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Signal Pathway in Precursor B-Cell Lymphoblastic Leukemia/Lymphoma

Tatsuaki Tsuruyama and Takuya Hiratsuka

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Abstract

Stat5, c-myc, Hipk2, Fiz1, and ZFP521 to lymphomagenesis precursor B-cell lymphoblastic lymphoma/leukemia have been previously identified as a putative gene involved in the induction of B-cell lymphomagenesis. In this review, we summarize the role of ZFP521 in B-cell lymphomagenesis. Zinc finger protein 521 (Zfp521) is a novel identified gene that is responsible for pre-B-lymphoblastic lymphomagenesis through activation of pre-B-cell receptor (pre-BCR)-signaling by upregulation of adaptor genes and related kinases in the signaling downstream. The pre-BCR-signaling molecules, FLT3, CD43, and IL-7 receptor (IL-7R) were positively regulated by these genes. Stimulation of pre-BCR and/or IL-7R signaling caused aberrant upregulation of other oncogene sets such as cyclin genes, thereby inducing the growth of pre-B cells. IL-7R/Janus kinase (JAK)/STAT signaling cascade is one of the key signaling pathways that are activated in precursor B-cell lymphoblastic lymphoma/leukemia. FLT3, CD43, and pre-BCR cascades crosstalk with JAK/STAT cascade. FLT3 and CD43 cascades have the potential to enhance JAK/STAT cascade effect on pre-B cell growth. On the other hand, pre-BCR and interleukin (IL)-7 receptor exerted competitive effects on pre-B-cell growth; thus, precursor B-cell lymphoblastic lymphomagenesis is a consequence through interaction with these cascades.

Keywords: pre-B-cell receptor, Stat/Jak pathway, Zfp521

1. Introduction

1.1. Summary

B-cell lymphoblastic leukemia/lymphoma (B-LBL) is a neoplasm that exhibits immature phenotype of the B-cell lineage with on-going immunoglobulin rearrangement. Understanding the activation of signal pathways in tumor cells provides significant knowledge on tumorigenesis.

Surface markers interleukin-7 receptor (IL-7R), FLT3, CD43, and phenotypic marker pre-B-cell receptor are aberrantly activated in tumor cells. IL-7R is one of the developmental stage markers and is closely associated with immunoglobulin gene rearrangement in mice. In addition, these IL-7R, FLT3, and CD43 signal pathways interact with each other. The signaling molecules, JAK3, Stat5a, Fcγ1, and Hspk2, play pivotal roles in these signaling pathways. In this review, we summarize the activation networks of these pathways from the perspective of the activation of adaptor molecules and immunoglobulin rearrangement.

1.2. Introduction

B-LBL is a neoplasm of B-lymphoid precursors and it is essentially identical to acute lymphocytic leukemia as it involves the bone marrow and peripheral blood [1, 2]. These lymphomas and leukemias are composed of medium-sized blast cells with scant cytoplasm, an oval nucleus, transparent nucleus, condensed chromatin, and often multiple nucleoli. The lymphoma tissues exhibit mitotic figures and are phagocytosed by macrophages after apoptosis—this histology is called “Starry sky” and is well known in Burkitt lymphoma. Distinguishing B-precursor types from T-precursor types is impossible because they share similar cytological features. Immunophenotypes of pre-B LBL resemble the normal immature B-cell lineages, primarily including pre-B cells, because pre-B LBL consists of ongoing immunoglobulin gene (*Ig*) rearrangements of heavy chains (*Igh*) or light chains (*Igl*). This rearrangement depends on the activity of recombination-activating gene 1 (*RAG1*) and *RAG2* under the high expression of the interleukin 7 receptor (IL-7R) [3]. In addition, pre-B receptors consist of lambda5 and Vpreb component, which are surrogate light-chain components at the time of completion of *Igh* rearrangement (Figure 1) [4, 5].

Figure 1. Scheme of B-cell development stage and IL-7R/pre-B-cell receptor (BCR) expression. CLP, common lymphocyte precursor.

