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Human and mouse early B cell development: So similar but so different

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ABSTRACT

Early B cell development in the bone marrow ensures the replenishment of the peripheral B cell pool. Immature B cells continuously develop from hematopoietic stem cells, in a process guided by an intricate network of transcription factors as well as chemokine and cytokine signals. Humans and mice possess somewhat similar regulatory mechanisms of B lymphopoiesis. The continuous discovery of monogenetic defects that impact early B cell development in humans substantiates the similarities and differences with B cell development in mice. These differences become relevant when targeted therapeutic approaches are used in patients; therefore, predicting potential immunological adverse events is crucial. In this review, we have provided a phenotypical classification of human and murine early progenitors and B cell stages, based on surface and intracellular protein expression. Further, we have critically compared the role of key transcription factors (Ikaros, E2A, EBF1, PAX5, and Aiolos) and chemo- or cytokine signals (FLT3, c-kit, IL-7R, and CXCR4) during homeostatic and aberrant B lymphopoiesis in both humans and mice.

1. Introduction

The peripheral B cell pool is maintained by continuous generation of immature B cells in the bone marrow (BM). Immature B cells develop from hematopoietic stem cells (HSCs). The activation of lymphoid genes results in specification into the lymphoid lineage, whereas subsequent suppression of alternative lineages ensures B cell fate commitment. Differences in multipotency, immunoglobulin heavy (IgH) and light chain (IgL) rearrangement, stage-specific transcription factors (TFs), and surface/intracellular markers lead to distinct developmental stages.

HSC maintenance and multilineage differentiation are controlled by signals provided by HSC niche. Specifically, the maintenance of the HSC pool depends on the expression of CXCL12 and stem cell factor (SCF) produced by bone marrow stromal cells [1,2]. HSCs give rise to a heterogenous population of multipotent progenitors (MPPs), which have the potential to reconstitute the lymphoid compartment [3]. The expression of EBF1 in MPPs favors lymphoid-primed multipotent progenitor (LMPP) fate by downregulating C/EBPα (Fig. 1). Alternatively, high C/EBPα and PU.1 levels promote common myeloid progenitor (CMP) differentiation [4,5]. In CMPs, PU.1 or GATA1 expression promote the development of granulocyte-monocyte progenitors (GMPs) or megakaryocyte-erythroid progenitors (MEPs), respectively. Fms-like tyrosine kinase 3 (FLT3) signaling promotes LMPP maturation into common lymphoid progenitors (CLPs) by upregulating lymphoid-specific genes (*E2a, Il7ra*, and *Ebf1*) [6]. CLPs give rise to B, T, innate lymphoid (ILCs), and NK cells. B cell commitment is defined by the expression of paired box protein 5 (PAX5) that represses alternative lineage genes, such as *Notch1* (T cells) or *Csfr1* (monocytes/macrophages), and concomitantly upregulates B cell-specific genes (*Cd19, Igll5*, and *Cd79a*) [7–9]. E2A and EBF1 in pro-B cells promote the expression of Recombination Activating Gene (RAG) proteins [10,11] and the initiation of the IgH DJ gene recombination [12]. Terminal deoxynucleotidyl transferase (TdT) enhances the diversity of the Ig repertoire by randomly adding nucleotides to DNA single strands. Cytoplasmic IgH expression characterizes the pre-BII large cell stage, when the IgH is paired with the surrogate IgL chain (SLC), which is

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composed of lambda 5 (λ5) and VpreB, to form the pre-B cell receptor (pre-BCR) [13]. Pre-BCR and IL-7 signaling induce several rounds of proliferation, leading to clonal expansion of pre-BII large cells that successfully recombine IgH. Pre-BII large cells exit the cell cycle, progress to the pre-BII small stage, and rearrange the IgL VJ genes. Ultimately, heavy and light chains are assembled into IgM/BCR and expressed on the surface of immature B cells. Central tolerance prevents the escape of self-reactive cells from the BM. The process involves engagement and signaling of the BCR [14] and depends on levels of PI3K activation [15]. Autoreactive B cells may undergo secondary IgL rearrangement (receptor editing). The remaining autoreactive cells either undergo apoptosis (clonal deletion), or become anergic with low BCR expression and signaling [16,17]. However, the regulatory processes are leaky and more than 50% of antibodies in the immature compartment are self-reactive or polyreactive [18].

Primary immunodeficiencies with defined genetic defects, targeted B-cell therapies, B-cell reconstitution after HSC transplantation, or B-cell depletion allow for the study of mechanisms and requirements for human B lymphopoiesis and highlight the differences between mouse and human B cell development. For example, B cell reconstitution requires approximately 6–12 weeks after B cell depletion in mice [19], however the same process takes 6–12 months in humans [20,21]. Furthermore, murine B lymphopoiesis requires IL-7 signaling, whereas the human counterpart is dependent more strongly on pre-BCR signaling rather than IL-7 signaling [22].

Pre-BCR signaling is an essential checkpoint during the transition from large to small pre-BII cell stage via regulation of allelic exclusion, positive/negative selection, and developmental progression, reviewed in [23]. Previous studies have reported the activation of the pre-BCR in a ligand-dependent or ligand-independent manner, whereby the contribution of each is not fully understood. Ligand-dependent pre-BCR activation is mediated by λ5 that binds to galectin-1 and heparane sulfate expressed by murine stromal cells [24–26]. The identification of galectin-1^{+} IL-7^{-} stromal cells supports existence of a pre-B niche, which favors the ligation of the pre-BCR [27]. The mechanism of ligand-independent (also known as autonomous) pre-BCR signaling was proposed after pre-BCR^{+} B cells were observed to proliferate in the absence of stromal cells in a culture [28]. Hereby, multiple pre-BCRs auto-aggregate using positively charged arginine residues located in the λ5, which are not required for galectin-1 binding but support the interactions between pre-BCR and heparane sulfate [24,29]. Therefore, the complete deletion of λ5 in mice results in more severe phenotype than the exchange of positively charged amino acids in the N-terminal of non-Ig-like tail of λ5 [29]. Recently, it has been proposed that ligand-dependent and -independent signaling can act synergistically by promoting extensive activation or compensating for each other if one is insufficient (such as poor ligand-independent signaling owing to low pre-BCR expression) [30].

The overall need for pre-BCR signaling during B lymphopoiesis varies between mice and humans, as discussed in [31] and [32]. Mutations in genes coding for signaling components of the pre-BCR signaling pathway result in agammaglobulinemia and B lymphopenia. X-linked agammaglobulinemia (XLA) is caused by mutations in the Bruton's tyrosine kinase (BTK). Human *BTK* mutations severely impair transition from pre-BI to cytoplasmic IgM^{+} (cyIgM^{+}) pre-BII cells and subsequently cause lymphopenia (<1% peripheral CD19^{+} B cells) [33]. In contrast, mutations in murine *Btk* result in a less severe phenotype with reduced peripheral B cells (50% of control) and normal frequencies and absolute numbers of BM B cell populations [34]. Mutations in the murine pre-BCR components (Igμ, VpreB, λ5, Igα, and Igβ) only partly resemble the human phenotype [32]. For instance, patients with mutations in the Igμ chain present with recurrent infections [35], extremely low peripheral B (<0.01% of peripheral cells), and BM cyIgM^{+}cells [36], which resembles homozygous Igμ-mutated mice showing a strong decrease in IgM^{+} immature B cells in the BM and the periphery [37]. A similar phenotype is observed in patients with Igα, Igβ, and λ5 mutations [38–40]. Conversely, murine deletion of the SLC (VpreB1$^{-/-}$VpreB2$^{-/-}$λ5$^{-/-}$) results in a decreased yet present development of immature (IgM^{+}CD19^{+}) and mature B cells (IgM^{+}CD19^{+}IgD$^{+/-}$) in the BM and spleen, respectively. The molecular mechanisms responsible for the distinct requirements for pre-BCR signaling in mice and humans remain to be elucidated. However, the compensatory effect of other Tec kinases possibly explains the relatively mild phenotype observed in BTK-mutant mice [41]. Interestingly, mutations in the zinc transporter ZIP7 result in diminished concentration of cytoplasmic free zinc, increased phosphatase activity, decreased phosphorylation of signaling molecules downstream of the pre-BCR, and reduced B cell numbers in mice. In humans, such mutations result in agammaglobulinemia [42]. Altogether, these data support the hypothesis that global impairment of pre-BCR signaling can also impair murine B cell development; however, it has more severe consequences in human B lymphopoiesis.

This review aims to highlight the similarities and differences in the early B cell development in mice and humans. Specifically, it focuses on the distinct phenotypical classification of early B cell subpopulations and the impact of central transcriptional and signaling networks in both species.

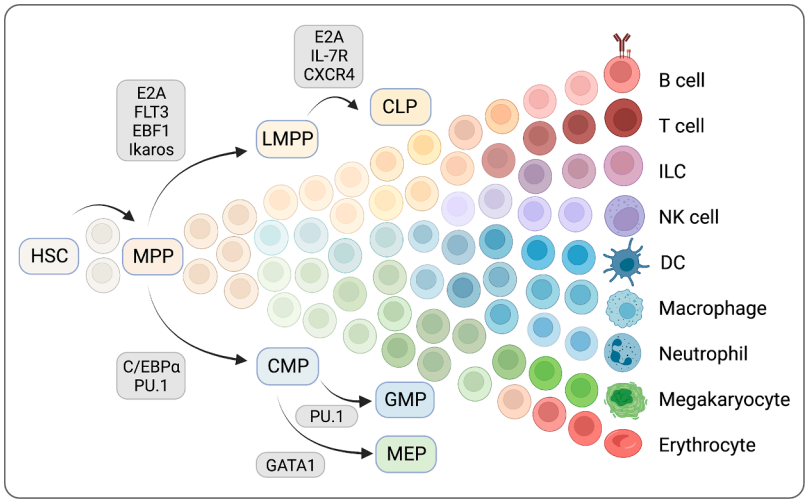

Fig. 1. Hematopoiesis is a continuous process of priming and specification into respective cell lineages. Hematopoietic stem cells (HSCs) give rise to multipotent progenitors (MPPs). Development of common myeloid progenitors (CMPs) requires high C/EBPα and PU.1 expression. CMPs develop into granulocyte-monocyte progenitors (GMPs) by high PU.1 expression and megakaryocyte-erythroid progenitors (MEP) by GATA1 expression. CMPs are progenitors of monocytes, dendritic cells (DCs) and neutrophils, while GMPs develop into megakaryocytes and erythrocytes. E2A, FLT3, EBF1, Ikaros guide MPPs towards lymphoid-primed multipotent progenitors (LMPPs). LMPPs develop through synergistic action of E2A, IL-7R and CXCR4 into common lymphoid progenitors (CLPs). CLPs give rise to T, NK, B and innate lymphoid cells (ILCs). Created with BioRender.com.

2. Definition of murine and human early B cell stages

The stages in B lymphopoiesis are defined by distinct gene signatures [43], nevertheless, flow cytometry remains the most common method to identify early B cells. In the early 1990's, Hardy et al. divided murine B lymphopoiesis into fractions, namely "Hardy's fractions", based on the expression of surface markers such as CD220, CD43, BP-1 and CD24 (Fig. 2) [44,45]. This classification is still in use [46,47].

Most of the studies on human B lymphopoiesis were conducted on BM samples [48,49] *ex vivo* and cultures of cord blood (CB)- or BM-derived $CD34^+$ progenitors [50,51] in vitro ([193]). As shown in Fig. 2, we propose key markers to define seven major subpopulations beginning from the CLP stage. The key markers include CD10, CD38, cytoplasmic CD79a (cyCD79a; Igα), CD19, cyIgM, cyCD179a (VpreB), and surface IgM (sIgM). Exclusion markers, such as CD33 for myeloid cells, facilitate flow cytometric analysis of early B cells. Evidently, distinct populations are defined by different markers in humans and mouse. This is mainly because key markers exhibit a different expression pattern in the two species. For example, CD34 expression identifies human HSCs and hematopoietic progenitors, whereas murine HSCs are enriched in the $CD34^{low/-}$ compartment [52]. CD10 marks human but not murine CLPs and developing B cells in the BM [53], whereas the expression of isoforms of CD45 differ between murine (CD45R/B220) and human (CD45RA) B cell development [54]. In addition, early B cells isolated from CB, BM or fetal liver may show differences in expression of selected markers. For example, the phenotype of early B cell progenitors appears to be different in human fetal and adult BM, especially with regard to the expression of CD10 in pre-pro-B cells (Fig. 2) [55].

The technological advancements in the field of multidimensional flow cytometry and mass cytometry (Cytometry by Time of Flight [CyTOF]) have improved the possibility of defining populations. Nevertheless, in some studies, as little as two markers (VpreB/IgM and CD22/CD45) are used to define up to eight subpopulations [56,57], thereby complicating comparisons among human studies. A further level of complexity is that the unequivocal assignment of marker expressions to specific stages is missing. For example, CD19 expression is attributed to pro-B or to pre-BI cell stage [58,59], underlying the need for harmonization in the definition of the developmental stages to improve comparability among studies.

