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The curious origins of Angioimmunoblastic T-Cell Lymphoma

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Abstract

Purpose of review—Once and obscure disease, recent studies have transformed our understanding of angioimmunoblastic T-cell lymphoma (AITL). In this review we summarize new major advances in the genetics and biology of AITL.

Recent findings—Genome wide sequencing studies have dissected the repertoire of the genetic alterations driving AITL uncovering a highly recurrent Gly17Val somatic mutation in the small GTPase RHOA and major role for mutations in epigenetic regulators, such as *TET2, DNMT3A* and *IDH2*, and signaling factors (e.g. FYN and CD28). These findings support a multistep model of follicular T helper cell transformation in AITL and pinpoint novel candidates for the development of targeted therapies in this disease.

Summary—AITL originates from follicular T helper cells and is characterized by the presence of RHOA G17V mutation together with genetic alterations in TET2, DNMT3A and IDH2. Research efforts now focus on the elucidation of the specific roles and interplay of these genetic alterations in the pathogenesis of AITL.

Keywords

Angioimmunoblastic T cell lymphoma; follicular T helper cell; RHOA; TET2; DNMT3A

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a clinically aggressive lymphoma derived from the malignant transformation of follicular T-helper (TFH) cells. AITL affects mostly elderly adults and accounts for 20% of peripheral T-cell lymphomas (1). Despite intensive therapy, 5 year overall survival rates in AITL are only about 30% (2), with little progress in the last two decades (3). However, recent studies have shed new light on the pathophysiology and genetics of this disease opening the field for the development of novel animal models and targeted therapies. Here we review the most recent advances on normal normal TFH cell development and the genetics of AITL.

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Conflicts of interest

There are no conflicts of interest.

Gene expression profiling insights in the classification and biology of AITL

Peripheral T-cell lymphomas are a highly heterogeneous and relatively poorly defined group of mature T-cell malignancies. Limitations in diagnosis and classification represent a clinical challenge that affects therapeutic options and clinical management. Systematic efforts to improve the classification of PTCLs using gene expression profiling has been instrumental in defining distinct molecular groups of PTCL and has provided new information on the pathobiology of these tumors (4–12).

Transcriptional characterization of PTCL tumor samples and their normal lymphocyte counterparts identified a unique transcriptional profile for AITL (7, 8). Importantly, this AITL-associated signature can be found in about 20% of tumors diagnosed as PTCL not otherwise specified (PTCL NOS) supporting that gene expression profiling provides a more accurate classification than histology for the diagnosis of PTCL (12–14). In addition, AITL gene expression programs reflect an important contribution of the tumor microenvironment and are enriched in B-cell and follicular dendritic cell (15). In this context, the AITL B-cell signature seems to be associated with a better outcome, while signatures related to immunosuppression could be linked to poor clinical outcome (13). Moreover, it is worth noting that AITL tumors show high levels of expression of VEGF, which may play a pathogenic role driving angiogenesis and stimulating lymphoma cell growth via autocrine or paracrine loops (16).

However, the most prominent finding of gene expression studies on the pathophysiology of AITL was the discovery of the cellular derivation of TFH cells, a subset of CD4+ T helper cells residing in the follicular centers, as the normal cellular counterpart of malignant AITL cells. This way, even though a relationship between AITL tumors cells and TFHs was first proposed based on the expression of the chemokine CXCL13 in AITLs samples (17, 18), this was ultimately and most clearly substantiated by gene expression studies, which established a close similarity between the expression signatures of TFH cells and AITL tumor biopsies (7, 8). In addition to *CXCL13*, TFH-characteristic genes highly expressed in AITL include the CD28-related inducible T-cell co-stimulator *ICOS, CD154, CD40L* and *NFATC1* (7, 18).

TFH development and AITL

TFH cells were initially described as a separate CD4+ T-cell population characterized by high levels of expression of the chemokine receptor CXCR5 (19–21). Since then, TFH have emerged as a distinct subset of effector T helper cells with a characteristic gene expression signature and functionally separate from other known CD4 T-cell subsets (22–24). TFHs are required for germinal center formation and play important roles in germinal center B-cell differentiation and survival and in the development of long-lived plasma cells and memory T-cells (25).