2. The characterization of spontaneous pre-B-cell lymphoma in SL/Kh mice

2.1. Experimental mouse model of spontaneous lymphoma

We established an inbred strain of mouse called the spontaneous lymphoma mouse strain (SL/Kh) as a model of murine leukemia virus (MLV) integration-induced B-LBL lymphomagenesis. In the experimental model, transgenic mice carrying chimera genes, such as Emu-myc mice, MT-BCR-ABL

mice, [6, 7], and TEL/AML1 mice rapidly develop pre-B LBL [8–10]. Unlike these models, the SL/Kh mouse develops spontaneously in the absence of artificially introduced gene mutation; however, Zfp521 is the gene that is spontaneously and constitutively mutated by MLV insertion after the birth [11, 12].

These mice share MLV with AKR-strain mice that are susceptible to T lymphoma [13, 14]. SL/Kh mice were found to have multiple copies of the pathogenic endogenous proviral genome that are genetically transmitted through the germ line on chr 7 [12, 15]. A type of MLV expressed from this provirus infects the hematopoietic cells and MLV genome is somatically re-integrated into the host cell genome. Subsequently, B-LBL spontaneously develops with a high frequency of 95% after 6 months of birth. These lymphoma cells are positive for lambda5 and Vpreb, which are a part of the pre-BCR. Myeloid leukemia, mature B-cell lymphoma, and T-cell lymphoma are known to occur in the inbred strain of mouse [16]. Such high occurrence of identical B-lymphoblastic lymphoma/leukemia phenotypes has not been reported in other mice. The initial growth of pre-B cells in SL/Kh was proven to be independent of the provirus integration, but dependent on the bone marrow pre-B1 (*Bomb1*) locus that includes BANK1 and the *enpep* gene that involves a glutamyl aminopeptidase (*BP-1*) (Mm.1193, UniGeneID) [17]. Clinically, the mice present with hepatosplenomegaly in which pre-B LBL invades via the portal tract and replace the splenocytes. In addition, the spinal bone becomes deformed, because of bone structure remodeling. As described later, the identified signal cascade promoting the MLV proviral element gives the clue for understanding of the development of lymphomagenesis through upregulation of signaling pathways and can serve as a model of clinical intervention by administration of anti-tumor drugs because of stable susceptibility for lymphomagenesis.

2.2. Flow cytometry analysis of B-LBL experimental lymphomas

Flow cytometric analysis is the one of the most important methods for analyzing pre-B cells. BP1, B220, IL-7R, CD24, and CD43 are the classical phenotypic markers of pre-B cells as well as lambda5 and Vpreb. These markers were available for Hardy's classification for murine B cell lineage (**Figures 2 and 3**) [18, 19]. These markers are a little different from those that are used for the classification of human B-cell lineages, because B220, BP-1, CD43, and CD24 are included.

2.3. Genetic background of pre-B lymphomagenesis

Bomb1, a quantitative trait locus (QTL), on *Mus musculus* (MMU) chromosome 3 is responsible for pre-B-cell expansion [20, 21] (**Figure 4**). In analysis of the congenic mice carrying SL/Kh alleles of *Bomb1*, polyclonal expansion of pre-B cells is observed. BANK1, an adaptor molecule of pre-BCR, is located near the *Bomb1* locus. We generated a congenic strain, NFS. SL/Kh-*Bomb1* mice, with the replacement of this locus with SL/Kh *Bomb1*, without pre-B-induced provirus. The congenic mice showed pre-B-cell expansion, but pre-B lymphomagenesis were not observed. Therefore, the pre-B-cell lymphomagenesis is probably induced by multiple genes, including MLV integration into the proto-oncogenes. Notably, this locus is

Figure 2. Surface phenotypic markers and Hardy’s classification. BP-1 and IgM are notable markers. Fr., fraction.

Figure 3. Ig recombination and B-cell development stage. VpreB and λ5 are components of surrogate light chain in the pre-BCR. Igα and β are adaptor molecules that are identical to CD79a and CD79b. Pre-BCR is tentatively formed in the stage of large pre-B.

also susceptible to high-frequency microsatellite instability (MSI) in the pre-B LBL in mouse chromosome 3 including the *Bomb1* [17] (**Figure 5**). MSI is confirmed at ≥2 markers in DNA derived from tumor tissues in 93.7% of SL/Kh mice. To date, there have been only few systematic analyses of MSI and our data are significant in the hematopoietic tumors. Irregular deletion and insertion are observed within *Bomb1* in the course of lymphoma tissue with a high frequency.