3. Regulatory transcriptional network during early B cell development

The timely and coordinated expression of TFs, such as Ikaros, E2A, EBF1, PAX-5, and Aiolos (Fig. 3) ensures functional development and prevents hematopoietic malignancies. In mice, TF function is often studied using genetic modifications, such as overexpression/knock-out/-down/-in. In contrast, human studies rely on patients with

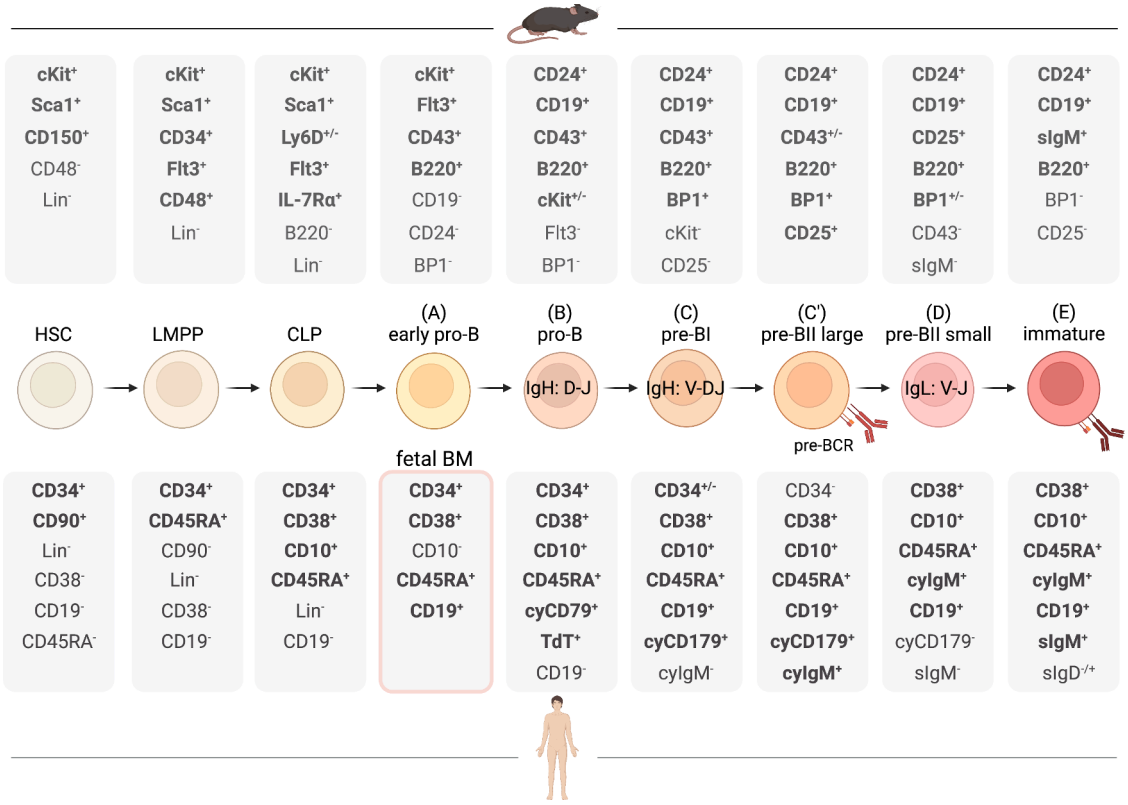

Fig. 2. Markers defining murine and human B cell precursors stages. Bold font indicates the expression of the respective marker in the specific population. Early pro-B cells are found in fetal but not in adult human B lymphopoiesis. HSC: hematopoietic stem cell; LMPP: lymphoid-primed multipotent progenitor; CLP: common lymphoid progenitors; Murine Hardy fractions (Frac. A-D) are indicated in parenthesis. Murine classification: HSC (Lin^-, c-kit^+, Sca-1^+, $CD150^+$, $CD48^-$); LMPP (Lin^-, c-kit^+, Sca-1^+, $CD48^+$, $Flt3^+$, $CD34^+$); CLP (c-kit^+, $Sca1^+$, $Flt3^+$, IL-$7R\alpha^+$, $Ly6D^{+/-}$, $B220^-$, $CD43^+$); Frac. A/early pro-B (c-kit^+, $Flt3^+$, $B220^+$, $CD43^+$, $CD19^-$, $CD24^-$, $BP1^-$); Frac. B/pro-B cells (c-$kit^{+/-}$, $Flt3^-$, $B220^+$, $CD43^+$, $CD19^+$, $CD24^+$, $BP1^-$); Frac. C/pre-BI cells (c-kit^-, $B220^+$, $CD43^+$, $CD19^+$, $CD24^+$, $BP1^+$, $CD25^-$); Frac. C'/pre-BII large cells ($B220^+$, $CD43^{+/-}$, $CD19^+$, $CD24^+$, $BP1^+$, $CD25^+$); Frac. D/pre-BII small cells ($B220^+$, $CD43^-$, $CD19^+$, $CD24^+$, $BP1^{+/-}$, $CD25^+$, surface IgM^-); Frac. E/immature B cells ($B220^+$, $CD19^+$, $CD24^+$, $BP1^-$, $CD25^-$, $sIgM^+$). Human classification: HSC ($CD34^+$, Lin^-, $CD38^-$, $CD90^+$, $CD45RA^-$) [191,192]; LMPP ($CD34^+$, Lin^-, $CD38^-$, $CD90^-$, $CD45RA^+$, $CD10^-$), CLP ($CD34^+$, Lin^-, $CD38^+$, $CD45RA^+$, $CD10^+$), early pro-B cells ($CD34^+$, $CD38^+$, $CD45RA^+$, $CD10^-$, $CD19^+$); pro-B cells ($CD34^+$, $CD38^+$, $CD45RA^+$, $CD10^+$, $CD19^-$, cytosolic $CD79a^+$, TdT^+); pre-BI cells ($CD34^{+/-}$, $CD38^+$, $CD45RA^+$, $CD10^+$, $CD19^+$, cyCD79a$^+$, $TdT^{+/-}$, cyCD179a$^+$, cyIgM$^-$); pre-BII large cells ($CD34^-$, $CD38^+$, $CD45RA^+$, $CD10^+$, $CD19^+$, cyCD79a$^+$, TdT^-, cyCD179a$^+$, cyIgM$^+$); pre-BII small cells ($CD38^+$, $CD45RA^+$, $CD10^+$, $CD19^+$, cyCD79a$^+$, cyCD179a$^{+/-}$, cyIgM$^+$, $sIgM^-$); immature B cells ($CD38^+$, $CD45RA^+$, $CD10^+$, $CD19^+$, cyCD79a$^+$, cyCD179a$^-$, cyIgM$^+$, $sIgM^+$, $IgD^{-/+}$). Created with BioRender.com.

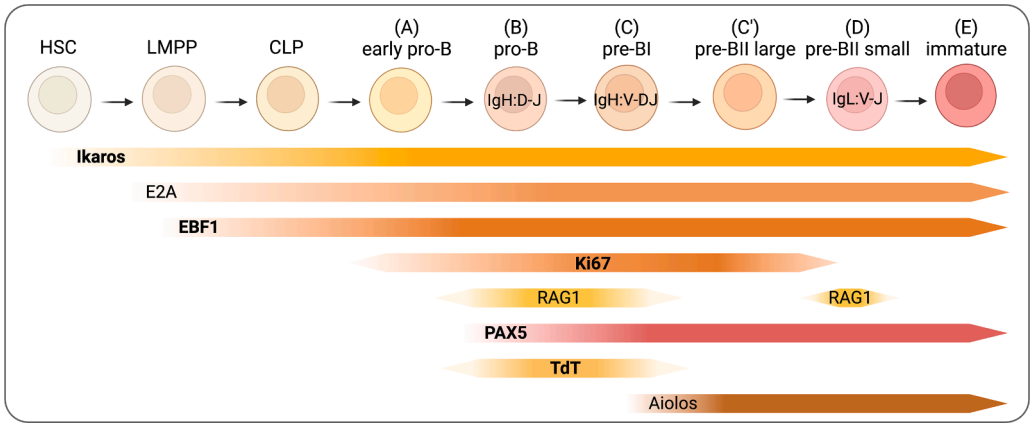

Fig. 3. Timely and coordinated expression of transcription factors (Ikaros, E2A, EBF1, PAX5, Aiolos) and intracellular proteins (Ki67, RAG1, TdT) in B lymphopoiesis. Bold font indicates marker expression that was also reported in humans (EBF1, PAX5: [193]; Ikaros: [61]; Ki67: [51]; TdT: [49]). Created with BioRender.com.

disease-causing genetic mutations or *in vivo/in vitro* studies. Here, we have reviewed the function of the above-mentioned TFs in murine and human B lymphopoiesis and their clinical relevance.

3.1. Ikaros

Ikaros (encoded by *IKZF1*) is expressed throughout B lymphopoiesis in the BM, beginning from the early progenitor stage in both mice and humans [60,61]. Ikaros is a member of the Ikaros protein family (Ikaros, Aiolos, Helios, Pegasus, and Eos) that contain zinc-finger domains at their N-terminus enabling DNA-binding and at the C-terminus enabling homodimerization and heterodimerization with other members of the family [62]. In murine B lymphopoiesis, Ikaros promotes lymphoid specification by inducing lymphoid-specific genes, such as *Flt3, Dntt, Il7r,* and *Rag1* [63]. A defect in Ikaros shows a drastic effect in B lymphopoiesis in mice — Ikaros$^{-/-}$ mice exhibit a complete lack of fetal and adult B cells [64], a conditional knock-out of Ikaros from the pro-B cell stage results in the blocking of B cell development at the pro- to pre-B cell transition (Table 1) [65]. B cells (also T and NK cells) are absent in homozygous carriers of mutations in the dimerization domain [66]. In humans, more than 30 variants in more than 100 individuals have been described. The impact on B lymphopoiesis ranges from a reduction in CLP development, near absence of B cells, and almost complete hypogammaglobulinemia for autosomal dominant heterozygous *IKZF1* mutation in the DNA binding domain [56,63], to extremely low B cell numbers in heterozygous mutations affecting the dimerization domain leading to haploinsufficiency. Moreover, heterozygous mutations affecting the DNA binding domain cause haploinsufficiency resulting in reduced B cell numbers and a progressive loss of B cells and Ig levels, reviewed in [67]. Notably, human *IKZF1* mutations also result in more severe phenotypes, such as combined immunodeficiency that is partly ameliorated by HSC transplantation [68]. However, direct comparison between murine and human Ikaros mutations remains difficult. Murine *IKZF1* mutations are often presented as homozygous exon deletions exhibiting severe phenotypes; whereas in humans, majority of Ikaros mutations are found as heterozygous point mutations [67]. Additionally, in mice, other Ikaros family members were shown to compensate for Ikaros deficiency [69]. Whether this can also occur in humans has not been studied. In fact, Helios may compensate for complete Ikaros loss as it is expressed in early progenitors and binds to similar DNA-sequences as those of Ikaros [70,71]. To date, Ikaros has been identified as a key protein during murine and human B lymphopoiesis, mutation or overexpression of which impairs lymphoid and/or early B cell development.

3.2. Ikaros and Aiolos as treatment targets

Ikaros acts as a tumor suppressor gene during the transition from large to small pre-BII cell stage, as its aberrant expression causes high-risk T- and B acute lymphoblastic leukemia (T- and B-ALL) in mice and humans [72–74]. In contrast, increased expression of Ikaros and Aiolos is observed in multiple myeloma (MM) and systemic lupus erythematosus (SLE) [75,76]. Immunomodulatory imide drugs (IMiDs) promote ubiquitination and subsequent degradation of Ikaros and Aiolos in the proteasome and are therefore used in the treatment of MM and investigated in the context of SLE. Treatment with IMiDs results in cell cycle exit and cell death of MM cells [76,77]. IMiD treatment in healthy controls rapidly reduces peripheral B cell numbers [78]. The effect of Ikaros and Aiolos degradation mediated by IMiDs on peripheral B cells versus early B cells remains to be elucidated. In summary, the role of Ikaros in regulating leukemogenesis was demonstrated in both mice and humans.

3.3. E2A/EBF1

E2A proteins, namely E12 and E47 (encoded by *Tcf3*), as well as EBF1 (encoded by *Ebf1*) are essential regulators of early B cell development, which establish permissive chromatin structure and directly activate lymphoid and B-specific genes [10,79]. In mice, E2A is expressed prior to EBF1 and regulates the quiescence of HSCs by promoting the expression of the G_1 checkpoint regulator p21. Mutation of p21 induces HSC expansion [80,81]. Later, E2A is required for the murine development of LMPPs in a dose-dependent manner because its homozygous mutation strongly reduces the number of LMPPs, whereas heterozygous mutation exhibits intermediate phenotype [82,83]. At the CLP stage, E2A induces the expression of *Foxo1, Il7r, Dntt*, and *Ebf1*, thereby promoting the B cell fate [84,85]. E2A has been shown to activate *Rag1* expression by positively regulating the enhancer/promoter regions and the chromatin accessibility of the *Rag1* locus [10]. Further, E2A induces and maintains the expression of PAX5 in murine pro-B cells and promotes the open chromatin structure of the *Igk* genes in both murine pre-B cell line and germinal center B cells [86–88]. In humans, autosomal dominant heterozygous mutations in *TCF3* (coding for E2A) have been reported (Table 1) [89–91]. A described mutation, localized in the part of gene that codes for the E47 subunit, impairs DNA binding. These patients present with agammaglobulinemia and markedly reduced but detectable peripheral B cells that have an unusual phenotype — they lack functional Ig rearrangement and surface BCR but demonstrate increased CD19 levels and express CD20, CD22, and CD38 [90]. Interestingly, homozygous missense mutations in E47 result in low B cell numbers and hypogammaglobulinemia, which is a milder

Table 1
Summary of murine and human mutations in key transcription factors and their respective phenotype.