TFH cell differentiation is initiated by the interaction of a naïve CD4+ T-lymphocyte with dendritic cells in a developing germinal center (26) (Figure 1). This interaction involves the activation of ICOS in the T-cell (27, 28), and the consequent activation of the PI3K pathway,

which leads to expression of the BCL6 transcription factor, a critical regulator of TFH development (29–31). The master regulator role of BCL6 in TFH development is demonstrated by the failure of *Bcl6*−/− cells to differentiate into TFH cells *in vivo* (32, 33). Moreover, constitutive expression of Bcl6 enhances T cell differentiation towards the TFH lineage (32, 34) and transcriptional repression defective forms of BCL6 block TFH cells differentiation (35). Although the precise mechanisms operating downstream of Bcl6 are not fully clarified yet, this transcriptional repressor seems to participate in the restriction of alternative cell fates during TFH cell development via repression of critical factors implicated in Th1 (T-bet), Th2 (GATA3) and Th17 (RORγt) development (31, 32, 35, 36). Following ICOS activation and induction of BCL6 expression, activated T cells upregulate the expression of PD1 and CXCR5 becoming TFH precursors, which migrate to the border of the B-cell follicle to engage in secondary cell-cell interactions with antigen-specific B-cells (32, 37). Then, and as antigen stimulation builds up a germinal center reaction, these precursors complete maturation and acquire a definitive TFH phenotype characterized by expression of high levels of CXCR5, PD1, BCL6, MAF and SAP (37) (Figure 1). In addition to BCL6, TFH development depends on multiple other transcription factors including ASCL2, c-MAF, IRF4, and AP-1 (25, 32, 33, 35, 38–40). Moreover, in addition to ICOS engagement, activation of JAK-STAT signaling by IL6, IL21 and IL12 play important roles in TFH cell development (25, 41–47).

Genomic analysis of AITL

Genomic profiling studies have started to dissect the repertoire of genetic alterations driving the pathogenesis of AITL and PTCL, NOS tumors. These studies have already uncovered a major role for mutations in the small GTPase *RHOA* and in epigenetic factor genes – including *TET2, DNMT3A* and *IDH2*– in the pathogenesis of these tumors and pointed to additional relevant pathways in these diseases.

The RHOA G17V mutation in AITL

The RHOA small GTPase protein regulates multiple biological processes, including cytoskeleton remodeling, cell adhesion, migration, proliferation and survival (48, 49). As other small GTPases, RHOA cycles between an active GTP-bound state and an inactive GDP-bound configuration. RHOA activation is catalyzed by RHO GEFs (Guanine Nucleotide Exchange Factors), which facilitate the incorporation of GTP. Conversely, RHOA GAPs (GTPase Activating Proteins), which stimulate the conversion of GTP to GDP to promote the transition of the RHOA protein to the inactive state (48, 49). Early studies using transgenics expressing dominant negative forms of RHOA or suppressing RhoA via expression of the exoenzyme C3 transferase, an ADP ribosyl transferase that selectively ribosylates and inactivates RhoA, RhoB and RhoC proteins, pointed to an essential role for RHOA in multiple T-cell functions including polarization, migration and signaling through the TCR (50–54). Moreover, RHOA inactivation causes a developmental blockade during thymocyte progression (55–57) and inactivation of RhoA in the thymus has been linked to development of T-cell lymphomas (58). More recently, the analysis of conditional *RhoA* knockout mice has demonstrated a role of RhoA in thymocyte proliferation and survival, beta-selection, positive selection, early single positive lineage commitment, and notably,

mitochondrial function (59). Moreover, altered Rho GTPase activity has been linked with the development of autoimmunity (60), one of the hallmarks of AITL.

