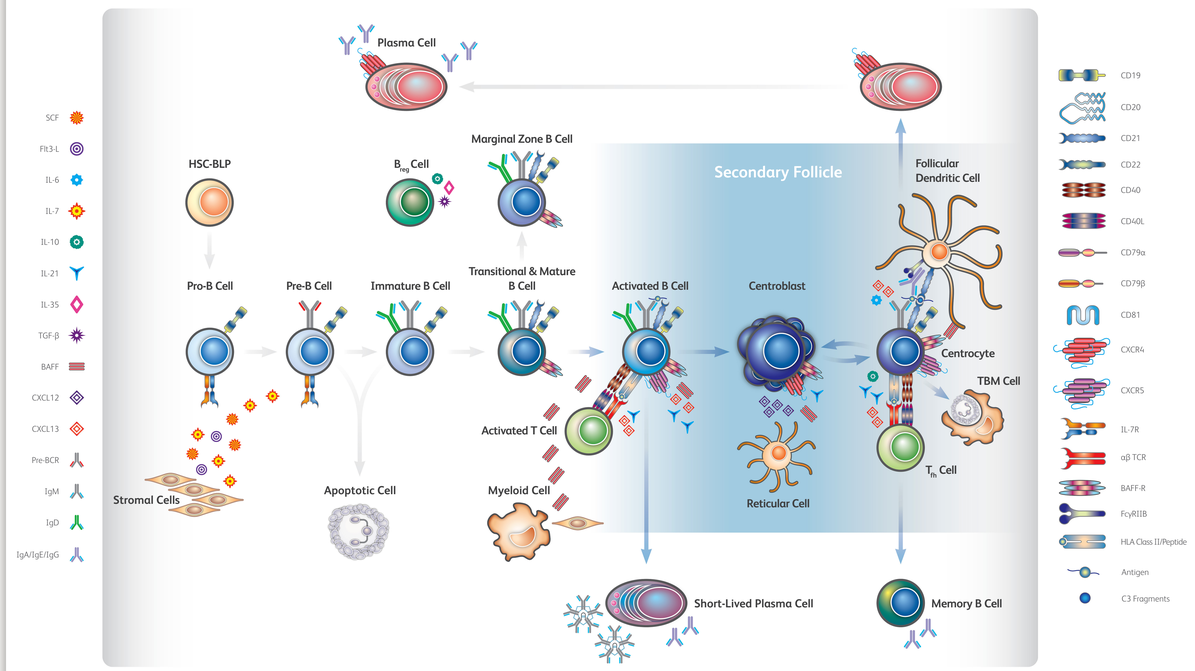
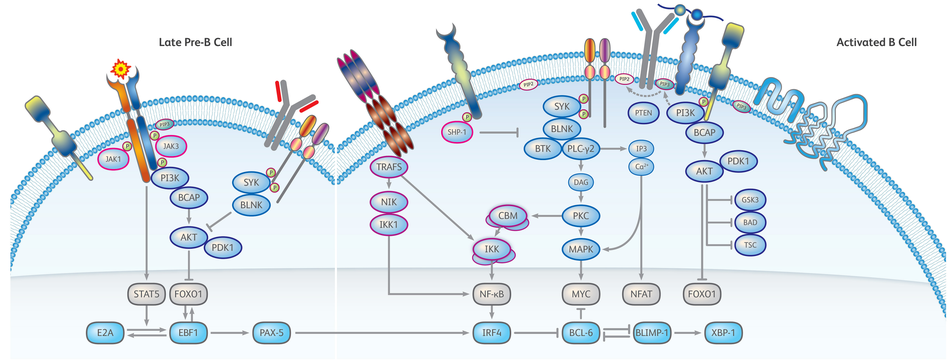
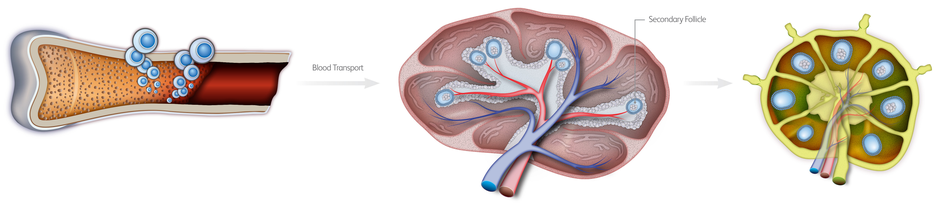
# Origin of Normal and Neoplastic B Cells