Figure 4. *Bomb1* locus and microsatellite markers on chromosome 3.

Figure 5. Microsatellite instability in the genome of lymphoma cells in the lane of healthy lymph node tissue [17]. Dinucleotide CT is deleted in the lymphoma genomes.

3. Upregulation of proto-oncogenes in pre-B lymphomas

Retroviral tagging, such as MLV insertion, is considered as a useful method for the identification of proto-oncogenes. RTCGD (Retrovirus and Transposon-tagged Cancer Gene Database, <http://variation.osu.edu/rtcgd/>) is one of the established registration systems of MLV integration, and many genes were identified as the common integration site (CIS) [16].

There many identified genes that are involved in the development of hematopoietic tumors. We summarize the signaling pathways that are associated with the target genes as described in the subsequent text.

3.1. IL-7R-signaling pathway and Stat5a

In both humans and mice, the IL-7R (also known as CD127) is expressed by early B-cell progenitors, and signaling via IL-7R α activates signal transducer and activator of transcription 5 (STAT5) and drives pro-B-cell proliferation, while inhibiting Igk recombination [22, 23].

Stat5a gene is one of the target genes of MLV integration in B-cell tumors (Table 1). The encoded STAT5 protein is a member of the signal inducer and activator of transcription (STAT) family and includes STAT5A and STAT5B subtypes. They are encoded by separate genes—the proteins are 90% identical at the amino acid level. These encoding genes are both targets of MLV. STAT5 proteins are activated by Janus kinases (JAKs) associated with transmembrane receptors such as interleukin receptor. Because, deletion of *Stat5a* and *Stat5b* arrests B-cell development at the pre–pro-B cell stage [24].

Binding of the cytokine ligands to these receptors on the outside of the cell activates the JAK3 [25]. Subsequently, the activated kinases add a phosphate group to tyrosine residues (Y449) on the IL-7R α chain of the receptor. STAT5 then binds to these phosphorylated tyrosines. STAT5 is subsequently phosphorylated by the JAK3. The phosphorylated STAT5 forms either homodimer. Phosphorylated STAT proteins have the potential to form a dimer that can translocate into the nucleus and upregulate transcriptional activity by binding to the gamma interferon activation site palindromic (GAS) element in the promoters of the target genes. The targets encode *c-Myc*, *Pim-1* [26], *Bcl-xL*, and *Cyclin D1* [27], which promote proliferation and apoptosis in hematopoietic cells [28]. STAT5A, in particular, contributes to IL-7–induced B-cell precursor expansion. IL-7R is highly expressed in pre–B cells during *Igh* recombination, and therefore Stat5a has been one of the responsible molecules for *Igh* recombination [29]. Attenuation of IL-7R signaling in both human and mouse pre–B cells is associated with the expression of *RAG1* and *RAG2*.

Gene	Mean interval (bp)	Number of integration sites
<i>Stat5a</i>	26.2	92
<i>c-myc</i>	55.5	16
<i>N-myc</i>	6	8
<i>Fiz1</i>	89.1	8
<i>Hipk2</i>	101.1	7
<i>Stat5b</i>	121.7	3
<i>MHC class heavy chain</i>	100	2

Table 1. Common integration site.

A comparison of the phenotype of SL/Kh lymphomas showed that when the *Stat5a* was highly expressed, clones completed *Igh* D_HJ_H recombination but not *Igh* variable segment— D_H recombination; on the other hand, when the *Stat5a* was relatively less expressed in clones, both D_HJ_H and *Igh* variable segment, D_H recombination, are completed. On the other hand, *Stat5a*-high clones highly express $\lambda 5$ but low for *Vpreb*; by contrast, *Stat5a*-low clones were constitutively high for both $\lambda 5$ and *Vpreb*. In summary, the *Stat5a*-high lymphoma clones are more immature than other lymphomas. *Stat5a* may contribute to the lymphomagenesis at the immature stage of B cells [29].