A central role of RHOA in the pathogenesis of AITL is supported by the identification of recurrent, highly prevalent heterozygous missense mutations in the *RHOA* gene in about 70% of AITLs (61–66). Among these, the RHOA G17V allele accounts for over 90% of RHOA mutations in AITL (61–63) (Figure 2). Biochemical analysis and cellular assays demonstrated that the RHOA G17V mutant does not bind GTP and functions as an inactive and dominant negative protein which interferes with the activity of wild type RHOA (61–63), most probably by sequestering and interfering with the activity of RHOA GEFs (61). The RHOA G17V mutation is highly characteristic of AITL. Thus, presence of RHOA G17V mutation in about 25% of PTCL NOS cases suggests that these tumors probably represent misdiagnosed AITLs (61). However, RHOA mutations have also been identified in Burkitt lymphoma, gastric carcinoma, and adult T-cell leukemia lymphoma samples (67–70).

Mutations in epigenetic regulators: *TET2, DNMT3A* and *IDH2*

Mutations in *TET2, DNMT3A* and *IDH2* are common in hematological malignancies. Originally described in myeloid malignancies, they were subsequently found in PTCL, being especially high in AITL and in a subgroup of PTCL, NOS with TFH features (71–73). Mutations in these epigenetic regulators are strongly associated with the expression of the *RHOA G17V allele*. In fact, analysis of 120 AITL samples from published data identifies mutations in at least one of these genes in 94% of *RHOA G17V* positive cases (Figure 3).

The Ten-Eleven Translocation 2 (*TET2*) encodes a 2 oxoglutarate/Fe^{2+}–dependent oxygenase that participates in the epigenetic control of gene expression through the oxidation of methylated cytosines and DNA demethylation by catalyzing the oxidation of DNA 5-methylcytosine to 5-hydroxymethylcytosine (74–76). *TET2* was originally identified as a tumor suppressor in myeloid malignancies (77, 78); however, several later studies have also demonstrated a high frequency of loss of function mutations in *TET2* in 70–80% of PTCLs (61, 62, 72, 79, 80), being particularly prevalent in AITL and PTCL, NOS (Figure 2). In PTCL, *TET2* mutations are associated with advanced stage disease, adverse clinical parameters at presentation and shorter progression free survival (80).

The role of loss of function mutations in *Tet2* has been investigated using mouse models, which showed that loss of *Tet2* leads to higher frequency of hematopoietic stem cells, increased competitive repopulation abilities and biased differentiation towards the myeloid lineage (71, 81–87). Knockout mouse models of *Tet2* are also associated with the development of hematopoietic malignancies, of both myeloid (71, 81, 82) and T-cell origin (88).

The DNA (cytosine-5) methyltransferase 3A (*DNMT3A*) gene encodes a methyltransferase involved in the epigenetic regulation of gene expression via methylation of cytosines in the DNA. Mutations in *DNMT3A* gene were originally described as highly recurrent in acute myeloid leukemia (AML) (89, 90), where they are associated with adverse survival (91).

Analysis of *DNMT3A* in PTCL identified the presence of recurrent loss of function mutations in this gene in 10%–40% of AITL samples (61–64, 72) (Figure 2), frequently co-occurring with *TET2* mutations and maybe even predating them in the process of malignant transformation (72) (Figure 3).

The Isocitrate Dehydrogenase 2 (*IDH2*) gene is mutated in about 30–40% of AITL cases (64, 73) (Figure 2). *IDH2* encodes a metabolic mitochondrial enzyme physiologically involved in the oxidative decarboxylation of isocitrate to 2-oxoglutarate. Notably, the resulting mutant enzymes have a neomorphic enzymatic activity catalyzing the conversion of alpha ketoglutarate to 2 hydroxyglutarate (2-HG), an oncometabolite that antagonizes the activity of alpha ketoglutarate dependent dioxygenases, including the TET family enzymes, leading to impairment of DNA and histone demethylation and abnormal regulation of gene transcription (64, 92). While recurrent mutations in *IDH2* can be frequently identified in other types of cancer, including AML, AITL is the only PTCL subgroup where *IDH2* mutations are found, and remarkably, they occur exclusively in position R172 (R172K, R172S) (64, 93), which is associated to increased production of 2-HG compared to other *IDH2* mutants alleles (94, 95). Of note, the presence of *IDH2* mutations is associated with poor prognosis in a subset of AML patients (96), but there is no significant association of *IDH2* mutations with survival in AITL (64). In contrast to AML, where *IDH2* and *TET2* mutations are mutually exclusive, AITLs frequently present co-occurring mutations in these epigenetic regulators (64) (Figure 3). Specifically, analysis of an AITL cohort (N=120) indicates than over 90% of the *IDH2* mutated samples also harbor mutations in *TET2* (Figure 3). Although methylation profiling reflected only a moderate effect of the double *TET2/IDH2* versus the *TET2* only mutant cases, gene expression profiling supports a cooperative effect of *IDH2* and *TET2* mutations on the regulation of the expression of TFH specific genes leading to a more polarized TFH signature that achieved by the presence of *TET2* mutations alone (64).