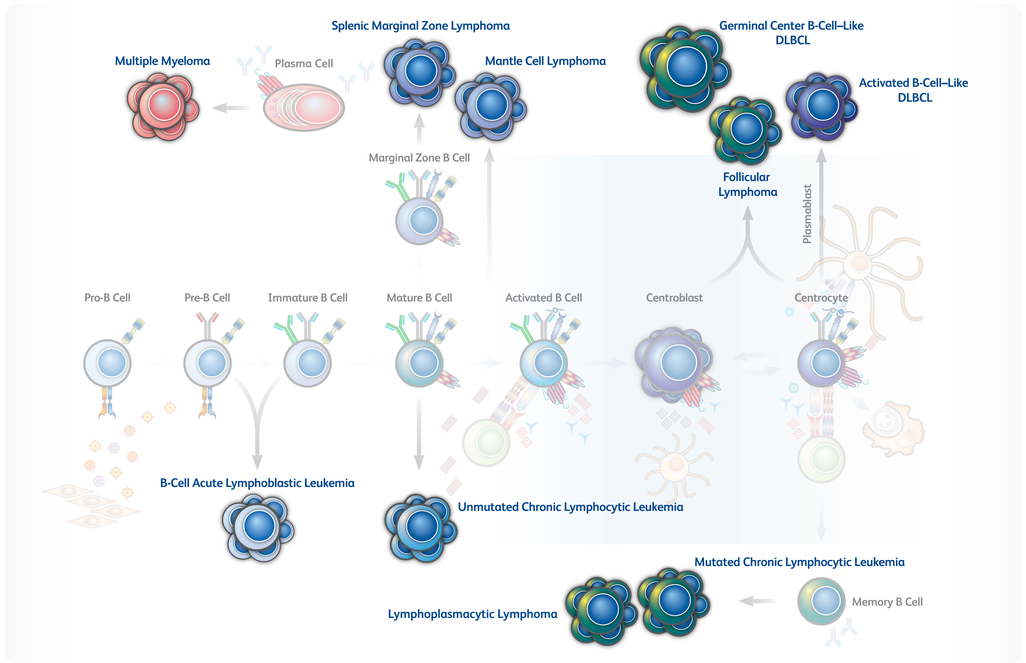
## B-Cell Maturation and Activation

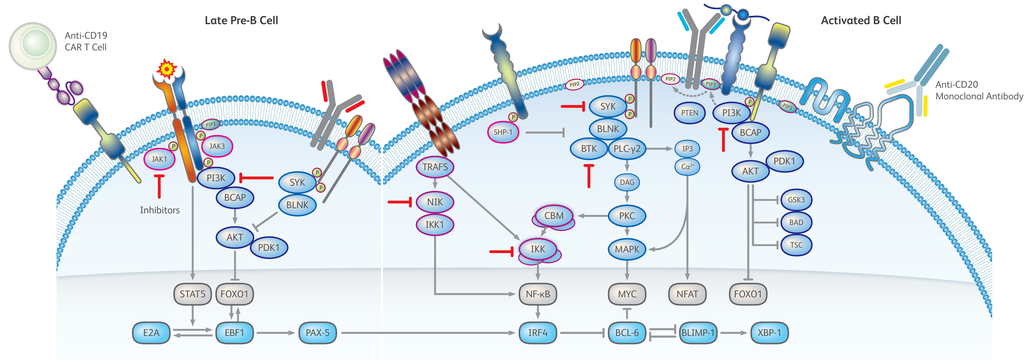


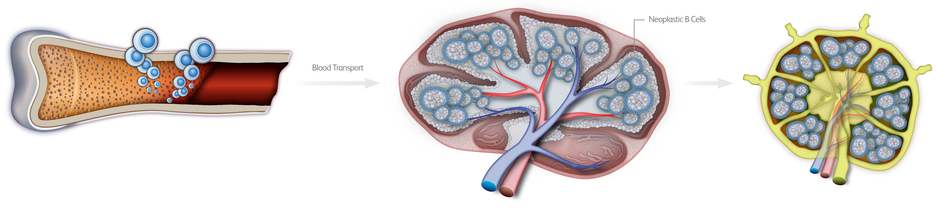




## B-Cell Transformation




## Normal B Cells

B-cell development and differentiation occurs in a stepwise process that is initiated in the fetal liver and postnatal bone marrow and continues in the peripheral lymphoid organs upon encounter with antigens. A regulatory circuit composed of surface receptors, signaling proteins and transcription factors controls the various stages of B-cell differentiation and function. Aberrant expression or deregulated activity of such components can affect B-cell lymphopoiesis and often results in malignant transformation.

### B-cell development in the bone marrow

#### Pro-B Cells and Pre-B Cells: IL-7R and Pre-BCR Signaling

Activate JAK-STAT5 and PI3K-AKT pathways and initiate the transcriptional programs that control B-cell development, survival and proliferation: Ikaros, Aiolos, E2A, EBF, PAX-5, FOXO1, IRF4, IRF8

- Regulation of recombination-activating genes (*RAG1, RAG2*), terminal deoxynucleotidyl transferase (*DNTT, Tdt*); B-cell genes [*CD19, CD79A, CD79B, VPREB1, IGLL1/λ5* surrogate light chain), *BLNK, BTK*); BCL2 family genes [*BCL2, BCL2L1 (BCL-XL), MCL1*, and *BCL2L11 (BIM)*]; and cell cycle regulators
- Repression of B-lineage non-appropriate genes: *CEBPA, ID2, FLT3, CSF1R*
- Clonal expansion of large pre-B cells
