NK) cell populations from bone marrow, in the proliferation of mature B-cell populations co-stimulated with anti-CD40, and in the proliferation of T cells co-stimulated with anti-CD3 (97). IL-21 could induce the apoptosis of resting primary murine B cells through a Bcl-2-interacting mediator of cell death (Bim)-dependent mitochondrial pathway and the induction correlated with a down-regulation in the expression of Bcl-2 and Bcl-xL, two antiapoptotic members of the Bcl-2 family (98). IL-21R consists of an IL-21R specific alpha-chain, which has no

intrinsic signaling ability, and the common gamma-chain, which is also found in the IL-2 receptor complex. IL-21 mediates its activity by binding to IL-21R through the JAK/STAT pathway. After binding of IL-21 to the IL-21Rα/γc complex, JAK1 and JAK3 undergo autophosphorylation and subsequent phosphorylation of STAT1 and STAT3 (99).

Increasing evidence suggests an involvement of IL-21 in hematopoietic malignancies. Follicular lymphoma cells show exceptionally high IL-21R expression and IL-21 decreases Bcl-2 expression but increases Bax expression (100). IL-21 enhances autologous CLL NK cell function against rituximab coated tumor cells, mediates direct apoptotic signaling that correlates with STAT1 signaling and BIM up-regulation, and enhances sensitivity to both fludarabine and rituximab mediated direct apoptosis (101). Brenne *et al* found that IL-21 induced proliferation and inhibited apoptosis in the IL-6-dependent human myeloma cell lines ANBL-6, IH-1 and OH-2. 4 of 9 purified samples of primary myeloma cells showed a significant increase in DNA synthesis on stimulation of the cells by IL-21 (102). In AML cells, Akamatsu *et al* surveyed IL-21R in HL60 (APL cell line), THP1 (acute monocytic leukemia cell line) and K562 (human erythroleukemia cell line) and found that they were IL-21R-negative (100). We detected the IL-21 levels in plasma samples taken from 24 AML patients before chemotherapy was administered, 20 AML patients with CR and 30 health adults, and found no significant differences between groups (data not shown). Demonstration of an effect of IL-21 in AML cell lines and AML patients remains unproven; therefore more research will be needed to address this question.

5. PERSPECTIVE

The Th17 lineage is a recently described branch of the immune system and ample evidence has implicated these cells in the pathogenesis of autoimmune diseases, such as rheumatoid arthritis. Increased evidence proves the facts discussed in this paper that Th17 related cytokines play an important role in the development of AML. It is clear that more than one Th17 related cytokine can be dysregulated in AML. However, the exact and specific biological mechanisms of action of these cytokines in AML are still not clear. Modulation of the Th17 pathway seems to be a new stage in addition to traditional chemotherapy agents to reach the ultimate goal of permanent remission or even to prevent the development of this crippling disease. The identification and classification of AML early in the disease course is becoming increasingly important because early and intensive treatment has been demonstrated to prevent the progress and to improve prognosis of patients. Th17 cytokines may be used to classify AML, thus guide a better and timely treatment. Furthermore, Th17 cytokines may be used as biomarkers to predict the response to chemotherapy and the survival in patients. However, since most experiments are done *in vitro* or only detected the expression of cytokines in AML, more research is needed to determine whether regulating Th17 cell activity or specific combinations of Th17 cytokines will have additional value in animals and patients. Studied comprehensively and systemically, these new helper T cells may lead to the new understanding of AML pathogenesis and treatment.

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Abbreviations: AML: Acute myeloid leukemia, IL: interleukin, IFN-gamma: interferon-gamma, TGF-beta: transforming growth factor-beta, HSCT: hematopoietic stem cell transplantation, GVL: graft-versus-leukemia, GVHD: graft-versus-host disease, SNP: single-nucleotide polymorphism, B-ALL: B-acute lymphoblastic leukemia, APL: acute promyelocytic leukemia, RARα: retinoic acid receptor alpha, PML: promyelocytic leukaemia, ATRA: all-trans retinoid acid, IL-1Ra: IL-1 receptor antagonist, AMKBL: acute megakaryoblastic leukemia, CSF: colony-stimulating factor, GM-CSF: granulocyte macrophage CSF, G-CSF: granulocyte CSF, Rb: retinoblastoma, mono-DC-CFU: monocyte-dendritic cell colony-forming unit, JAK: Janus kinase, STAT: Signal Transducers and Activators of Transcription, CTLA-8: cytotoxic T lymphocyte-associated antigen-8, CR: complete remission, NK: natural killer cell

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Send correspondence to: Chunyan Ji, Department of Hematology, Qilu Hospital, Shandong University, 107 West Wenhua Road, Jinan, 250012, P. R. China, Tel: 86-531-82169051, Fax: 86-531-86115887, E-mail: jichunyan@sdu.edu.cn