Loss of function mutations in *TET2* and *DNMT3A* seem to occur at an early stage of hematopoietic development, as mutations in those genes have been found in normal elderly individuals and as germline events in AML and PTCL patients (62, 71, 72, 97). Actually, the presence of somatic mutations in the blood of otherwise healthy individuals is associated with a higher risk of developing hematopoietic tumors (98, 99). Clonality and germline analysis in the context of AITL supports a transformation model in which *TET2* and *DNMT3A* mutations constitute an initial or pre-malignant lesion in hematopoietic progenitors that could eventually lead to clonal expansion and malignant transformation both within the T-cell and myeloid lineages. In this context, the presence of mutations in *IDH2* and *RHOA*, usually at a lower allelic frequency (62, 64) reflects a second hit that likely modulates lineage specification towards TFH cells orchestrating the cells into developing AITL.

Additional mutations in the TCR pathway

Gene expression profiling studies have proposed that AITL tumors may be driven by increased T-cell receptor signaling (12). Consistently, genomic studies have uncovered the

presence of recurrent, albeit relatively rare, genetic alterations affecting the *FYN and CD28* genes, two important elements in the TCR signaling cascade (61, 100).

The FYN tyrosine kinase is, together with LCK, the predominant SRC family kinase found in T lymphocytes and plays an important role in T-cell activation upon T-cell receptor stimulation (101). *FYN* mutations found in PTCL NOS and AITL cases specifically disrupt the intramolecular inhibitory interaction of the FYN SH2 domain with C-terminal phosphorylated FYN Tyr531 resulting in increased tyrosine kinase signaling (61) (Figure 2).

Recurrent mutations in CD28, a member of the immunoglobulin subfamily and the major co-stimulatory molecule for TCR-mediated activation, have been recently described in AITL (100, 102). PTCL-associated CD28 mutations affect the D124 and T195 residues (Figure 2) and result in increased signaling via increased ligand-receptor interaction and signal transduction (100). CD28-mutated AITL patients have inferior survival to non-mutated cases (100). Given the prominent role of CD28 signaling in normal TFH development, and the presence of activating mutations in CD28 in AITL, it is possible that CD28 directed therapies may be of relevance for the treatment of this disease.

The promise for targeted therapies

Understanding the mechanisms relevant for TFH differentiation, proliferation or function offers a number of novel therapeutic opportunities for targeting malignant TFH cells (Figure 4). In this perspective, BCL6 arises as one the most promising targets, since within T cells; BCL6 expression is restricted to TFH subset and is necessary for TFH survival (103). Thus, blocking BCL6 is an attractive targeted therapy for AITL. Indeed, small molecule or peptomimetic BCL6 inhibitors have been developed as targeted therapies in diffuse large cell lymphoma (104–106) and breast cancer (106).

Given the close relationship between TFH cells and AITL tumor lymphocytes, potentially same therapies evaluated for autoimmune disorders where TFH cells are involved might be relevant for AITL. Thus, Abatacept, a recombinant antibody which blocks both CTLA4 and CD28 signaling, suppresses TFH generation in an experimental model of autoimmunity (107), suggesting a potential therapeutic use in AITL. However, recent studies have shown the prominent role of ICOS in the development and maintenance of TFH cells (27–29, 37), indicating that ICOS could be a more specific target for therapy in AITL. A phase I trial of ICOS blockade in systemic lupus erythematosus demonstrates the feasibility of administering this antibody to human subjects (108). As ICOS function is critically dependent on the activity of phosphoinositide 3-kinase (PI3K), small molecule inhibitors of this kinase offers an alternative approach to abrogate ICOS signaling. Pharmacological inhibition of the PI3K/AKT signaling pathway has already shown promise as an effective therapy in experimental models of autoimmunity and is currently being evaluated in clinical trials in CLL and follicular lymphoma (109). Both CD28 and ICOS function as co-stimulators of TCR, consequently, the inhibition of FYN, a key molecule in TCR signaling could also be evaluated in AITL. In this sense, PTCL-associated mutant active FYN proteins can be effectively inhibited with dasatinib, a multikinase inhibitor with activity against ABL1 and SRK kinases supporting a potential role for this inhibitor as targeted therapy (61).