- Cell cycle exit enabling *V(D)J* and *VJ* rearrangements of immunoglobulin μ heavy-chain and light-chain genes, respectively
- Elimination of cells expressing truncated pre-B cell receptor (BCR) or BCR at the pre-B cell or immature B-cell stage, respectively

#### Immature B Cells: BCR Complex "Tonic" Signaling

Activate PI3K-AKT and MAPK pathways and enable selection of the BCR repertoire and migration of B cells to peripheral tissues

- Inactivation or apoptosis of self-reactive cells. Alternatively, induction of receptor editing to change BCR specificity and rescue B cells from apoptosis
- A discrete subset of B cells with regulatory functions ($B_{reg}$) presents a similar phenotype as immature B cells and secretes anti-inflammatory cytokines

### B-cell maturation and differentiation in peripheral tissues

#### Mature Naive B Cells: BCR Complex "Tonic" Signaling and BAFF-R Signaling

Activate PI3K-AKT, MAPK and NF-κB pathways and control B cell homeostasis and further maturation into mature B-cell subsets

- Regulation of the balance between anti-apoptotic [*BCL2, BCL2L1 (BCL-XL), MCL1, BCL2A1*] and pro-apoptotic [*BCL2L11 (BIM), BAD*] gene-encoded factors

#### Activated B Cells: BCR Complex, Co-receptors and Cytokine Receptors Signaling

Activate PI3K-AKT, MAPK and NF-κB pathways upon engagement with cognate antigen and drive the transcription programs that control terminal B-cell differentiation and functions