Target	Phenotype mouse	Clinical phenotype	Ref.
Ikaros	*Ikzf1*$^{DN/DN}$ (Δex4–5, KO of DNA-binding domains 1–3): no B, T, NK cells, increased postnatal death *Ikzf1*$^{DN/+}$: normal lymphopoiesis, predisposition for thymic derived leukemia *Ikzf1*$^{-/-}$ (Δex8, absent protein expression): absent lymphocyte progenitors, absent B, T, NK cells *Ikzf1*$^{L/L}$ (hypomorphic Δex2, reduced protein expression): impaired development at the pro- and pre-B cell transition	Heterozygous mutations: haploinsufficiency/dominant negative disease-causing mutations: immunodeficiency (hypogammaglobulinemia, B lymphopenia), autoimmunity (SLE-like), and malignancy (T-ALL, B-ALL, MM) Enhanced expression: malignancy (MM), autoimmunity (SLE)	[67,75, 77]
E2A	Homozygous mutations (E47$^{-/-}$, absent protein expression): Decrease in all: LMPPs, CLPs, ETPs, B cells, increased postnatal death, impaired postnatal growth Heterozygous mutation (E47$^{\pm/-}$): intermediate phenotype (LMPPs, CLPs, ETPs, B cells ↓)	Heterozygous mutations: autosomal dominant phenotype: agammaglobulinemia, reduced pro-, pre-and mature B cells, presence of BCR-negative peripheral B cells Homozygous mutations: Low B cells, hypogammaglobulinemia, subclasses deficiency, B-ALL	[82, 89-91, 188]
EBF1	Homo-/heterozygous mutation (EBF$^{-/-}$, absent protein expression): developmental block at the pro-B cell stage, absent peripheral B cells, malignancy (B-ALL)	Heterozygous mutation: second hit mutation resulting in malignancy (B-ALL)	[92,96, 97]
PAX5	Homozygous mutation (Δex2, KO of DNA-binding domain, absent protein expression): developmental block at the pre-B stage, lethality after 3 weeks of birth, altered midbrain development	Compound heterozygous mutations: severe hypogammaglobulinemia and neurologic disorders, malignancy (B-ALL)	[103, 111-114]
Aiolos	Homozygous mutation: Ikzf3$^{-/-}$ (Δex7, absent protein expression): reduced IgM^{+} B cells in BM, B cell lymphoma Ikzf3^{G158R}: developmental block at the pre-pro-B to pre-B cell stage, reduced splenic B cells Ikzf3^{N159S}: decrease in all: peripheral B cells, serum IgG/IgA/IgM, follicular B cells, IgD expression Heterozygous mutation: Ikzf3^{G158R}: Similar phenotype (milder) compared to homozygous mutation Ikzf3^{N159S}: normal peripheral B cells, reduced follicular B cells, increased marginal zone B cells	Heterozygous mutation, dominant-negative phenotype: Aiolos (G159R): reduced peripheral B cells, hypogammaglobulinemia, lymphoma Aiolos (N160S): normal to increased B cells, hypogammaglobulinemia, infections Enhanced expression: malignancy (MM, CLL), autoimmunity (SLE)	[75,77, 119-122]

Abbreviations: Knock-out (KO); Systemic lupus erythematosus (SLE); T acute lymphoblastic leukemia (T-ALL); B acute lymphoblastic leukemia (B-ALL); multiple myeloma (MM); lymphoid-primed multipotent progenitor (LMPP); common lymphoid progenitor (CLP); early T-cell progenitor (ETP); B cell receptor (BCR); bone marrow (BM); multiple myeloma (MM); chronic lymphocytic leukemia (CLL).

phenotype compared to heterozygous mutations [89,91]. In mice, E2A appears to play a fundamental role in the first phase of lymphoid differentiation, as homozygous E2A mutations result in a block at the LMPP stage. In contrast, E2A (E47) appears to be required in humans at a later stage of development in a dose-dependent manner as B cells are reduced yet present in homozygous TCF3 mutations. Additionally, in humans, E2A appears to be fundamental in regulating BCR rearrangement, as the generated B cells are devoid of surface BCR, whereas in mice, this phenotype has not been observed.

EBF1 mutations have a severe impact on murine B lymphopoiesis. *Ebf1*$^{-/-}$ mice lack peripheral B cells and exhibit a developmental block at the B220^{+}CD43^{+} stage [92]. Further, EBF1 promotes permissive chromatin state for B-lymphoid enhancers in murine MPP populations and restricts myelopoiesis by downregulating C/EBPα expression, thereby facilitating B lymphopoiesis [4]. The Rag1^{high} CLPs strongly upregulate *Ebf1* expression, which is modulated by two promoters with binding sites for E2A, Ikaros, and PAX5 [93]. When upregulated, EBF1 together with E2A and FOXO1 form positive feedback loops and a TF network that altogether regulate the B cell fate [6,85]. PAX5 antagonizes EBF1 by repressing *Myc* expression, thereby regulating the proliferation of murine pro-B cells [94]. At the pre-BI stage, EBF1 induces the *Igll1* (λ5) expression by outcompeting Ikaros at the promoter site [95].

To date, there have been no reports of mutations in EBF1 resulting in primary immunodeficiency. In human and murine B-ALL, mono- and biallelic mutations of EBF1 synergizing with other regulators (such as PAX5) have been observed, implying a role for EBF1 in tumor suppression [96–98]. Indeed, EBF1 induces *CD79A, CD79B*, and *CD19* in human lymphoma cell lines but fails to promote the expression of direct targets, such as *PAX5* or *FOXO1*, indicating cell- or stage-specific function. [99,100]. Another potentially conserved function of EBF1 to induce *Myc* expression has recently been demonstrated in an EBV infection model of human tonsillar B cells [101,102]. In summary, E2A and EBF1 proteins represent major regulators of murine B lymphopoiesis by regulating the chromatin structure and promoting the expression of *Pax5, CD19, CD79A/B*, and *Dntt*. In contrast, E2A appears to have a prominent role in regulation of heavy chain rearrangement and B cell output in humans. For both E2A and EBF1, further studies in humans will be required to determine their role in promoting early B cell development.

3.4. PAX5

The key role of PAX5 in early B lymphopoiesis was discovered by Busslinger et al., who first described the impaired development of B220^{+}CD43^{+} progenitors and subsequent strong reduction in surface IgM^{+} immature B cells in the BM of *Pax5*$^{-/-}$ mice [103]. PAX5 promotes the expression of critical B cell genes such as *Cd19, Cd79a, Vpreb*, and *Ikzf3* while repressing the genes for early progenitor (*Flt3*), T (*Notch1*), and myeloid cells (*Csfr1*) [7,8,104,105]. PAX5 is required to maintain

the B cell fate. If PAX5 is absent, as in conditional *Pax5* knockout in committed $IgM^{+}IgD^{high}$ B cells, B cells can dedifferentiate into uncommitted progenitors that can further differentiate and finally establish normal distribution of T cell populations when transplanted into T-cell deficient *Rag2*$^{-/-}$mice [106]. Further, PAX5 regulates the global genomic structure in murine pro-B cells as it promotes distal V_H gene segment recombination by recruiting the CTCF and cohesin complex [107,108]. Of note, several transcriptional networks, which are based on gene expression profiles and protein–DNA or protein–protein interactions, identify PAX5 together with Ikaros, EBF1, FOXO1, and RUNX1 as central components in B cell commitment, whereas concurrent mutations within the network provoke human B-ALL [109,110]. In fact, murine and human PAX5 mutations either initiate B-ALL or serve as second hit mutations leading to malignant transformation by changing cell metabolism with extensive glucose uptake and ATP production in pre-B cells [111,112]. Furthermore, murine heterozygous PAX5 mutation (*Pax5*$^{+/-}$) and constitutive STAT5 signaling synergize to induce B-ALL in 100% of mutated mice by derepressing the expression of *Myc* and *Bcl2* oncogenes [113]. Compound heterozygous mutations in PAX5 have been described in one patient, with hypogammaglobulinemia, severe B lymphopenia, and autism spectrum disorders [114]. Knock-in mutations in a mouse model presented the phenotypes of impaired transition after the pro-B cell stage, hypogammaglobulinemia, and neurological disorders, indicating a similar role for PAX5 in both species [114]. Thus, PAX5 plays a crucial role during murine and human B cell commitment by inducing and maintaining B cell fate while repressing the development of alternative lineages and the formation of B-ALL.

3.5. Aiolos

Aiolos (encoded by *IKZF3*) is a member of the Ikaros protein family. In mice, Aiolos is strongly upregulated by interferon regulating factors 4 and 8 (IRF4/IRF8) during the transition from large to small pre-BII cell stage and forms homo- or heterodimers with Ikaros [115,116]. Together with Ikaros, Aiolos downregulates the expression of pre-BCR components VpreB and λ5 to cease proliferation induced by the pre-BCR and IL-7R signaling, thereby promoting further development into pre-BII small cells [117,118]. In mice, Aiolos deficiency reduces the frequency of BM-derived IgM^{+} cells and promotes an activated phenotype of peripheral B cells and B cell lymphomas [119]. Interestingly, human heterozygous point mutations in DNA-binding zinc finger domain 2 of the *IKZF3* gene have different outcomes. $Aiolos^{G159R}$ patients exhibit diminished B cell development, low B cell numbers, and susceptibility to lymphomas, whereas $Aiolos^{N160S}$ patients display normal or increased B cell numbers [120,121]. The corresponding mouse models reflect the phenotype observed in the heterozygous $Aiolos^{G159R}$ patient confirming reduction of peripheral B cells owing to a partial block at the pre-pro-B to pre-B cell transition [120]. Further, similar to SLE and MM, overexpression of Aiolos promotes cell survival in chronic lymphocytic leukemia (CLL) [122]. In summary, Aiolos' synergy with Ikaros to downregulate pre-BCR signaling during the transition from pre-BII large to pre-BII small cells has been demonstrated in mice but not yet in humans. In contrast, aberrant Aiolos expression inducing leukemia (B-ALL, MM) was confirmed in both species.

4. Cytokine and chemokine signaling

Alterations in cytokine and chemokine signaling lead to aberrant early B cell development and leukemogenesis in both mice and humans (Table 2). Here, we have reviewed the existing knowledge about major murine and human cyto- and chemokine signals during early B cell development.

4.1. FLT3/c-kit signaling

In murine B lymphopoiesis, FLT3 is expressed between the short-term HSC (ST-HSCs) and the pro-B cell stages, where its downregulation by PAX5 is an essential developmental step [105,123]. Ikaros activates the expression of FLT3, which ensures the development of LMPPs; as demonstrated in Ikaros, FLT3, and FLT3 ligand (FLT3L) mutant mice that show low LMPP frequency [104,124,125]. Most of our knowledge about FLT3 signaling during early B cell development is based on murine (conditional) knockout and overexpression models of FLT3 or FLT3L [126]. FLT3 signaling induces the proliferative burst of LMPPs, multipotent $Ly6D^{-}$ and B cell-primed $Ly6D^{+}$ CLPs, thereby expanding the pool of early progenitors. FLT3 signaling must be regulated since its overabundance not only strongly impairs the development of murine pre-B and immature B cells, presumably owing to reduced *Ebf1* and *Pax5* expression, but also diminishes erythroid and megakaryocytic output causing anemia after 10 weeks of birth [127,128]. Therefore, whether FLT3 signaling has a permissive or an instructive role during B lymphopoiesis is still debated, as it either promotes proliferation of $FLT3^{+}$ progenitors or actively regulates the fate decision between lymphoid/myeloid and megakaryocyte/erythrocyte lineages, respectively.

In humans, the addition of FLT3 to IL-3/IL-6/SCF in vitro stimulated BM-derived early progenitors ($CD34^{+}CD38^{-}$) and increased their expansion by 15.6-fold after 21 days of culture compared to the IL-3/IL-

Table 2
Summary of murine and human mutations in key chemokines and cytokines and their respective phenotype.

Target	Phenotype mouse	Clinical phenotype	Ref.
FLT3(L) signaling	Loss-of-function mutation: Reduction of all: LMPP, CLPs and IgM^{+} B cells Gain-of-function mutations: anemia; reduction of platelets and erythroid progenitors	Gain-of-function mutations: malignancy (AML, B-ALL)	[124-127,130, 131]
c-kit/SCF signaling	Loss-of-function mutation: synergy with FLT3 mutation: strong reduction of $B220^{+}$ progenitors and pro-B cells Gain-of-function mutations: B-ALL-like disease	Gain-of-function mutations: mastocytosis	[134,141]
IL-7(R) signaling	Loss-of-function mutation: developmental block at pro-B cell stage, lack of peripheral B cells Gain-of-function mutations: malignancy (T-ALL, B-ALL)	Loss-of-function mutations: T-, B+, NK+ SCID (reduced diversity of IgH repertoire in B cells), partial block at pro-B cell stage, reduced pro-B cell proliferation, reduced expression of PAX-5, EBF1 and E2A Gain-of-function mutations: malignancy (T-ALL, B-ALL)	[151,152,161, 167–169,193]
CXCR4/ CXCL12 signaling	Loss-of-function mutation: reduction of CLP, expansion of HSCs Gain-of-function mutations: WHIM-like disease, malignancy (CLL)	Gain-of-function mutations: WHIM syndrome (hypogammaglobulinemia, reduced B cells); phosphorylation connected to poor outcome of B-ALL	[181,182,184, 189,190]

Some of the phenotypes were added in the table but were not described in the main text.
Abbreviations: lymphoid-primed multipotent progenitor (LMPP); common lymphoid progenitor (CLP); acute myeloid leukemia (AML); B acute lymphoblastic leukemia (B-ALL); T acute lymphoblastic leukemia (T-ALL); severe combined immunodeficiency (SCID); hematopoietic stem cell (HSC); chronic lymphocytic leukemia (CLL).

6/SCF-only condition [129]. Interestingly, CB-derived $CD34^+CD38^-$ progenitors exhibited a mere 2-fold increase, indicating higher dependence on FLT3 signaling during adult B lymphopoiesis. FLT3 mutations resulting in constitutive receptor signaling and consequent proliferation of early progenitors cause acute myeloid leukemia (AML) and B-ALL [130,131]. Selective FLT3 inhibitors were approved for treating AML. The inhibitors present an opportunity to study the functions of FLT3 signaling in human B lymphopoiesis either during clinical studies or by applying FLT3-inhibitor to $CD34^+$ progenitor-based in vitro cultures [132].