IL6 and IL21 are key cytokines required for TFH induction and differentiation through a STAT3 dependent mechanism, therefore, inhibition of those signals may abrogate TFH differentiation and survival. Tocilizimab, an anti-IL6R antibody reduces circulating TFH cell numbers and IL21 production in patients with rheumatoid arthritis (110) and IL-21R blockade arrested the disease progression and mortality in a mouse model of SLE (111). An alternative may be the use of STAT3 specific inhibitors. Thus, Stattic, a specific STAT3 small molecule inhibitor has been shown to induce apoptosis in Sézary syndrome cells (112) and AZD9150, an antisense oligonucleotide inhibitor of STAT3 has been reported to have effect in vivo in lymphoma models (113).

CXCL13 determines TFH homing by engaging with the cell surface receptor CXCR5, higly expressed in AITL tumor cells. Anti-CXCL13 treatment diminishes the number of germinal centers in immunized mice and demonstrates efficacy in models of rheumatoid arthritis and multiple sclerosis (114). Currently pre-clinical studies have been initiated with anti-CXCL13 antibodies (VX5).

Finally, both *IDH2* and *TET2* mutations can lead to promoter hypermethylation, suggesting a potential role for hypomethylating agents as possible therapy for AITL. In this regard, the use of hypomethylating agents has already been reported to induce responses in *TET2* mutated myelodysplastic syndromes (115), and a recent case report showed efficacy of 5-AZT in an AITL patient whose tumor carried a *TET2* mutation (116). Additionally, AG-221, a small molecule inhibitor targeting mutant IDH2, has shown promising results in AML (117), and its use as a targeted therapy in AITL is being currently tested in a clinical trial (118). In the case of AITL, the frequent co-occurrence of *TET2* mutations in *IDH2* mutated cases might support the combination of hypomethylating agents with *IDH2* inhibitors to increase efficacy for targeting AITL (64).

Conclusion

AITLs constitute a group of poor prognosis lymphoma derived from T-cell follicular helper cells, a subset of T-cells normally present in germinal centers with a helper function to germinal center B-cells. Gene expression profiling has improved the diagnosis and classification of PTCLs, demonstrating the association of AITL, as well as a subgroup of AITL-like PTCL NOS cases, with a TFH-like gene expression signature. Genomic analyses have identified multiple genes frequently mutated in AITL, including mutations epigenetic regulators *TET2, DNMT3A* and *IDH2*; the small GTPase *RHOA* gene, and components of the TCR pathway, including *CD28* and *FYN*. The process of malignant transformation leading to AITL fits a multistep model with pre-malignant mutations in *TET2* or *DNMT3A* occurring as initiating events followed by the acquisition of the *RHOA G17V* or *IDH2 R172* mutation (Figure 1). Significant efforts are underway to develop cell and animal models for AITL. These models will provide powerful tools for the study of the pathogenesis of AITL and the identification and development of molecularly targeted therapies to treat this disease.

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Key points

- Mutations in the small GTPase *RHOA* gene, specifically the dominant negative G17V allele, are present in over 70% of the patients with AITL and almost 20% of PTCL, NOS cases.
- Loss of function mutation in epigenetic regulators *TET2* and *DNMT3A* are a frequent event in the pathogenesis of AITL
- *IDH2 R172* is the only mutated allele found in AITL, is generally associated with *TET2* mutations and define a specific subgroup within this disease
- Mutations in elements of the TCR pathway –*CD28* and *FYN*- lead to increased TCR signaling in AITL
- The current model for AITL development suggest the existence of a pre-malignant lesion in the *TET2* or *DNMT3A* epigenetic regulators, followed by a secondary mutation in *RHOA G17V* or *IDH2 R172* that results in the malignant transformation of mature T-cells with a TFH phenotype.