3.2. *Zfp521* and pre-BCR pathway

The *Zfp521* gene was identified at the MLV integration site in the genomes of B-cell lymphomas in the AKXD mouse strain [30, 31]. This gene is also the most frequent integration site as well in the genome of pre-B-cell lymphoma in SL/Kh mice (**Figure 6**) and is related to immature B lymphomagenesis [11, 32]. *Zfp521* expression contributes to neural crest formation and the development of adipose cells, chondrocytes [33, 34], bone [34–36], and neural crest [35]. Recently, we reported that ZFP521 regulates and activates pre-B-cell receptor signal pathways, and it modulates the IL-7-signaling pathway [11].

The pre-BCR is expressed on large pre-B cells in which *Igh* recombination is completed. In the initiation of Ig κ or Ig λ gene rearrangement, signals of the IL-7 receptor gradually attenuate in pre-B cells, and B-cell maturation proceeds. Although both the IL-7R and the pre-BCR are required for murine B-cell lymphopoiesis, the orchestration of signal pathways has remained controversial. The responsiveness to IL-7 and stimulation through pre-BCR controls the development of pre-B cells into mature B cells [22, 23]. During the development of pro-B cells into pre-B cells, IL-7 signaling is the major mediator. The mature BCR replaces the pre-BCR. *Zfp521* is expressed from professional pre-B cell of Fraction A (Fr. A) to Fr. B-C according to Hardy's classification. In this pre-B stage, *Zfp521* may interact with adaptor molecules of Cd79a/b such as BANK1, Blnk, and Btk. *Zfp521* may play as a transcriptional factor, because of a stimulation of this gene expression in a cell line, and the signal was located in the nucleus [30]. However, the binding motif on DNA is not clearly identified. The IL-7 receptor pathway interfered with Vpreb stimulation through the upregulation of BANK1 near or on *Bomb1* by ZFP521. BANK1 is disrupted by IL-7R signaling and interacts with phospholipase gamma 2 [37]. In fact, BANK1-PLC γ 2 binding is enhanced by B-lymphocyte kinase (BLK) [37]. Therefore, complicated per-BCR adaptors are hypothesized (**Figure 7**).

Cyclin D3 and Cyclin D2 are upregulated by overexpression of the ZFP521 gene. Pre-BCR was shown to mediate Ras-MEK-extracellular signal-regulated kinase (ERK)-signaling pathway activation and light-chain recombination by silencing Cyclin D3 [38].

In humans, the fusion of the Pax5, which is essential for pre-B-cell development gene, exon 7 to ZFP521 exon 4, has been observed in pre-B-cell acute lymphocytic leukemia by genome-wide analysis of genetic alterations [39]. Dysregulation of ZFP521 gene leads to pre-B-cell lymphomagenesis through the activation of pre-B-cell-specific molecular-signaling pathways [11]. Therefore, ZFP521 could be considered as a target for molecular-targeted therapy.

Figure 6. (a) Schematic representation of MLV integration in *Zfp521* in SL/Kh mice. By the age of 2–3 months, the MLV host cell has grown in BM, and the endogenous MLV integrates into the genome of the host lymphocytes. The host cells clonally grow with higher expression of the *Zfp521* gene. The tandem box in the upper scheme represents long terminal repeat (LTR) of the provirus.

3.3. FLT3 signaling and LBL development via Fiz1

(a) Fms like tyrosine kinase 3 (FLT3) belongs to the immunoglobulin superfamily CD135 also known as fetal liver kinase-2 (Flk2). This protein is the receptor for the cytokine Flt3 ligand (FLT3L). FLT3 is a type III receptor tyrosine kinase with five immunoglobulin-like motifs in the extracellular region. In the intracellular region, a tyrosine kinase region (TK) and a C-terminal region composed of a juxtamembrane region (JM) and a kinase insert are contained. This protein is constitutively expressed in the hematopoietic stem and progenitor cells. On the other hand, the ligands that bind to the FLT3 receptor (FL) are produced in bone marrow stromal cells. FL directly stimulates hematopoietic stem cells or together with other cytokines and plays an important role in its survival, proliferation, and differentiation. FLT3 is also one of the critical developmental factors for B- and T-lymphocyte development [40].

Figure 7. Pre-BCR pathway and Zfp521.