C-kit and FLT3 belong to the same protein family of tyrosine kinases and their similarities in protein and genomic loci structure indicate a common ancestral gene and similar function in B lymphopoiesis [133]. In fact, FLT3- and c-kit- double knockout mice exhibit a more severe phenotype with a significant decrease in absolute and relative numbers of $B220^+$ lymphocytes and pro-/pre-B cells and neonatal death compared to FLT3-deficient mice [134]. Further, synergy of SCF and CXCL12 promotes the survival and/or proliferation of unipotent $Lin^-c\text{-}kit^+IL\text{-}7R^+$ B cell precursors (CLPs) [135]. However, the role of SCF/c-kit signals after the CLP stage appears to be negligible in mice, as c-kit expression is downregulated at the CLP/pro-B cell stage. Similar to FLT3, the dependence of B lymphopoiesis on c-kit signaling appears to vary during ontogeny, as implicated by the ability of c-kit-deficient fetal liver cells to develop into IgM^+immature B cells after transfer into *Rag2*$^{-/-}$ mice [136,137]. The role of c-kit in controlling the proliferation of hematopoietic progenitors is supported by its high expression in cycling murine HSCs and the observation that blocking anti-c-kit-antibody 2 (ACK-2) causes a transient depletion of ~99% of murine HSCs [138–140]. Interestingly, c-kit mutations resulting in constitutive activation of c-kit provoke B-ALL-like disease in mice. However, thus far, such incidents have not been reported in human patients with B-ALL [141]. Notably, the binding of SCF to c-kit in human $CD34^+$ progenitors not only induces proliferation similar to mice but also promotes adherence to fibronectin, which is a prevalent protein within the BM niche [142]. Also, microscopic images reveal c-kit/SCF signaling to anchor HSCs in the endosteal region of murine BM [143]. In summary, FLT3 signaling has been primarily linked to the proliferative response of both murine and human early hematopoietic progenitors (HSCs, MPPs). In contrast, enhanced proliferation of early progenitors by synergistic effect of FLT3 and c-kit was confirmed in mice but not in humans. Further, c-kit regulates the retention of early progenitors in murine and human BM niches.

4.2. IL-7R signaling

BM stromal cells produce IL-7, which binds to the IL-7 receptor (IL-7R). IL-7R comprises the IL-7Rα (CD127) and common γ chain (IL-7Rγ, CD132) and signals via transphosphorylation of the associated Janus kinases (JAK1 and JAK3), which in turn phosphorylate STAT1 and STAT5. Activation of STAT1 and STAT3 is crucial for the pre-pro-B to pro-B cell transition as observed in STAT3-deficient mice [144,145]. IL-7R signaling also induces the MAPK/Erk and the phosphoinositide-3-kinase (PI3K) pathways that together with pre-BCR signals promote the proliferation of murine pre-B cells [146]. However, the roles of IL-7 and pre-BCR signaling during the proliferative burst of pre-B cells are still discussed. Here, IL-7R signaling was proposed as the main driver of pre-B cell expansion. In support of this model, murine IL-7, but not pre-BCR signaling, was shown to induce the PI3K-AKT pathway [146], whereas the MAPK/Erk axis downstream of the pre-BCR promotes cell cycle exit and LC recombination [118]. In contrast, pre-BCR signaling was reported to support pre-B cell proliferation by lowering the threshold of the required IL-7 concentration through the MAPK/Erk pathway [147,148]. In particular, pre-BCR regulates the sensitivity towards IL-7 through Igα (CD79a), which is dispensable for pre-B cell proliferation but not development [149]. Also, the absence of both IL-7R and pre-BCR ($VpreB^{-/-}$) exacerbates the loss of pre-BII cells by 7–8-fold compared to IL-7R mutation alone, after correcting for the potential effect of IL-7R mutation on pre-BI cells [150]. Still, the loss of pre-BII cells was more dependent on IL-7R than on pre-BCR, as indicated by a 160- and 20-fold decrease in pre-BII cells, respectively, in singly mutated mice.

Murine IL-7/IL-7Rα mutations abrogate B cell development at the $B220^+CD24^+$ pro-B cell stage and result in a lack of IgM^+ immature B cells [151,152]. IL-7 was shown to regulate various critical aspects of both murine and human B lymphopoiesis such as proliferation, apoptosis, recombination, and stage-specific gene expression, as reviewed in [153]. In mice, IL-7 signaling maintains the LMPP population and promotes B cell commitment in CLPs by inducing *Ebf1*, which conversely upregulates *Pax5* expression [154]. Further, IL-7 regulates the expression of anti-apoptotic Bcl2 protein, thereby facilitating the survival of murine pro-B cells [155]. Later, CXCR4-CXCL12 signaling and the downregulation of adhesion proteins (focal adhesion kinase [FAK] and VLA-4) promote the withdrawal of murine pre-B cells from IL-7-producing stromal cells [156]. Attenuated IL-7 signaling, combined with Ikaros and Aiolos, promotes cell cycle exit by *Myc* downregulation during the transition from large to small pre-BII cells, simultaneously activating *Rag1/2, Igκ*, and *Igλ* expression [157,158]. One of the mechanisms that promote *Igκ* expression upon IL-7 withdrawal might involve replacing STAT5 from the *Igκ* loci with Ikaros, thereby reducing the suppressive histone methylation by Ezh2 [159,160].

In contrast to those in mice, mutations in IL-7Rα, IL-7Rγ, or JAK3 in humans result in severe combined immunodeficiency (SCID) with impaired T cell development. However, early B cell development is conserved, as revealed by the normal frequency of $CD20^+$ peripheral B cells [22,161]. Therefore, human B lymphopoiesis is considered to be less dependent on IL-7 signaling. In vitro culture studies, recapitulating B lymphopoiesis from CB-derived $CD34^+$ early progenitors [51], revealed that IL-7 induces proliferation of CLP/pro-B cells ($CD19^-IgM^-$) in humans, similar to that in mice. In contrast, human $CD10^+CD34^-cyIgM^+$ pre-B cells do not proliferate upon IL-7 stimulation [162]. A potential explanation for this is that the outcome of IL-7R engagement is species- and cell stage-specific. In particular, human IL-7 activates the JAK/STAT and the PI3K pathways in $CD34^+$ thymocytes, whereas in $CD10^+CD19^+$ B cell precursors, IL-7 involves only the JAK/STAT and not the PI3K axis [163]. This is in contrast to the observations in mice, where IL-7 activates both pathways in $CD10^+CD19^+$ B cell precursors. A recent study of the BM of IL-7Rα deficient patients revealed that IL-7 signaling has an instructive role on human B cell development, by promoting EBF1, E2A and PAX-5 expression and pro-B cell proliferation and inhibiting myeloid development ([193]).

The existing data suggest that IL-7-dependence increases from fetal to adult B lymphopoiesis in both mice and humans [50]. In fact, murine HSCs from the fetal liver of IL-7Rα-mutated mice continued to produce $B220^+IgM^+$ peripheral B cells in contrast to HSCs isolated from BM of 4-week-old mice [164]. Human IL-7Rα expression increases from fetal BM-derived pro-B cells to its pediatric counterpart, indicating higher IL-7 dependence after birth [165]. FLT3 expression shows an opposite trend — higher expression in fetal pro-B cells compared to pediatric pro-B cells, potentially explaining the lower IL-7 dependence in fetal B lymphopoiesis as FLT3 also promotes proliferation and survival of murine CLPs [166]. IL-7R signaling drives N-nucleotide addition during IgH rearrangement by promoting TdT expression in IL-7Rα-mutated patients, indicating a role of IL-7 signaling in shaping the diversity of the repertoire [165]. However, constitutive IL-7 signaling caused by IL-7Rα or STAT5 gain-of-function mutations favors T- and B-ALL in mice and humans [167–169]. In the murine model of B-ALL, caused by heterozygous PAX5 mutation, transient administration of a JAK1/JAK2 inhibitor, ruxolitinib, was shown to prevent B-ALL by increasing apoptosis in the pre-leukemic cells [170]. JAK inhibitors (ruxolitinib, tofacitinib) are established in the treatment of autoimmune diseases (such as rheumatoid arthritis). Interestingly, JAK inhibitor treatment results in a transient increase in peripheral B cell numbers [171,172]. Whether the

increase in B cell number is caused by the enhanced BM B cell maturation remains unknown. Altogether, the similarities and differences between mice and humans warrant further studies to define the role of IL-7 signaling in human B cell development.

4.3. CXCR4 signaling

CXCR4 and its ligand CXCL12 (alternatively: SDF-1α) mediate B cell development, migration, and ultimately central tolerance during both murine and human B lymphopoiesis. In mice, conditional CXCR4-deficiency in hematopoietic progenitors impairs the development of MPPs, first into multipotent CLPs and later into B-cell-primed Ly6D$^+$ CLPs, as shown by their 3- and 8-fold decrease, respectively [173]. Moreover, CXCR4 ensures coordinated migration of early B cells within the BM niche. CXCR4 guides CLPs into the proximity of CXCL12$^+$IL-7$^+$ stromal cells where CLPs develop into proliferative and non-motile pro-B cells that exhibit increased adherence to the stroma by expressing the α4β1 (VLA-4) heterodimer and FAK [156,173]. Upon pre-BCR signaling, large pre-BII cells downregulate the expression of α4β1/FAK, concomitantly upregulating CXCR4 and migrating towards IL-7$^-$CXCL12$^+$ stromal cells [174]. In general, CXCR4 is a part of an intricate regulatory network that facilitates the transition of large to small pre-BII cells as the CXCR4-mediated withdrawal from IL-7-producing cells leads to transcriptional changes and CXCR4 induces NFκB signaling, which is essential for the formation of small pre-BII cells [175]. Moreover, CXCR4 builds a feed-forward loop by inducing *Irf4* and *Irf8*, which in turn induce *Cxcr4* and *Ikzf3,* ultimately downregulating pre-BCR signaling [115,174]. CXCR4 signaling promotes ERK activation, which is crucial for *Igκ* transcription in murine small pre-BII cells [174]. At the immature cell stage, CXCR4 signaling is downregulated, which induces the migration of non-autoreactive immature B cells into periphery [176]. In contrast, self-antigen engagement, indicating autoreactivity, increases CXCR4 expression and prevents egress of murine immature B cells from the BM [177]. This process also appears to be active in human immature cells as shown in humanized immunodeficient mice that express a self-antigen (Hcκ) and are reconstituted with human CB HSCs [178]. Thus, Igκ$^+$ immature B cells are autoreactive and exhibit higher CXCR4 expression compared to non-autoreactive control cells. In this model, autoreactive Igκ$^+$ immature B cells show a 2-fold increase in the periphery upon CXCR4 antagonist (AMD3100, plerixafor) treatment, validating the role of CXCR4 in preventing the leakage of human autoreactive cells into the periphery. In mice and humans, AMD3100 treatment also mobilizes CD34$^+$ progenitors that are normally contained in the BM niche because of CXCR4 [179,180]. However, prolonged AMD3100 treatment may promote proliferation of the mobilized progenitors as CXCR4 regulates the quiescence of murine HSCs as shown by the expansion of LSK (Lin$^-$Sca-1$^+$ *c*-kit$^+$) cells in *Cxcl12*$^{-/-}$ mice [181]. Gain-of-function mutations in CXCR4 result in WHIM syndrome, characterized by warts, hypogammaglobulinemia, infections, and myelokathexis. In these patients, BM is hypercellular, whereas the B cell compartment features hypogammaglobulinemia, markedly reduced circulating B cells, restricted IgH variable region diversity, impaired class switching, and poor responses towards vaccines [182]. The immature B cells appear sequestered in the BM because of CXCR4 as observed after AMD3100 treatment in patients with WHIM, which increases the transitional/immature B cell numbers within hours of drug administration [183]. In human disease, the phosphorylated form of CXCR4 was connected to poor outcome in adult patients with B-ALL [184], however, further CXCR4-mediated mechanisms in human B lymphopoiesis are yet to be elucidated. Overall, CXCR4 signaling was shown to mediate retention and the migration of early progenitors/B cells in the BM niche, facilitating the large to small pre-BII cell transition and preventing the egress of autoreactive B cells into the periphery, in both mice and humans.

5. Outlook

Existing studies highlight the differences between mouse and human B cell development, particularly with regard to the role played by pre-BCR and cytokine signaling as well as the function of specific transcription factors. Hence, there is a need for more detailed human studies to dissect the signals that guide B lymphopoiesis. Several tools have been used to uncover the molecular mechanisms driving B cell development. For example, the mechanism through which CXCR4 signaling regulates central tolerance has been demonstrated in humanized mice [178]. In vitro modeling of B cell development from CD34$^+$ progenitors could uncover intrinsic defects and non-permissive BM environment in common variable immunodeficiency (CVID) [132]. Healthy subjects treated with Ikaros/Aiolos modulator iberdomide during a phase 1 study showed rapid decrease in peripheral B cells [78]. BM-organoids have been demonstrated to reproduce monocyte and macrophage lineage but not B cell development. Nevertheless, BM organoids, mimicking the complexity of a HSC niche, might be used in future to investigate patient-specific B lymphopoiesis and/or as a drug-testing platform [185,186]. Furthermore, the modeling of specific human mutations into mice can facilitate the transfer of knowledge and observations between the species. *IKZF3* or *PAX5* specific mutations found in patients were modeled into mice, revealing a phenotype strikingly similar to that observed in humans [114,120].

Several questions remain unaddressed regarding the control of early B cell development. One pertains to the role of human IL-7 signaling in fetal and adult B lymphopoiesis. Another pertains to the mechanistical function of Ikaros/Aiolos, CXCR4, and FLT3/c-kit in human B lymphopoiesis. This is important because modulators of these signals (lenalidomide, AMD3100, gilteritinib) have already been approved for treatment. The study of human early B cell development upon lenalidomide treatment could provide insights into the observed occurrence of secondary malignancies [187]. Deeper understanding of signals and regulation of human early B cell development enables the prediction of potential adverse events from targeted therapies and paves the way for the identification of new targets to modulate development. This can be of importance both in autoimmune diseases and in the carcinogenic transformation of early B cell stages.

Declaration of Competing Interest

The authors declare no conflict of interest.

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References

[1] T. Sugiyama, H. Kohara, M. Noda, T. Nagasawa, Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches, Immunity 25 (2006) 977–988.
[2] L. Ding, T.L. Saunders, G. Enikolopov, S.J. Morrison, Endothelial and perivascular cells maintain haematopoietic stem cells, Nature 481 (2012) 457–462.
[3] P. Sommerkamp, M.C. Romero-Mulero, A. Narr, L. Ladel, L. Hustin, K. Schonberger, S. Renders, S. Altamura, P. Zeisberger, K. Jacklein, et al., Mouse multipotent progenitor 5 cells are located at the interphase between hematopoietic stem and progenitor cells, Blood 137 (2021) 3218–3224.
[4] A. Lenaerts, I. Kucinski, W. Deboutte, M. Derecka, P. Cauchy, T. Manke, B. Gottgens, R. Grosschedl, EBF1 primes B-lymphoid enhancers and limits the myeloid bias in murine multipotent progenitors, J. Exp. Med. (2022) 219.
[5] K.S. Mak, A.P. Funnell, R.C. Pearson, M. Crossley, PU.1 and haematopoietic cell fate: dosage matters, Int. J. Cell Biol. 2011 (2011), 808524.
[6] S. Boller, R. Grosschedl, The regulatory network of B-cell differentiation: a focused view of early B-cell factor 1 function, Immunol. Rev. 261 (2014) 102–115.