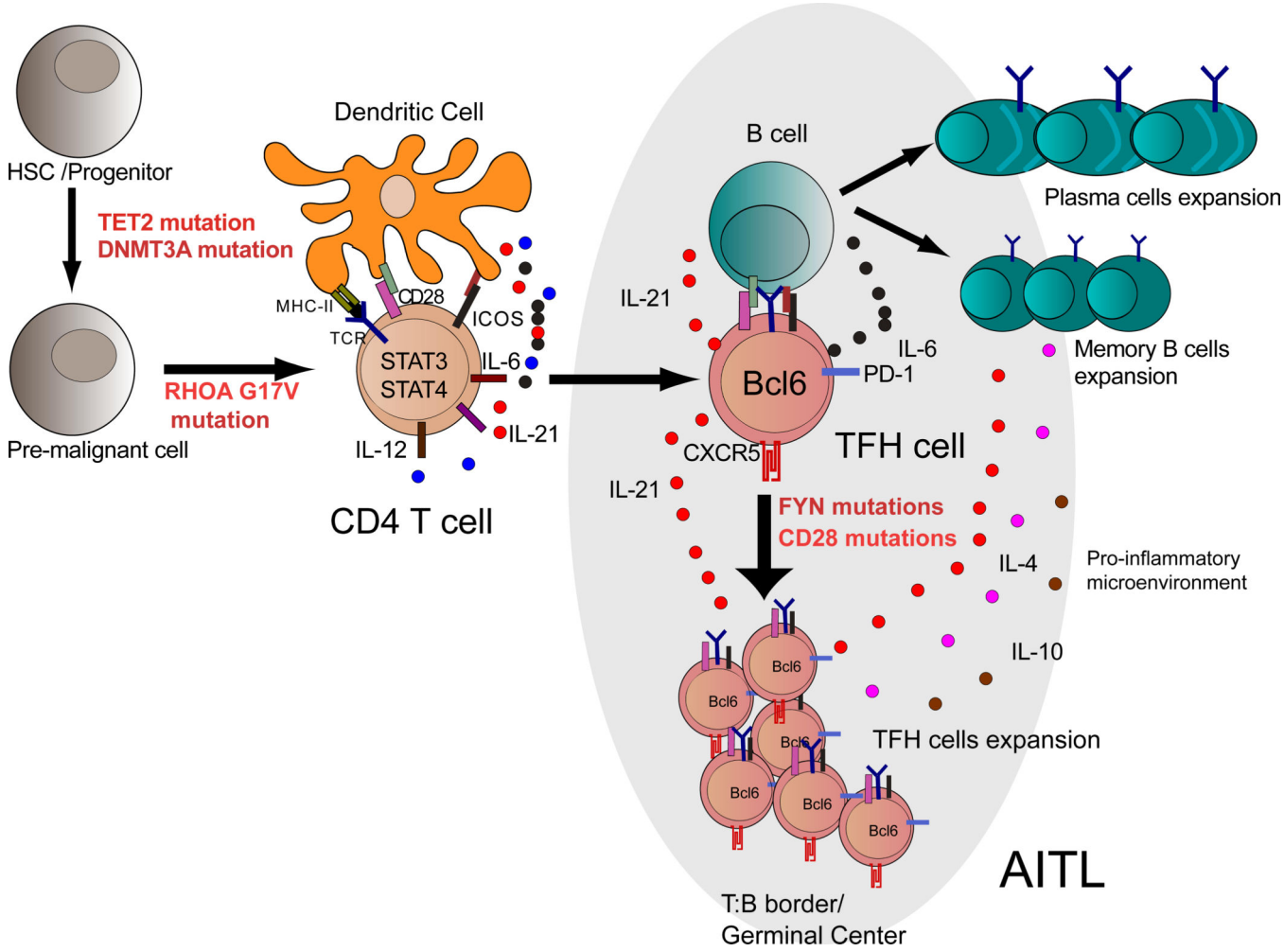


Figure 1. Normal development and malignant transformation of TFH cells

TFH cell differentiation is initiated by activation of CD4 naïve T cells by dendritic cells in presence of IL6, IL21 and IL12 leading to STAT3/STAT4 activation. Activation of ICOS induces the upregulation of BCL6 and CXCR5, allowing them to migrate to B cell follicles to induce germinal centers formation. Stimulation of TFH cells and antigen presentation by B cells leads to full development of TFH cells, whose mission is supporting B-cells and facilitating the generation of long-lived plasma cells and memory B cells. Malignant