- Antigen-stimulated B cells can either migrate to extrafollicular areas of lymphoid tissues and produce low-affinity antibodies or enter into germinal center (GC) reactions to generate high-affinity cells
- Co-ligation of the CD19/CD21/CD81 complex with the BCR synergistically enhances phospholipid metabolism, $Ca^{2+}$ mobilization and the activity of downstream protein kinase targets. Complement-tagged antigens further enhance BCR activation
- Inhibitory receptors (CD22, FcγRIIB) control kinase activity and B-cell homeostasis
- Follicular dendritic cells retain large amounts of complement-tagged immunocomplexes, facilitating the capture of antigens by B cells
- Processing and antigen presentation to follicular helper T ($T_{fh}$) cells induce the expression of activation-induced cytidine deaminase (AID), which drives class-switch recombination and somatic hypermutation (SHM) of immunoglobulin genes
- T-cell help via CD40-CD40L engagement is essential for AID expression. ICOS-ICOSL and other receptor interactions are also crucial in GC reactions
- Bcl-6 ensures genomic stability by repressing genes of DNA damage responses during B-cell centroblast proliferation in the dark zone of the secondary follicle
- Resting B cells in the light zone (centrocytes) receive signals to repress *BCL6* expression and activate MYC and other transcription factors involved in further cell differentiation
- Following several rounds of SHM and $T_{fh}$-mediated selection, high-affinity B cells exit the secondary follicle fully differentiated into class-switched memory cells or plasma cells
- B cells expressing low-affinity receptors undergo apoptosis and can be phagocytosed by tingible body macrophages (TBMs), which may also process and present immunocomplexes, helping in the regulation of GC reactions

## Neoplastic B Cells

By virtue of the requirements for somatic antibody diversity and correct rearrangements of immunoglobulin genes, B cells can accumulate deleterious mutations that may cause genome instability. Such "off-target" alterations in B-cell proliferation or apoptosis can lead to overgrowth in peripheral tissues, a hallmark of B-cell leukemias and lymphomas. B-cell neoplasms often resemble normal stages of B-cell differentiation, and extensive characterization of normal B-cell subsets has enabled proper classification of these malignancies. Progress in biology knowledge has also resulted in a large number of targeted therapies designed against surface markers, cell signaling pathways and key molecules involved in cellular metabolism, cell cycle and apoptosis.

### Common oncogenic lesions and targeted therapies in B-cell neoplasms

#### B-Cell Acute Lymphoblastic Leukemia

- t(12;21), t(9;22) translocations
- Mutations in *CRLF2, MLL, JAK, IKZF1, PAX5, FLT3*
- JAK, PI3K6 inhibitors; Anti-CD19, Anti-CD22 CAR T cells

#### Splenic Marginal Zone B-Cell Lymphoma

- 7q deletion or translocation
- Mutations in *NOTCH2, NF-κB* signaling genes, *KLF2*
- BTK, PI3K6 inhibitors; Anti-CD20 monoclonal antibody (mAb)

#### Mantle Cell Lymphoma

- t(11;14) translocation enhances *CCND1* expression
- Mutations in *MLL2, ATM, TP53, TRAF2, NOTCH1*
- SYK, BTK, NIK, PI3K6 inhibitors; Anti-CD20 mAb

#### Follicular Lymphoma

- t(14;18) translocation enhances *BCL2* expression
- Mutations in *MLL2, BCL6*
- BTK, PI3K6 inhibitors; Anti-CD20 mAb

#### Activated B-Cell–Like Diffuse Large B-Cell Lymphoma (ABC-DLBCL)

- *BCL6* translocation
- Mutations in *MLL2, FOXO1, NF-κB, CD79A/B, MYD88, CARD11, PRDM1*
- NF-κB inhibitors, BTK, PI3K6 inhibitors; Anti-CD20 mAb