[7] A. Souabni, C. Cobaleda, M. Schebesta, M. Busslinger, Pax5 promotes B lymphopoiesis and blocks T cell development by repressing Notch1, Immunity 17 (2002) 781–793.
[8] H. Tagoh, R. Ingram, N. Wilson, G. Salvagiotto, A.J. Warren, D. Clarke, M. Busslinger, C. Bonifer, The mechanism of repression of the myeloid-specific c-fms gene by Pax5 during B lineage restriction, EMBO J. 25 (2006) 1070–1080.
[9] S.L. Nutt, B.L. Kee, The transcriptional regulation of B cell lineage commitment, Immunity 26 (2007) 715–725.
[10] K. Miyazaki, H. Watanabe, G. Yoshikawa, K. Chen, R. Hidaka, Y. Aitani, K. Osawa, R. Takeda, Y. Ochi, S. Tani-Ichi, et al., The transcription factor E2A activates multiple enhancers that drive Rag expression in developing T and B cells, Sci. Immunol. (2020) 5.
[11] W.J. Romanow, A.W. Langerak, P. Goebel, I.L. Wolvers-Tettero, J.J. van Dongen, A.J. Feeney, C. Murre, E2A and EBF act in synergy with the V(D)J recombinase to generate a diverse immunoglobulin repertoire in nonlymphoid cells, Mol. Cell 5 (2000) 343–353.
[12] M.S. Krangel, Gene segment selection in V(D)J recombination: accessibility and beyond, Nat. Immunol. 4 (2003) 624–630.
[13] R.C. Rickert, New insights into pre-BCR and BCR signalling with relevance to B cell malignancies, Nat. Rev. Immunol. 13 (2013) 578–591.
[14] D. Nemazee, Mechanisms of central tolerance for B cells, Nat. Rev. Immunol. 17 (2017) 281–294.
[15] R. Pelanda, S.A. Greaves, T. Alves da Costa, L.M. Cedrone, M.L. Campbell, R. M. Torres, B-cell intrinsic and extrinsic signals that regulate central tolerance of mouse and human B cells, Immunol. Rev. 307 (2022) 12–26.
[16] C.C. Goodnow, J. Crosbie, S. Adelstein, T.B. Lavoie, S.J. Smith-Gill, R.A. Brink, H. Pritchard-Briscoe, J.S. Wotherspoon, R.H. Loblay, K. Raphael, et al., Altered immunoglobulin expression and functional silencing of self-reactive B lymphocytes in transgenic mice, Nature 334 (1988) 676–682.
[17] B.J. Vilen, S.J. Famiglietti, A.M. Carbone, B.K. Kay, J.C. Cambier, B cell antigen receptor desensitization: disruption of receptor coupling to tyrosine kinase activation, J. Immunol. 159 (1997) 231–243.
[18] H. Wardemann, S. Yurasov, A. Schaefer, J.W. Young, E. Meffre, M. C. Nussenzweig, Predominant autoantibody production by early human B cell precursors, Science 301 (2003) 1374–1377.
[19] D. Häusler, S. Häusser-Kinzel, L. Feldmann, S. Torke, G. Lepennetier, C.C. A. Bernard, S.S. Zamvil, W. Brück, K. Lehmann-Horn, M.S. Weber, Functional characterization of reappearing B cells after anti-CD20 treatment of CNS autoimmune disease, Proc. Natl. Acad. Sci. U S A 115 (2018) 9773–9778.
[20] M.J. Leandro, G. Cambridge, M.R. Ehrenstein, J.C. Edwards, Reconstitution of peripheral blood B cells after depletion with rituximab in patients with rheumatoid arthritis, Arthritis Rheum 54 (2006) 613–620.
[21] P. Roll, A. Palanichamy, C. Kneitz, T. Dorner, H.P. Tony, Regeneration of B cell subsets after transient B cell depletion using anti-CD20 antibodies in rheumatoid arthritis, Arthritis Rheum 54 (2006) 2377–2386.
[22] A. Puel, S.F. Ziegler, R.H. Buckley, W.J. Leonard, Defective IL7R expression in T (-)B(+)NK(+) severe combined immunodeficiency, Nat. Genet. 20 (1998) 394–397.
[23] I.L. Martensson, N. Almqvist, O. Grimsholm, A.I. Bernardi, The pre-B cell receptor checkpoint, FEBS Lett. 584 (2010) 2572–2579.
[24] L. Elantak, M. Espeli, A. Boned, O. Bornet, J. Bonzi, L. Gauthier, M. Feracci, P. Roche, F. Guerlesquin, C. Schiff, Structural basis for galectin-1-dependent pre-B cell receptor (pre-BCR) activation, J. Biol. Chem. 287 (2012) 44703–44713.
[25] M. Espeli, S.J. Mancini, C. Breton, F. Poirier, C. Schiff, Impaired B-cell development at the pre-BII-cell stage in galectin-1-deficient mice due to inefficient pre-BII/stromal cell interactions, Blood 113 (2009) 5878–5886.
[26] H. Bradl, J. Wittmann, D. Milius, C. Vettermann, H.M. Jack, Interaction of murine precursor B cell receptor with stroma cells is controlled by the unique tail of lambda 5 and stroma cell-associated heparan sulfate, J. Immunol. 171 (2003) 2338–2348.
[27] F. Mourcin, C. Breton, J. Tellier, P. Narang, L. Chasson, A. Jorquera, M. Coles, C. Schiff, S.J. Mancini, Galectin-1-expressing stromal cells constitute a specific niche for pre-BII cell development in mouse bone marrow, Blood 117 (2011) 6552–6561.
[28] A.G. Rolink, T. Winkler, F. Melchers, J. Andersson, Precursor B cell receptor-dependent B cell proliferation and differentiation does not require the bone marrow or fetal liver environment, J. Exp. Med. 191 (2000) 23–32.
[29] C. Vettermann, K. Herrmann, C. Albert, E. Roth, M.R. Bosl, H.M. Jack, A unique role for the lambda5 nonimmunoglobulin tail in early B lymphocyte development, J. Immunol. 181 (2008) 3232–3242.
[30] R. Ubelhart, M. Werner, H. Jumaa, Assembly and function of the precursor B-cell receptor, Curr. Top Microbiol. Immunol. 393 (2016) 3–25.
[31] M.E. Conley, A.K. Dobbs, D.M. Farmer, S. Kilic, K. Paris, S. Grigoriadou, E. Coustan-Smith, V. Howard, D. Campana, Primary B cell immunodeficiencies: comparisons and contrasts, Annu. Rev. Immunol. 27 (2009) 199–227.
[32] A. Berglof, J.J. Turunen, O. Gissberg, B. Bestas, K.E. Blomberg, C.I. Smith, Agammaglobulinemia: causative mutations and their implications for novel therapies, Expert Rev. Clin. Immunol. 9 (2013) 1205–1221.
[33] D. Campana, J. Farrant, N. Inamdar, A.D. Webster, G. Janossy, Phenotypic features and proliferative activity of B cell progenitors in X-linked agammaglobulinemia, J. Immunol. 145 (1990) 1675–1680.
[34] W.N. Khan, F.W. Alt, R.M. Gerstein, B.A. Malynn, I. Larsson, G. Rathbun, L. Davidson, S. Muller, A.B. Kantor, L.A. Herzenberg, et al., Defective B cell development and function in Btk-deficient mice, Immunity 3 (1995) 283–299.
[35] E. Lopez Granados, A.S. Porpiglia, M.B. Hogan, N. Matamoros, S. Krasovec, C. Pignata, C.I. Smith, L. Hammarstrom, J. Bjorkander, B.H. Belohradsky, et al., Clinical and molecular analysis of patients with defects in micro heavy chain gene, J. Clin. Invest. 110 (2002) 1029–1035.
[36] L. Yel, Y. Minegishi, E. Coustan-Smith, R.H. Buckley, H. Trubel, L.M. Pachman, G. R. Kitchingman, D. Campana, J. Rohrer, M.E. Conley, Mutations in the mu heavy-chain gene in patients with agammaglobulinemia, N. Engl. J. Med. 335 (1996) 1486–1493.
[37] D. Kitamura, J. Roes, R. Kuhn, K. Rajewsky, A B cell-deficient mouse by targeted disruption of the membrane exon of the immunoglobulin mu chain gene, Nature 350 (1991) 423–426.
[38] Y. Minegishi, E. Coustan-Smith, L. Rapalus, F. Ersoy, D. Campana, M.E. Conley, Mutations in Igalpha (CD79a) result in a complete block in B-cell development, J. Clin. Invest. 104 (1999) 1115–1121.
[39] S. Ferrari, V. Lougaris, S. Caraffi, R. Zuntini, J. Yang, A. Soresina, A. Meini, G. Cazzola, C. Rossi, M. Reth, et al., Mutations of the Igbeta gene cause agammaglobulinemia in man, J. Exp. Med. 204 (2007) 2047–2051.
[40] Y. Minegishi, E. Coustan-Smith, Y.H. Wang, M.D. Cooper, D. Campana, M. E. Conley, Mutations in the human lambda5/14.1 gene result in B cell deficiency and agammaglobulinemia, J. Exp. Med. 187 (1998) 71–77.
[41] W. Ellmeier, S. Jung, M.J. Sunshine, F. Hatam, Y. Xu, D. Baltimore, H. Mano, D. R. Littman, Severe B cell deficiency in mice lacking the tec kinase family members Tec and Btk, J. Exp. Med. 192 (2000) 1611–1624.
[42] C. Anzilotti, D.J. Swan, B. Boisson, M. Deobagkar-Lele, C. Oliveira, P. Chabosseau, K.R. Engelhardt, X. Xu, R. Chen, L. Alvarez, et al., An essential role for the Zn(2+) transporter ZIP7 in B cell development, Nat. Immunol. 20 (2019) 350–361.
[43] D. Morgan, V. Tergaonkar, Unraveling B cell trajectories at single cell resolution, Trends Immunol. 43 (2022) 210–229.
[44] R.R. Hardy, C.E. Carmack, S.A. Shinton, J.D. Kemp, K. Hayakawa, Resolution and characterization of pro-B and pre-pro-B cell stages in normal mouse bone marrow, J. Exp. Med. 173 (1991) 1213–1225.
[45] R.R. Hardy, K. Hayakawa, B cell development pathways, Annu. Rev. Immunol. 19 (2001) 595–621.
[46] J.W. Tung, M.D. Mrazek, Y. Yang, L.A. Herzenberg, L.A. Herzenberg, Phenotypically distinct B cell development pathways map to the three B cell lineages in the mouse, Proc. Natl. Acad. Sci. U S A 103 (2006) 6293–6298.
[47] M. Aurrand-Lions, S.J.C. Mancini, Murine bone marrow niches from hematopoietic stem cells to B cells, Int. J. Mol. Sci. (2018) 19.
[48] M.C. van Zelm, M. van der Burg, D. de Ridder, B.H. Barendregt, E.F. de Haas, M. J. Reinders, A.C. Lankester, T. Revesz, F.J. Staal, J.J. van Dongen, Ig gene rearrangement steps are initiated in early human precursor B cell subsets and correlate with specific transcription factor expression, J. Immunol. 175 (2005) 5912–5922.
[49] M.W.J. Wentink, T. Kalina, M. Perez-Andres, L. Del Pino Molina, H. IJ, F. G. Kavelaars, A.C. Lankester, Q. Lecrevisse, J.J.M. van Dongen, A. Orfao, et al., Delineating human B cell precursor development with genetically identified PID cases as a model, Front. Immunol. 10 (2019) 2680.
[50] Y.K. Parrish, I. Baez, T.A. Milford, A. Benitez, N. Galloway, J.W. Rogerio, E. Sahakian, M. Kagoda, G. Huang, Q.L. Hao, et al., IL-7 Dependence in human B lymphopoiesis increases during progression of ontogeny from cord blood to bone marrow, J. Immunol. 182 (2009) 4255–4266.
[51] H. Kraus, S. Kaiser, K. Aumann, P. Bönelt, U. Salzer, D. Vestweber, M. Erlacher, M. Kunze, M. Burger, K. Pieper, et al., A feeder-free differentiation system identifies autonomously proliferating B cell precursors in human bone marrow, J. Immunol. 192 (2014) 1044–1054.
[52] M. Osawa, K. Hanada, H. Hamada, H. Nakauchi, Long-term lymphohematopoietic reconstitution by a single CD34-low/negative hematopoietic stem cell, Science 273 (1996) 242–245.
[53] S.L. Kalled, N. Siva, H. Stein, E.L. Reinherz, The distribution of CD10 (NEP 24.11, CALLA) in humans and mice is similar in non-lymphoid organs but differs within the hematopoietic system: absence on murine T and B lymphoid progenitors, Eur. J. Immunol. 25 (1995) 677–687.
[54] J.J. Bleesing, T.A. Fleisher, Human B cells express a CD45 isoform that is similar to murine B220 and is downregulated with acquisition of the memory B-cell marker CD27, Cytometry B Clin. Cytom. 51 (2003) 1–8.
[55] S. O'Byrne, N. Elliott, S. Rice, G. Buck, N. Fordham, C. Garnett, L. Godfrey, N. T. Crump, G. Wright, S. Inglott, et al., Discovery of a CD10-negative B-progenitor in human fetal life identifies unique ontogeny-related developmental programs, Blood 134 (2019) 1059–1071.
[56] A. Hoshino, S. Okada, K. Yoshida, N. Nishida, Y. Okuno, H. Ueno, M. Yamashita, T. Okano, M. Tsumura, S. Nishimura, et al., Abnormal hematopoiesis and autoimmunity in human subjects with germline IKZF1 mutations, J. Allergy Clin. Immunol. 140 (2017) 223–231.
[57] V. Lougaris, D. Moratto, M. Baronio, T. Lorenzini, S. Rossi, L. Gazzurelli, M. P. Bondioni, A. Plebani, Early B cell developmental impairment with progressive B cell deficiency in NFKB2 mutated CVID disease without autoimmunity, Clin. Immunol. 205 (2019) 153–155.
[58] L. Basso-Ricci, S. Scala, R. Milani, M. Migliavacca, A. Rovelli, M.E. Bernardo, F. Ciceri, A. Aiuti, L. Biasco, Multiparametric whole blood dissection: a one-shot comprehensive picture of the human hematopoietic system, Cytometry A 91 (2017) 952–965.
[59] K. Jensen, M.B. Rother, B.S. Brusletto, O.K. Olstad, H.C. Dalsbotten Aass, M. C. van Zelm, P. Kierulf, K.M. Gautvik, Increased ID2 levels in adult precursor B cells as compared with children is associated with impaired Ig locus contraction and decreased bone marrow output, J. Immunol. 191 (2013) 1210–1219.
[60] C.A. Klug, S.J. Morrison, M. Masek, K. Hahm, S.T. Smale, I.L. Weissman, Hematopoietic stem cells and lymphoid progenitors express different Ikaros