transformation of TFH leads to the development of AITL following a multistep tumor model where TET2 and/or DNMT3A mutations would be acquired first, followed by specification into the TFH lineage guided by expression of the RHOA G17V mutant and enhanced by hyper activation of the TCR signaling pathway. Deregulated expansion and/or function of TFH could induce the generation of cytokines (IL4, IL6, IL21 and IL10) which play a prominent role in the early stages of lymphoma progression and in setting the abundant inflammatory component of AITL tumor lesions.

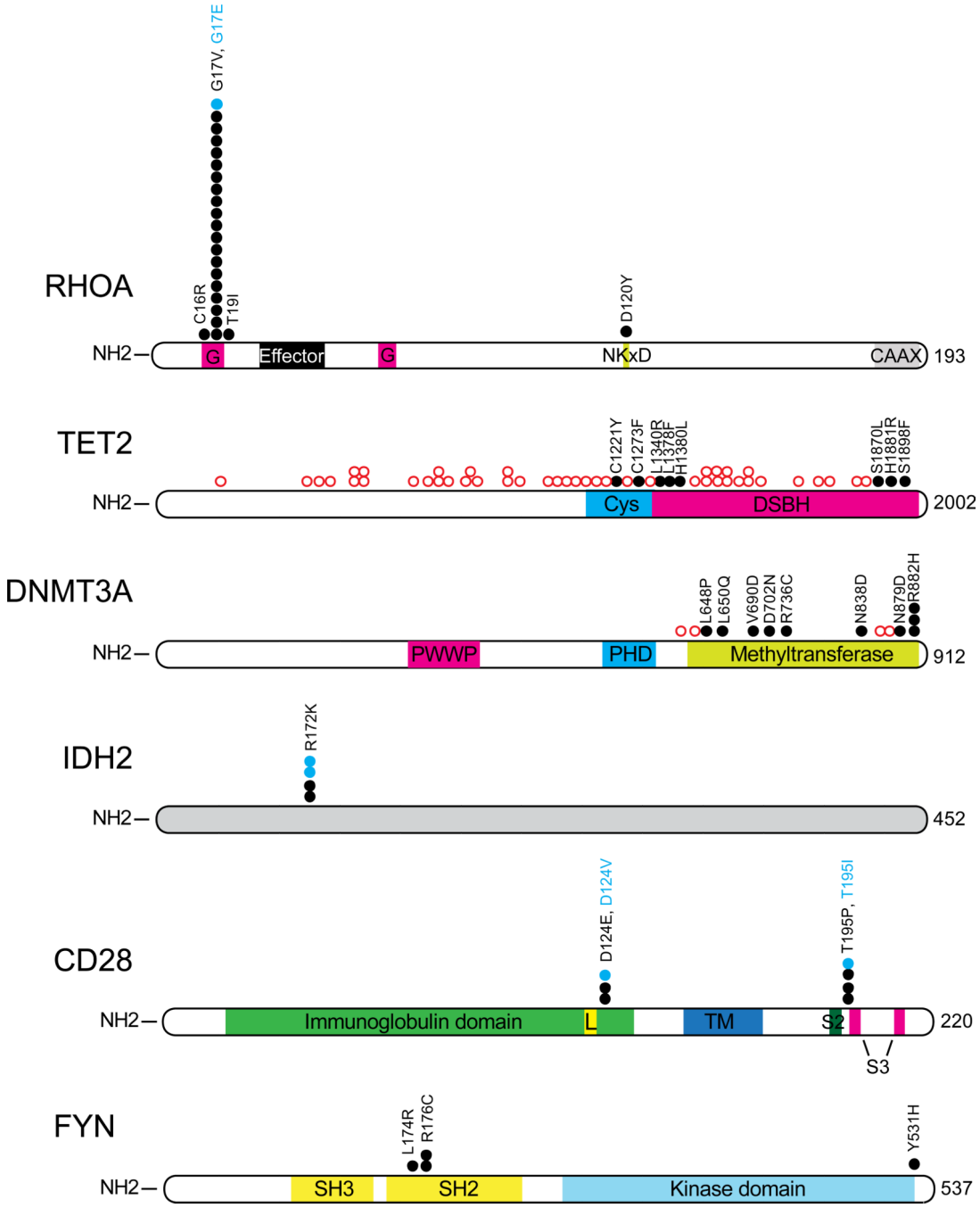
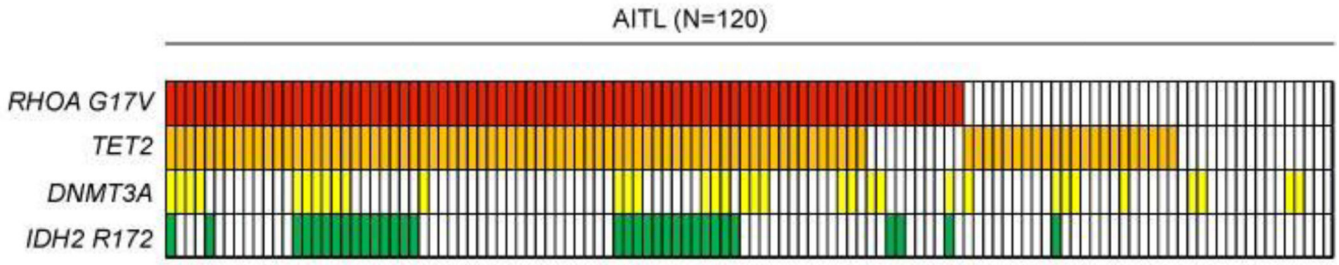