#### Germinal Center B-Cell–Like Diffuse Large B-Cell Lymphoma (GCB-DLBCL)

- *MYC* and *BCL2* translocations
- Mutations in *EZH2, PTEN, GNA13, miR17-92, TP53*
- SYK, PI3K6, BET, CXCR4, Bcl-2 inhibitors; Anti-CD20 mAb

#### Unmutated and Mutated B-Cell Chronic Lymphocytic Leukemias

- 17p deletion, 11q deletion and 13q deletion
- Mutations in *ATM, TP53, BIRC3, SF3B1, CCND1, NOTCH1, KLHL6*
- SYK, BTK, PI3K6 inhibitors; Anti-CD20 mAb

#### Lymphoplasmacytic Lymphoma (Waldenstrom Macroglobulinemia)

- 6q deletion and trisomy 4
- Mutations in *MYD88, CXCR4, ARID1A*
- BTK inhibitors; proteasome inhibitors; Anti-CD20 mAb

#### Multiple Myeloma

- t(11;14) translocation
- Mutations in *NF-κB* signaling genes, *BRAF, FCRL4, CCND1, MAF, FGFR3, IRF4*
- Proteasome inhibitors; histone deacetylase inhibitors; immunomodulators; Anti-CD38 mAb, Anti-SLAMF7 mAb

### Abbreviations:

αβ **TCR**, alpha-beta T-cell receptor; **AKT**, protein kinase B; **BAD**, Bcl-2-associated death promoter; **BAFF-R**, CD268, B-cell activating factor receptor; **BCAP**, B-cell adaptor for PI3K; **BCR**, B cell receptor; **BLIMP-1**, PRDM1, PR domain zinc finger protein 1; **BLNK**, B-cell linker protein; **BTK**, Bruton's tyrosine kinase; **C3**, complement component 3; **CBM**, CARMA1-BCL10-MALT1 signalosome complex; **CXCR4**, CD184; **CXCR5**, CD185; **DAG**, diacylglycerol; **E2A**, TCF3, transcription factor 3; **EBF1**, early B-cell factor 1; **FcγRIIB**, low-affinity Ig Fc receptor II-B; **Flt3-L**, Fms-related tyrosine kinase 3 ligand; **FOXO1**, Forkhead box protein O1; **GSK3**, glycogen synthase kinase 3; **HLA** Class II, human leukocyte antigen; **HSC-BLP**, hematopoietic stem cell and B-cell lymphoid progenitor; **IKK1**, inhibitor of NF-κB kinase subunit alpha; **IP3**, inositol trisphosphate; **IRF4**, interferon regulatory factor 4; **JAK**, janus kinase; **MAPK**, A mitogen-activated protein kinase; **MYC**, avian myelocytomatosis viral oncogene homolog; **NFAT**, nuclear factor of activated T-cells; **NF-κB**, nuclear factor kappa-light-chain-enhancer of activated B cells; **NIK**, mitogen-activated protein kinase, **MCSF-R**, macrophage colony-stimulating factor receptor; **PAX-5**, paired box protein 5; **PDK1**, pyruvate dehydrogenase lipoamide kinase isozyme 1; **PI3K**, phosphatidylinositol-4, 5-bisphosphate 3-kinase; **PIP2**, phosphatidylinositol 4,5-bisphosphate; **PIP3**, phosphatidylinositol (3,4,5)-trisphosphate; **PKC**, protein kinase C; **PLC-γ2**, 1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma-2; **PTEN**, phosphatase and tensin homolog; **SCF**, stem cell factor; **SHP-1**, tyrosine-protein phosphatase non-receptor type 6; **STAT5**, signal transducer and activator of transcription 5; **SYK**, spleen tyrosine kinase; **TGF-β**, transforming growth factor beta; **TBM**, tingible body macrophage; **TRAFs**, tumor necrosis factor receptor-associated factors; **TSC**, tuberous sclerosis proteins 1,2; **XBP-1**, X-box-binding protein 1


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