isoforms, and Ikaros is localized to heterochromatin in immature lymphocytes, Proc. Natl. Acad. Sci. U S A 95 (1998) 657–662.
[61] H. Nakayama, F. Ishimaru, Y. Katayama, K. Nakase, N. Sezaki, K. Takenaka, K. Shinagawa, K. Ikeda, K. Niiya, M. Harada, Ikaros expression in human hematopoietic lineages, Exp. Hematol. 28 (2000) 1232–1238.
[62] L. Sun, A. Liu, K. Georgopoulos, Zinc finger-mediated protein interactions modulate Ikaros activity, a molecular control of lymphocyte development, Embo J. 15 (1996) 5358–5369.
[63] S.Y. Ng, T. Yoshida, J. Zhang, K. Georgopoulos, Genome-wide lineage-specific transcriptional networks underscore Ikaros-dependent lymphoid priming in hematopoietic stem cells, Immunity 30 (2009) 493–507.
[64] J.H. Wang, A. Nichogiannopoulou, L. Wu, L. Sun, A.H. Sharpe, M. Bigby, K. Georgopoulos, Selective defects in the development of the fetal and adult lymphoid system in mice with an Ikaros null mutation, Immunity 5 (1996) 537–549.
[65] T.A. Schwickert, H. Tagoh, S. Gültekin, A. Dakic, E. Axelsson, M. Minnich, A. Ebert, B. Werner, M. Roth, L. Cimmino, et al., Stage-specific control of early B cell development by the transcription factor Ikaros, Nat. Immunol. 15 (2014) 283–293.
[66] K. Georgopoulos, M. Bigby, J.H. Wang, A. Molnar, P. Wu, S. Winandy, A. Sharpe, The Ikaros gene is required for the development of all lymphoid lineages, Cell 79 (1994) 143–156.
[67] B. Boast, C.J. Nunes-Santos, H.S. Kuehn, S.D. Rosenzweig, Ikaros-associated diseases: from mice to humans and back again, Front. Pediatr. 9 (2021), 705497.
[68] D. Boutboul, H.S. Kuehn, Z. Van de Wyngaert, J.E. Niemela, I. Callebaut, J. Stoddard, C. Lenoir, V. Barlogis, C. Farnarier, F. Vely, et al., Dominant-negative IKZF1 mutations cause a T, B, and myeloid cell combined immunodeficiency, J. Clin. Invest. 128 (2018) 3071–3087.
[69] P. Papathanasiou, A.C. Perkins, B.S. Cobb, R. Ferrini, R. Sridharan, G.F. Hoyne, K. A. Nelms, S.T. Smale, C.C. Goodnow, Widespread failure of hematolymphoid differentiation caused by a recessive niche-filling allele of the Ikaros transcription factor, Immunity 19 (2003) 131–144.
[70] C.M. Kelley, T. Ikeda, J. Koipally, N. Avitahl, L. Wu, K. Georgopoulos, B. A. Morgan, Helios, a novel dimerization partner of Ikaros expressed in the earliest hematopoietic progenitors, Curr. Biol. 8 (1998) 508–515.
[71] K. Hahm, B.S. Cobb, A.S. McCarty, K.E. Brown, C.A. Klug, R. Lee, K. Akashi, I. L. Weissman, A.G. Fisher, S.T. Smale, Helios, a T cell-restricted Ikaros family member that quantitatively associates with Ikaros at centromeric heterochromatin, Genes Dev. 12 (1998) 782–796.
[72] H. Schjerven, E.F. Ayongaba, A. Aghajanirefah, J. McLaughlin, D. Cheng, H. Geng, J.R. Boyd, L.M. Eggesbo, I. Lindeman, J.L. Heath, et al., Genetic analysis of Ikaros target genes and tumor suppressor function in BCR-ABL1(+) pre-B ALL, J. Exp. Med. 214 (2017) 793–814.
[73] I. Joshi, T. Yoshida, N. Jena, X. Qi, J. Zhang, R.A. Van Etten, K. Georgopoulos, Loss of Ikaros DNA-binding function confers integrin-dependent survival on pre-B cells and progression to acute lymphoblastic leukemia, Nat. Immunol. 15 (2014) 294–304.
[74] N. Yoshida, H. Sakaguchi, H. Muramatsu, Y. Okuno, C. Song, S. Dovat, A. Shimada, M. Ozeki, H. Ohnishi, T. Teramoto, et al., Germline IKAROS mutation associated with primary immunodeficiency that progressed to T-cell acute lymphoblastic leukemia, Leukemia 31 (2017) 1221–1223.
[75] P.H. Schafer, Y. Ye, L. Wu, J. Kosek, G. Ringheim, Z. Yang, L. Liu, M. Thomas, M. Palmisano, R. Chopra, Cereblon modulator iberdomide induces degradation of the transcription factors Ikaros and Aiolos: immunomodulation in healthy volunteers and relevance to systemic lupus erythematosus, Ann. Rheum Dis. 77 (2018) 1516–1523.
[76] J. Krönke, N.D. Udeshi, A. Narla, P. Grauman, S.N. Hurst, M. McConkey, T. Svinkina, D. Heckl, E. Comer, X. Li, et al., Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells, Science 343 (2014) 301–305.
[77] C.C. Bjorklund, L. Lu, J. Kang, P.R. Hagner, C.G. Havens, M. Amatangelo, M. Wang, Y. Ren, S. Couto, M. Breider, et al., Rate of CRL4(CRBN) substrate Ikaros and Aiolos degradation underlies differential activity of lenalidomide and pomalidomide in multiple myeloma cells by regulation of c-Myc and IRF4, Blood Cancer J. 5 (2015) e354.
[78] Y. Ye, A. Gaudy, P. Schafer, M. Thomas, D. Weiss, N. Chen, L. Liu, Y. Xue, L. Carayannopoulos, M. Palmisano, First-in-Human, single- and multiple-ascending-dose studies in healthy subjects to assess pharmacokinetics, pharmacodynamics, and safety/tolerability of iberdomide, a novel cereblon E3 Ligase modulator, Clin. Pharmacol. Drug Dev. 10 (2021) 471–485.
[79] S. Boller, S. Ramamoorthy, D. Akbas, R. Nechanitzky, L. Burger, R. Murr, D. Schubeler, R. Grosschedl, Pioneering activity of the C-terminal domain of EBF1 shapes the chromatin landscape for B cell programming, Immunity 44 (2016) 527–541.
[80] C.L. Semerad, E.M. Mercer, M.A. Inlay, I.L. Weissman, C. Murre, E2A proteins maintain the hematopoietic stem cell pool and promote the maturation of myelolymphoid and myeloerythroid progenitors, Proc. Natl. Acad. Sci. U S A 106 (2009) 1930–1935.
[81] T. Cheng, N. Rodrigues, H. Shen, Y. Yang, D. Dombkowski, M. Sykes, D. T. Scadden, Hematopoietic stem cell quiescence maintained by p21cip1/waf1, Science 287 (2000) 1804–1808.
[82] S. Dias, R. Mansson, S. Gurbuxani, M. Sigvardsson, B.L. Kee, E2A proteins promote development of lymphoid-primed multipotent progenitors, Immunity 29 (2008) 217–227.
[83] J. Ahsberg, J. Ungerback, T. Strid, E. Welinder, J. Stjernberg, M. Larsson, H. Qian, M. Sigvardsson, Early B-cell factor 1 regulates the expansion of B-cell progenitors in a dose-dependent manner, J. Biol. Chem. 288 (2013) 33449–33461.
[84] E. Welinder, R. Mansson, E.M. Mercer, D. Bryder, M. Sigvardsson, C. Murre, The transcription factors E2A and HEB act in concert to induce the expression of FOXO1 in the common lymphoid progenitor, Proc. Natl. Acad. Sci. U S A 108 (2011) 17402–17407.
[85] Y.C. Lin, S. Jhunjhunwala, C. Benner, S. Heinz, E. Welinder, R. Mansson, M. Sigvardsson, J. Hagman, C.A. Espinoza, J. Dutkowski, et al., A global network of transcription factors, involving E2A, EBF1 and Foxo1, that orchestrates B cell fate, Nat. Immunol. 11 (2010) 635–643.
[86] K. Kwon, C. Hutter, Q. Sun, I. Bilic, C. Cobaleda, S. Malin, M. Busslinger, Instructive role of the transcription factor E2A in early B lymphopoiesis and germinal center B cell development, Immunity 28 (2008) 751–762.
[87] S. Sakamoto, K. Wakae, Y. Anzai, K. Murai, N. Tamaki, M. Miyazaki, K. Miyazaki, W.J. Romanow, T. Ikawa, D. Kitamura, et al., E2A and CBP/p300 act in synergy to promote chromatin accessibility of the immunoglobulin kappa locus, J. Immunol. 188 (2012) 5547–5560.
[88] M. Wohner, H. Tagoh, I. Bilic, M. Jaritz, D.K. Poliakova, M. Fischer, M. Busslinger, Molecular functions of the transcription factors E2A and E2-2 in controlling germinal center B cell and plasma cell development, J. Exp. Med. 213 (2016) 1201–1221.
[89] M. Ben-Ali, J. Yang, K.W. Chan, I. Ben-Mustapha, N. Mekki, C. Benabdesselem, F. Mellouli, M. Bejaoui, W. Yang, L. Aissaoui, et al., Homozygous transcription factor 3 gene (TCF3) mutation is associated with severe hypogammaglobulinemia and B-cell acute lymphoblastic leukemia, J. Allergy Clin. Immunol. 140 (2017) 1191–1194, e1194.
[90] A.K. Dobbs, A. Bosompem, E. Coustan-Smith, G. Tyerman, F.T. Saulsbury, M. E. Conley, Agammaglobulinemia associated with BCR(-) B cells and enhanced expression of CD19, Blood 118 (2011) 1828–1837.
[91] S. Qureshi, M.D.A. Sheikh, F.N. Qamar, Autosomal recessive agammaglobulinemia - first case with a novel TCF3 mutation from Pakistan, Clin. Immunol. 198 (2019) 100–101.
[92] H. Lin, R. Grosschedl, Failure of B-cell differentiation in mice lacking the transcription factor EBF, Nature 376 (1995) 263–267.
[93] S. Roessler, I. Gyory, S. Imhof, M. Spivakov, R.R. Williams, M. Busslinger, A. G. Fisher, R. Grosschedl, Distinct promoters mediate the regulation of Ebf1 gene expression by interleukin-7 and Pax5, Mol. Cell Biol. 27 (2007) 579–594.
[94] R. Somasundaram, C.T. Jensen, J. Tingvall-Gustafsson, J. Åhsberg, K. Okuyama, M. Prasad, J.R. Hagman, X. Wang, S. Soneji, T. Strid, et al., EBF1 and PAX5 control pro-B cell expansion via opposing regulation of the Myc gene, Blood 137 (2021) 3037–3049.
[95] E.C. Thompson, B.S. Cobb, P. Sabbattini, S. Meixlsperger, V. Parelho, D. Liberg, B. Taylor, N. Dillon, K. Georgopoulos, H. Jumaa, et al., Ikaros DNA-binding proteins as integral components of B cell developmental-stage-specific regulatory circuits, Immunity 26 (2007) 335–344.
[96] C.G. Mullighan, S. Goorha, I. Radtke, C.B. Miller, E. Coustan-Smith, J.D. Dalton, K. Girtman, S. Mathew, J. Ma, S.B. Pounds, et al., Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia, Nature 446 (2007) 758–764.
[97] R.P. Kuiper, E.F. Schoenmakers, S.V. van Reijmersdal, J.Y. Hehir-Kwa, A.G. van Kessel, F.N. van Leeuwen, P.M. Hoogerbrugge, High-resolution genomic profiling of childhood ALL reveals novel recurrent genetic lesions affecting pathways involved in lymphocyte differentiation and cell cycle progression, Leukemia 21 (2007) 1258–1266.
[98] M.A. Prasad, J. Ungerback, J. Ahsberg, R. Somasundaram, T. Strid, M. Larsson, R. Mansson, A. De Paepe, H. Lilljebjorn, T. Fioretos, et al., Ebf1 heterozygosity results in increased DNA damage in pro-B cells and their synergistic transformation by Pax5 haploinsufficiency, Blood 125 (2015) 4052–4059.
[99] V. Bohle, C. Doring, M.L. Hansmann, R. Kuppers, Role of early B-cell factor 1 (EBF1) in Hodgkin lymphoma, Leukemia 27 (2013) 671–679.
[100] C.E. Bullerwell, P.P. Robichaud, P.M.L. Deprez, A.P. Joy, G. Wajnberg, D. D'Souza, S. Chacko, S. Fournier, N. Crapoulet, D.A. Barnett, et al., EBF1 drives hallmark B cell gene expression by enabling the interaction of PAX5 with the MLL H3K4 methyltransferase complex, Sci. Rep. 11 (2021) 1537.
[101] S. Beer, L.E. Wange, X. Zhang, C. Kuklik-Roos, W. Enard, W. Hammerschmidt, A. Scialdone, B. Kempkes, EBNA2-EBF1 complexes promote MYC expression and metabolic processes driving S-phase progression of Epstein-Barr virus-infected B cells, Proc. Natl. Acad. Sci. U S A 119 (2022), e2200512119.
[102] M. Busslinger, Transcriptional control of early B cell development, Annu. Rev. Immunol. 22 (2004) 55–79.
[103] P. Urbanek, Z.Q. Wang, I. Fetka, E.F. Wagner, M. Busslinger, Complete block of early B cell differentiation and altered patterning of the posterior midbrain in mice lacking Pax5/BSAP, Cell 79 (1994) 901–912.
[104] I.D.R. Revilla, I. Bilic, B. Vilagos, H. Tagoh, A. Ebert, I.M. Tamir, L. Smeenk, J. Trupke, A. Sommer, M. Jaritz, et al., The B-cell identity factor Pax5 regulates distinct transcriptional programmes in early and late B lymphopoiesis, EMBO J. 31 (2012) 3130–3146.
[105] M.L. Holmes, S. Carotta, L.M. Corcoran, S.L. Nutt, Repression of Flt3 by Pax5 is crucial for B-cell lineage commitment, Genes Dev. 20 (2006) 933–938.
[106] C. Cobaleda, W. Jochum, M. Busslinger, Conversion of mature B cells into T cells by dedifferentiation to uncommitted progenitors, Nature 449 (2007) 473–477.
[107] T.M. Johanson, A.T.L. Lun, H.D. Coughlan, T. Tan, G.K. Smyth, S.L. Nutt, R. S. Allan, Transcription-factor-mediated supervision of global genome architecture maintains B cell identity, Nat. Immunol. 19 (2018) 1257–1264.