In the absence of FL, FLT3 remains in the inactivated monomeric form. When FLT3 binds to FL, a ternary complex is formed in which two FLT3 molecules are bridged by one (homodimeric) FLT3L. Ligand binding promotes conformational changes in FLT3 for dimerization, phosphorylation, and association with adaptor proteins such as Fcγ1. The complex formation brings the intracellular domains close to each other, promoting initial phosphorylation of the kinase domain. Activated dimeric FLT3 transduces signals to the downstream effectors. In the pathogenesis analysis, FLT3 is expressed on the cell surface of most AML and ALL cells through proliferation activation and apoptosis suppression, which are caused by the stimulation of FL [41–43].

Internal tandem duplications (ITDs) occur in exon 14 or 15 of the JM, which are located directly between the transmembrane domain (TM) and tyrosine kinase region TK1 [44]. Insertions, deletions, and point mutations are frequently found in exon 20 of another tyrosine kinase region TK2. The functional kinase region is kept, and only the JM region is elongated. ITDs probably promote ligand-independent dimerization and activation of FLT3 by changing the conformation of the expressed receptor [44, 45]. In addition, another mutation was identified within the kinase activation loop, a part of the functional core. The conformational changes associated with ITDs might change the structure of the receptor such that unique adaptor proteins such as Fcγ1 can now dock.

(b) Fcγ1: This gene encodes the zinc finger protein, which interacts with a receptor tyrosine kinase involved in the regulation of hematopoietic and lymphoid cells. This gene product also interacts with a transcription factor that regulates the expression of rod-specific genes in the retina. Fcγ1 binds to the catalytic domain of Flt3 but not to c-Kit, Fms, or platelet-derived

growth factor receptor [46, 47]. In a part of B-LBL in SL/Kh, Fiz1 is upregulated by MLV genome insertion and interaction with IL-7R pathway is observed. FLT3 stimulation enhances IL-7R signaling cascade by promotion of Stat5a phosphorylation [48]. Therefore, FLT3 and IL-7R signal pathways interact with each other in the development of B-LBL/ALL.

3.4. CD43 and Hipk2 in the development of B-LBL/ALL

HIPK2 is a conserved serine/threonine nuclear kinase that interacts with homeodomain transcription factors. This protein interacts with the cytoplasmic domain of CD43, which is expressed on immature pro- to pre-B cells, Fr. A-C in Hardy classification. In this immature stage, IL-7R is highly expressed and the CD43 pathway may interact with IL-7R pathway recruiting STAT5A. Hipk2 promotes Wnt signaling by stabilizing beta-catenin [49]. Hipk2 interacts with lymphoid-enhancing factor 1, which acts as a transcriptional factor, promoting c-Myc and cyclin D1 expression [50]. CD43 is an E-selectin counter-receptor highly expressed in human pre-B-cell leukemia NALL-1 cell line [51]. In our study, CD43 cross-linking resulted in an increase in STAT5A phosphorylation, when IL-7 was supplied. CD43 signaling may enhance the IL-7R signal pathway [48, 52].

4. Signaling pathway network responsible for pre-B lymphomagenesis

Probably, multiple genes are related to the activation of IL-7R-signaling pathway. Hipk2 and Fiz 1 are candidates of interaction with IL-7R pathway as well as Stat5. Considering the activation of FLT3 pathway in AML, B-LBL may share the activation pathway with AML [10]. We propose a scheme of interactions among the IL-7-, CD43-, and FLT3-signaling pathways (**Figure 8**) [48]. Thus, we hypothesize that these three pathways form an interacting network

Figure 8. Signaling pathway network in association with IL-7R.

and affect B-LBL development. By contrast, pre-BCR pathway is activated by Zfp521 through the upregulation of BLNK [53, 54], BANK1 [37], Btk, and other pre-BCR-related molecules. Pre-BCR pathway has been considered to contribute to pre-B-cell development rather than to proliferation. Therefore, although stimulation of pre-BCR promotes pre-B cell proliferation, Zfp521 may not directly contribute to lymphomagenesis, but contribute to the stabilization of phenotype of B-LBL. Or interaction with IL-7R and pre-BCR may promote aberrant proliferation or development. Further research is required for precise understanding of the interaction between these two pathways in B-cell development.

Author details

Tatsuaki Tsuruyama* and Takuya Hiratsuka

*Address all correspondence to: tsuruyam@kuhp.kyoto-u.ac.jp

Department of Pathology, Graduate School of Medicine, Kyoto University, Kyoto, Kyoto Prefecture, Japan

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