[108] J. Medvedovic, A. Ebert, H. Tagoh, I.M. Tamir, T.A. Schwickert, M. Novatchkova, Q. Sun, P.J. Huis In 't Veld, C. Guo, H.S. Yoon, et al., Flexible long-range loops in the VH gene region of the Igh locus facilitate the generation of a diverse antibody repertoire, Immunity 39 (2013) 229–244.
[109] K. Okuyama, T. Strid, J. Kuruvilla, R. Somasundaram, S. Cristobal, E. Smith, M. Prasad, T. Fioretos, H. Lilljebjorn, S. Soneji, et al., PAX5 is part of a functional transcription factor network targeted in lymphoid leukemia, PLoS Genet. 15 (2019), e1008280.
[110] T. Miyai, J. Takano, T.A. Endo, E. Kawakami, Y. Agata, Y. Motomura, M. Kubo, Y. Kashima, Y. Suzuki, H. Kawamoto, et al., Three-step transcriptional priming that drives the commitment of multipotent progenitors toward B cells, Genes Dev. 32 (2018) 112–126.
[111] Z. Gu, M.L. Churchman, K.G. Roberts, I. Moore, X. Zhou, J. Nakitandwe, K. Hagiwara, S. Pelletier, S. Gingras, H. Berns, et al., PAX5-driven subtypes of B-progenitor acute lymphoblastic leukemia, Nat. Genet. 51 (2019) 296–307.
[112] L.N. Chan, Z. Chen, D. Braas, J.W. Lee, G. Xiao, H. Geng, K.N. Cosgun, C. Hurtz, S. Shojaee, V. Cazzaniga, et al., Metabolic gatekeeper function of B-lymphoid transcription factors, Nature 542 (2017) 479–483.
[113] L.M. Heltemes-Harris, M.J. Willette, L.B. Ramsey, Y.H. Qiu, E.S. Neeley, N. Zhang, D.A. Thomas, T. Koeuth, E.C. Baechler, S.M. Kornblau, et al., Ebf1 or Pax5 haploinsufficiency synergizes with STAT5 activation to initiate acute lymphoblastic leukemia, J. Exp. Med. 208 (2011) 1135–1149.
[114] F.M.P. Kaiser, S. Gruenbacher, M.R. Oyaga, E. Nio, M. Jaritz, Q. Sun, W. van der Zwaag, E. Kreidl, L.M. Zopf, V. Dalm, et al., Biallelic PAX5 mutations cause hypogammaglobulinemia, sensorimotor deficits, and autism spectrum disorder, J. Exp. Med. (2022) 219.
[115] S. Ma, S. Pathak, L. Trinh, R. Lu, Interferon regulatory factors 4 and 8 induce the expression of Ikaros and Aiolos to down-regulate pre-B-cell receptor and promote cell-cycle withdrawal in pre-B-cell development, Blood 111 (2008) 1396–1403.
[116] B. Morgan, L. Sun, N. Avitahl, K. Andrikopoulos, T. Ikeda, E. Gonzales, P. Wu, S. Neben, K. Georgopoulos, Aiolos, a lymphoid restricted transcription factor that interacts with Ikaros to regulate lymphocyte differentiation, EMBO J. 16 (1997) 2004–2013.
[117] A. Karnowski, C. Cao, G. Matthias, S. Carotta, L.M. Corcoran, I.L. Martensson, J. A. Skok, P. Matthias, Silencing and nuclear repositioning of the lambda5 gene locus at the pre-B cell stage requires Aiolos and OBF-1, PLoS ONE 3 (2008) e3568.
[118] M. Mandal, S.E. Powers, K. Ochiai, K. Georgopoulos, B.L. Kee, H. Singh, M. R. Clark, Ras orchestrates exit from the cell cycle and light-chain recombination during early B cell development, Nat. Immunol. 10 (2009) 1110–1117.
[119] J.H. Wang, N. Avitahl, A. Cariappa, C. Friedrich, T. Ikeda, A. Renold, K. Andrikopoulos, L. Liang, S. Pillai, B.A. Morgan, et al., Aiolos regulates B cell activation and maturation to effector state, Immunity 9 (1998) 543–553.
[120] M. Yamashita, H.S. Kuehn, K. Okuyama, S. Okada, Y. Inoue, N. Mitsuiki, K. Imai, M. Takagi, H. Kanegane, M. Takeuchi, et al., A variant in human AIOLOS impairs adaptive immunity by interfering with IKAROS, Nat. Immunol. 22 (2021) 893–903.
[121] H.S. Kuehn, J. Chang, M. Yamashita, J.E. Niemela, C. Zou, K. Okuyama, J. Harada, J.L. Stoddard, C.J. Nunes-Santos, B. Boast, et al., T and B cell abnormalities, pneumocystis pneumonia, and chronic lymphocytic leukemia associated with an AIOLOS defect in patients, J. Exp. Med. (2021) 218.
[122] K. Billot, J. Soeur, F. Chereau, I. Arrouss, H. Merle-Beral, M.E. Huang, D. Mazier, V. Baud, A. Rebollo, Deregulation of Aiolos expression in chronic lymphocytic leukemia is associated with epigenetic modifications, Blood 117 (2011) 1917–1927.
[123] H. Oguro, L. Ding, S.J. Morrison, SLAM family markers resolve functionally distinct subpopulations of hematopoietic stem cells and multipotent progenitors, Cell Stem Cell 13 (2013) 102–116.
[124] A. Zriwil, C. Boiers, T.A. Kristiansen, L. Wittmann, J. Yuan, C. Nerlov, E. Sitnicka, S.E.W. Jacobsen, Direct role of FLT3 in regulation of early lymphoid progenitors, Br. J. Haematol. 183 (2018) 588–600.
[125] J.J. Dolence, K. Gwin, E. Frank, K.L. Medina, Threshold levels of Flt3-ligand are required for the generation and survival of lymphoid progenitors and B-cell precursors, Eur. J. Immunol. 41 (2011) 324–334.
[126] K.L. Medina, Flt3 signaling in B lymphocyte development and humoral immunity, Int. J. Mol. Sci. (2022) 23.
[127] P. Tsapogas, L.K. Swee, A. Nusser, N. Nuber, M. Kreuzaler, G. Capoferri, H. Rolink, R. Ceredig, A. Rolink, In vivo evidence for an instructive role of fms-like tyrosine kinase-3 (FLT3) ligand in hematopoietic development, Haematologica 99 (2014) 638–646.
[128] L. von Muenchow, L. Alberti-Servera, F. Klein, G. Capoferri, D. Finke, R. Ceredig, A. Rolink, P. Tsapogas, Permissive roles of cytokines interleukin-7 and Flt3 ligand in mouse B-cell lineage commitment, Proc. Natl. Acad. Sci. U S A 113 (2016) E8122–E8130.
[129] A.J. Shah, E.M. Smogorzewska, C. Hannum, G.M. Crooks, Flt3 ligand induces proliferation of quiescent human bone marrow CD34+CD38- cells and maintains progenitor cells in vitro, Blood 87 (1996) 3563–3570.
[130] Y. Zhang, Y. Zhang, F. Wang, M. Wang, H. Liu, X. Chen, P. Cao, X. Ma, W. Teng, X. Zhang, et al., The mutational spectrum of FLT3 gene in acute lymphoblastic leukemia is different from acute myeloid leukemia, Cancer Gene Ther. 27 (2020) 81–88.
[131] T.E. Knight, H. Edwards, S. Meshinchi, J.W. Taub, Y. Ge, FLipping" the story: flt3-mutated acute myeloid leukemia and the evolving role of FLT3 inhibitors, Cancers (Basel) (2022) 14.
[132] A. Troilo, C. Wehr, I. Janowska, N. Venhoff, J. Thiel, J. Rawluk, N. Frede, J. Staniek, R. Lorenzetti, M.T. Schleyer, et al., Nonpermissive bone marrow environment impairs early B-cell development in common variable immunodeficiency, Blood 135 (2020) 1452–1457.
[133] S.D. Lyman, S.E. Jacobsen, c-kit ligand and Flt3 ligand: stem/progenitor cell factors with overlapping yet distinct activities, Blood 91 (1998) 1101–1134.
[134] K. Mackarehtschian, J.D. Hardin, K.A. Moore, S. Boast, S.P. Goff, I.R. Lemischka, Targeted disruption of the flk2/flt3 gene leads to deficiencies in primitive hematopoietic progenitors, Immunity 3 (1995) 147–161.
[135] T. Egawa, K. Kawabata, H. Kawamoto, K. Amada, R. Okamoto, N. Fujii, T. Kishimoto, Y. Katsura, T. Nagasawa, The earliest stages of B cell development require a chemokine stromal cell-derived factor/pre-B cell growth-stimulating factor, Immunity 15 (2001) 323–334.
[136] M. Kondo, I.L. Weissman, K. Akashi, Identification of clonogenic common lymphoid progenitors in mouse bone marrow, Cell 91 (1997) 661–672.
[137] S. Takeda, T. Shimizu, H.R. Rodewald, Interactions between c-kit and stem cell factor are not required for B-cell development in vivo, Blood 89 (1997) 518–525.
[138] Y. Matsuoka, Y. Sasaki, R. Nakatsuka, M. Takahashi, R. Iwaki, Y. Uemura, Y. Sonoda, Low level of c-kit expression marks deeply quiescent murine hematopoietic stem cells, Stem Cells 29 (2011) 1783–1791.
[139] A. Czechowicz, D. Kraft, I.L. Weissman, D. Bhattacharya, Efficient transplantation via antibody-based clearance of hematopoietic stem cell niches, Science 318 (2007) 1296–1299.
[140] J.Y. Shin, W. Hu, M. Naramura, C.Y. Park, High c-Kit expression identifies hematopoietic stem cells with impaired self-renewal and megakaryocytic bias, J. Exp. Med. 211 (2014) 217–231.
[141] R.R. Weidemann, R. Behrendt, K.B. Schoedel, W. Muller, A. Roers, A. Gerbaulet, Constitutive Kit activity triggers B-cell acute lymphoblastic leukemia-like disease in mice, Exp. Hematol. 45 (2017) 45–55, e46.
[142] J.P. Levesque, D.N. Haylock, P.J. Simmons, Cytokine regulation of proliferation and cell adhesion are correlated events in human CD34+ hemopoietic progenitors, Blood 88 (1996) 1168–1176.
[143] R.L. Driessen, H.M. Johnston, S.K. Nilsson, Membrane-bound stem cell factor is a key regulator in the initial lodgment of stem cells within the endosteal marrow region, Exp. Hematol. 31 (2003) 1284–1291.
[144] D.C. van der Plas, F. Smiers, K. Pouwels, L.H. Hoefsloot, B. Löwenberg, I.P. Touw, Interleukin-7 signaling in human B cell precursor acute lymphoblastic leukemia cells and murine BAF3 cells involves activation of STAT1 and STAT5 mediated via the interleukin-7 receptor alpha chain, Leukemia 10 (1996) 1317–1325.
[145] W.C. Chou, D.E. Levy, C.K. Lee, STAT3 positively regulates an early step in B-cell development, Blood 108 (2006) 3005–3011.
[146] K. Ochiai, M. Maienschein-Cline, M. Mandal, J.R. Triggs, E. Bertolino, R. Sciammas, A.R. Dinner, M.R. Clark, H. Singh, A self-reinforcing regulatory network triggered by limiting IL-7 activates pre-BCR signaling and differentiation, Nat. Immunol. 13 (2012) 300–307.
[147] A.J. Marshall, H.E. Fleming, G.E. Wu, C.J. Paige, Modulation of the IL-7 dose-response threshold during pro-B cell differentiation is dependent on pre-B cell receptor expression, J. Immunol. 161 (1998) 6038–6045.
[148] H.E. Fleming, C.J. Paige, Pre-B cell receptor signaling mediates selective response to IL-7 at the pro-B to pre-B cell transition via an ERK/MAP kinase-dependent pathway, Immunity 15 (2001) 521–531.
[149] B. Storch, S. Meixlsperger, H. Jumaa, The Ig-alpha ITAM is required for efficient differentiation but not proliferation of pre-B cells, Eur. J. Immunol. 37 (2007) 252–260.
[150] L. Erlandsson, S. Licence, F. Gaspal, P. Lane, A.E. Corcoran, I.L. Martensson, Both the pre-BCR and the IL-7Ralpha are essential for expansion at the pre-BII cell stage in vivo, Eur. J. Immunol. 35 (2005) 1969–1976.
[151] U. von Freeden-Jeffry, P. Vieira, L.A. Lucian, T. McNeil, S.E. Burdach, R. Murray, Lymphopenia in interleukin (IL)-7 gene-deleted mice identifies IL-7 as a nonredundant cytokine, J. Exp. Med. 181 (1995) 1519–1526.
[152] J.J. Peschon, P.J. Morrissey, K.H. Grabstein, F.J. Ramsdell, E. Maraskovsky, B. C. Gliniak, L.S. Park, S.F. Ziegler, D.E. Williams, C.B. Ware, et al., Early lymphocyte expansion is severely impaired in interleukin 7 receptor-deficient mice, J. Exp. Med. 180 (1994) 1955–1960.
[153] M.R. Clark, M. Mandal, K. Ochiai, H. Singh, Orchestrating B cell lymphopoiesis through interplay of IL-7 receptor and pre-B cell receptor signalling, Nat. Rev. Immunol. 14 (2014) 69–80.
[154] P. Tsapogas, S. Zandi, J. Åhsberg, J. Zetterblad, E. Welinder, J.I. Jönsson, R. Månsson, H. Qian, M. Sigvardsson, IL-7 mediates Ebf-1-dependent lineage restriction in early lymphoid progenitors, Blood 118 (2011) 1283–1290.
[155] S. Malin, S. McManus, C. Cobaleda, M. Novatchkova, A. Delogu, P. Bouillet, A. Strasser, M. Busslinger, Role of STAT5 in controlling cell survival and immunoglobulin gene recombination during pro-B cell development, Nat. Immunol. 11 (2010) 171–179.
[156] C. Fistonich, S. Zehentmeier, J.J. Bednarski, R. Miao, H. Schjerven, B. P. Sleckman, J.P. Pereira, Cell circuits between B cell progenitors and IL-7(+) mesenchymal progenitor cells control B cell development, J. Exp. Med. 215 (2018) 2586–2599.
[157] B. Heizmann, P. Kastner, S. Chan, Ikaros is absolutely required for pre-B cell differentiation by attenuating IL-7 signals, J. Exp. Med. 210 (2013) 2823–2832.
[158] S. Ma, S. Pathak, M. Mandal, L. Trinh, M.R. Clark, R. Lu, Ikaros and Aiolos inhibit pre-B-cell proliferation by directly suppressing c-Myc expression, Mol. Cell Biol. 30 (2010) 4149–4158.
[159] B. Heizmann, S. Le Gras, C. Simand, P. Marchal, S. Chan, P. Kastner, Ikaros antagonizes DNA binding by STAT5 in pre-B cells, PLoS ONE 15 (2020), e0242211.
[160] M. Mandal, S.E. Powers, M. Maienschein-Cline, E.T. Bartom, K.M. Hamel, B. L. Kee, A.R. Dinner, M.R. Clark, Epigenetic repression of the Igk locus by STAT5-

mediated recruitment of the histone methyltransferase Ezh2, Nat. Immunol. 12 (2011) 1212–1220.
[161] S. Giliani, L. Mori, G. de Saint Basile, F. Le Deist, C. Rodriguez-Perez, C. Forino, E. Mazzolari, S. Dupuis, R. Elhasid, A. Kessel, et al., Interleukin-7 receptor alpha (IL-7Ralpha) deficiency: cellular and molecular bases, Analysis of clinical, immunological, and molecular features in 16 novel patients, Immunol. Rev. 203 (2005) 110–126.
[162] B.N. Dittel, T.W. LeBien, The growth response to IL-7 during normal human B cell ontogeny is restricted to B-lineage cells expressing CD34, J. Immunol. 154 (1995) 58–67.
[163] S.E. Johnson, N. Shah, A.A. Bajer, T.W. LeBien, IL-7 activates the phosphatidylinositol 3-kinase/AKT pathway in normal human thymocytes but not normal human B cell precursors, J. Immunol. 180 (2008) 8109–8117.
[164] K. Kikuchi, M. Kondo, Developmental switch of mouse hematopoietic stem cells from fetal to adult type occurs in bone marrow after birth, Proc. Natl. Acad. Sci. U S A 103 (2006) 17852–17857.
[165] M.B. Rother, K. Jensen, M. van der Burg, F.S. van de Bovenkamp, R. Kroek, I.W. F. van, V.H. van der Velden, T. Cupedo, O.K. Olstad, J.J. van Dongen, et al., Decreased IL7Rα and TdT expression underlie the skewed immunoglobulin repertoire of human B-cell precursors from fetal origin, Sci. Rep. 6 (2016) 33924.
[166] J. Ahsberg, P. Tsapogas, H. Qian, J. Zetterblad, S. Zandi, R. Mansson, J.I. Jonsson, M. Sigvardsson, Interleukin-7-induced Stat-5 acts in synergy with Flt-3 signaling to stimulate expansion of hematopoietic progenitor cells, J. Biol. Chem. 285 (2010) 36275–36284.
[167] A.R.M. Almeida, J.L. Neto, A. Cachucho, M. Euzébio, X. Meng, R. Kim, M. B. Fernandes, B. Raposo, M.L. Oliveira, D. Ribeiro, et al., Interleukin-7 receptor α mutational activation can initiate precursor B-cell acute lymphoblastic leukemia, Nat. Commun. 12 (2021) 7268.
[168] C.D.S. Katerndahl, L.M. Heltemes-Harris, M.J.L. Willette, C.M. Henzler, S. Frietze, R. Yang, H. Schjerven, K.A.T. Silverstein, L.B. Ramsey, G. Hubbard, et al., Antagonism of B cell enhancer networks by STAT5 drives leukemia and poor patient survival, Nat. Immunol. 18 (2017) 694–704.
[169] P.P. Zenatti, D. Ribeiro, W. Li, L. Zuurbier, M.C. Silva, M. Paganin, J. Tritapoe, J. A. Hixon, A.B. Silveira, B.A. Cardoso, et al., Oncogenic IL7R gain-of-function mutations in childhood T-cell acute lymphoblastic leukemia, Nat. Genet. 43 (2011) 932–939.
[170] A. Casado-Garcia, M. Isidro-Hernandez, N. Oak, A. Mayado, C. Mann-Ran, J. Raboso-Gallego, S. Aleman-Arteaga, A. Buhles, D. Sterker, E.G. Sanchez, et al., Transient inhibition of the JAK/STAT pathway prevents B-ALL development in genetically predisposed mice, Cancer Res. 82 (2022) 1098–1109.
[171] R. van Vollenhoven, E.B. Lee, S. Strengholt, C. Mojcik, H. Valdez, S. Krishnaswami, P. Biswas, I. Lazariciu, A. Hazra, J.D. Clark, et al., Evaluation of the short-, mid-, and long-term effects of tofacitinib on lymphocytes in patients with rheumatoid arthritis, Arthritis Rheumatol. 71 (2019) 685–695.
[172] M. Rizzi, R. Lorenzetti, K. Fischer, J. Staniek, I. Janowska, A. Troilo, V. Strohmeier, M. Erlacher, M. Kunze, B. Bannert, et al., Impact of tofacitinib treatment on human B-cells in vitro and in vivo, J. Autoimmun. 77 (2017) 55–66.
[173] A. Cordeiro Gomes, T. Hara, V.Y. Lim, D. Herndler-Brandstetter, E. Nevius, T. Sugiyama, S. Tani-Ichi, S. Schlenner, E. Richie, H.R. Rodewald, et al., Hematopoietic stem cell niches produce lineage-instructive signals to control multipotent progenitor differentiation, Immunity 45 (2016) 1219–1231.
[174] M. Mandal, M.K. Okoreeh, D.E. Kennedy, M. Maienschein-Cline, J. Ai, K. C. McLean, N. Kaverina, M. Veselits, I. Aifantis, F. Gounari, et al., CXCR4 signaling directs Igk recombination and the molecular mechanisms of late B lymphopoiesis, Nat. Immunol. 20 (2019) 1393–1403.
[175] E. Jimi, R.J. Phillips, M. Rincon, R. Voll, H. Karasuyama, R. Flavell, S. Ghosh, Activation of NF-kappaB promotes the transition of large, CD43+ pre-B cells to small, CD43- pre-B cells, Int. Immunol. 17 (2005) 815–825.
[176] J.P. Pereira, J. An, Y. Xu, Y. Huang, J.G. Cyster, Cannabinoid receptor 2 mediates the retention of immature B cells in bone marrow sinusoids, Nat. Immunol. 10 (2009) 403–411.
[177] T.C. Beck, A.C. Gomes, J.G. Cyster, J.P. Pereira, CXCR4 and a cell-extrinsic mechanism control immature B lymphocyte egress from bone marrow, J. Exp. Med. 211 (2014) 2567–2581.
[178] T. Alves da Costa, J.N. Peterson, J. Lang, J. Shulman, X. Liang, B.M. Freed, S. A. Boackle, P. Lauzurica, R.M. Torres, R. Pelanda, Central human B cell tolerance manifests with a distinctive cell phenotype and is enforced via CXCR4 signaling in hu-mice, Proc. Natl. Acad. Sci. U S A (2021) 118.
[179] W.C. Liles, H.E. Broxmeyer, E. Rodger, B. Wood, K. Hubel, S. Cooper, G. Hangoc, G.J. Bridger, G.W. Henson, G. Calandra, et al., Mobilization of hematopoietic progenitor cells in healthy volunteers by AMD3100, a CXCR4 antagonist, Blood 102 (2003) 2728–2730.
[180] H.E. Broxmeyer, C.M. Orschell, D.W. Clapp, G. Hangoc, S. Cooper, P.A. Plett, W. C. Liles, X. Li, B. Graham-Evans, T.B. Campbell, et al., Rapid mobilization of murine and human hematopoietic stem and progenitor cells with AMD3100, a CXCR4 antagonist, J. Exp. Med. 201 (2005) 1307–1318.
[181] Y.S. Tzeng, H. Li, Y.L. Kang, W.C. Chen, W.C. Cheng, D.M. Lai, Loss of Cxcl12/Sdf-1 in adult mice decreases the quiescent state of hematopoietic stem/progenitor cells and alters the pattern of hematopoietic regeneration after myelosuppression, Blood 117 (2011) 429–439.
[182] S. Majumdar, P.M. Murphy, Adaptive Immunodeficiency in WHIM Syndrome, Int. J. Mol. Sci. (2018) 20.
[183] D.C. Dale, A.A. Bolyard, M.L. Kelley, E.C. Westrup, V. Makaryan, A. Aprikyan, B. Wood, F.J. Hsu, The CXCR4 antagonist plerixafor is a potential therapy for myelokathexis, WHIM syndrome, Blood 118 (2011) 4963–4966.
[184] S. Konoplev, J.L. Jorgensen, D.A. Thomas, E. Lin, J. Burger, H.M. Kantarjian, M. Andreeff, L.J. Medeiros, M. Konopleva, Phosphorylated CXCR4 is associated with poor survival in adults with B-acute lymphoblastic leukemia, Cancer 117 (2011) 4689–4695.
[185] A.O. Khan, A. Rodriguez-Romera, J.S. Reyat, A.A. Olijnik, M. Colombo, G. Wang, W.X. Wen, N. Sousos, L.C. Murphy, B. Grygielska, et al., Human bone marrow organoids for disease modelling, discovery and validation of therapeutic targets in hematological malignancies, Cancer Discov. (2022).
[186] S. Giger, M. Hofer, M. Miljkovic-Licina, S. Hoehnel, N. Brandenberg, R. Guiet, M. Ehrbar, E. Kleiner, K. Gegenschatz-Schmid, T. Matthes, et al., Microarrayed human bone marrow organoids for modeling blood stem cell dynamics, APL Bioeng. 6 (2022), 036101.
[187] M. Tan, R. Fong, M. Lo, R. Young, Lenalidomide and secondary acute lymphoblastic leukemia: a case series, Hematol. Oncol. 35 (2017) 130–134.
[188] Y. Zhuang, P. Soriano, H. Weintraub, The helix-loop-helix gene E2A is required for B cell formation, Cell 79 (1994) 875–884.
[189] R. Lewis, H.C. Maurer, N. Singh, I. Gonzalez-Menendez, M. Wirth, M. Schick, L. Zhang, K. Isaakidis, A.K. Scherger, V. Schulze, et al., CXCR4 hyperactivation cooperates with TCL1 in CLL development and aggressiveness, Leukemia 35 (2021) 2895–2905.
[190] K. Balabanian, E. Brotin, V. Biajoux, L. Bouchet-Delbos, E. Lainey, O. Fenneteau, D. Bonnet, L. Fiette, D. Emilie, F. Bachelerie, Proper desensitization of CXCR4 is required for lymphocyte development and peripheral compartmentalization in mice, Blood 119 (2012) 5722–5730.
[191] J.D. Buenrostro, M.R. Corces, C.A. Lareau, B. Wu, A.N. Schep, M.J. Aryee, R. Majeti, H.Y. Chang, W.J. Greenleaf, Integrated single-cell analysis maps the continuous regulatory landscape of human hematopoietic differentiation, Cell 173 (2018) 1535–1548, e1516.
[192] S. Doulatov, F. Notta, K. Eppert, L.T. Nguyen, P.S. Ohashi, J.E. Dick, Revised map of the human progenitor hierarchy shows the origin of macrophages and dendritic cells in early lymphoid development, Nat. Immunol. 11 (2010) 585–593.
[193] F.M.P. Kaiser, I. Janowska, R. Menafra, M. de Gier, J. Korzhenevich, I. Pico-Knijnenburg, I. Khatri, A.S. Schulz, T.W. Kuijpers, A.C. Lankester, L. Konstantinidis, M. Erlacher, S.L. Kloet, P.A. van Schouwenburg, M. Rizzi, M. van der Burg, IL-7 receptor signaling drives human B-cell progenitor differentiation and expansion, Blood (2023) 2023019721.