Figure 2. Recurrent mutations in AITL

Schematic representation of the structure of the most frequently mutated proteins in AITL: RHOA, TET2, DNMT3A, IDH2, FYN and CD28. (Data adapted from Palomero et al, 2014 (for RHOA, TET2, DNMT3A, IDH2 and FYN) or Wang et al, 2015 (for CD28)).Black circles represent amino acid substitutions while open red circles indicate truncating mutations. G:GTP/GDP binding domain; Effector: effector interaction domain; NKXD: NKXD GTP-binding domain; CAAX: CAAX box prenylation domain; Cys: cysteine-rich domain; DSBH: double-stranded beta helix fold domain; PWWP: PWWP domain; PHD:

plant homeodomain; Immunoglobulin domain: Ig variable region-like domain CD28 and CTLA4; TM, transmembrane domain. L: ligand interaction site; S2: SH2-binding motif; pink: S3: SH3-binding motifs; SH3: SH3 domain; SH2: SH2 domain.

a



b

	co-occurrence [n **(%)**]				
	RHOA G17V	*TET2*	*DNMT3A*	*IDH2 R172*	cases
RHOA G17V	n/a	72 **(88)**	30 **(36.5)**	31 **(37.8)**	82
TET2	72 **(76.6)**	n/a	29 **(30.8)**	29 **(30.8)**	94
DNMT3A	30 **(83)**	29 **(80.5)**	n/a	15 **(41.6)**	36
IDH2 R172	31 **(97)**	29 **(90.6)**	15 **(46.8)**	n/a	32

Figure 3. Co-occurrence of frequent mutations in AITL

(a) Analysis of the mutational status of RHOA G17V, TET2, DNMT3A and IDH2 in a cohort of 120 AITL (information extracted from published data (61–64)). Each column represents a patient sample; each row represent mutations in each of the genes of interest. (b) Quantification of the co-occurrence of mutations in RHOA G17V and epigenetic regulators. In the column on the right are represented the cases mutated for RHOA G17V, TET2, DNMT3A and IDH2 R172; on the upper row the co-occurrence indicated by the number of cases on the left category that also carry the mutation in the genes indicated on the top (n) and the percentage of co-occurrence calculated from the total number of cases [(%) in bold].

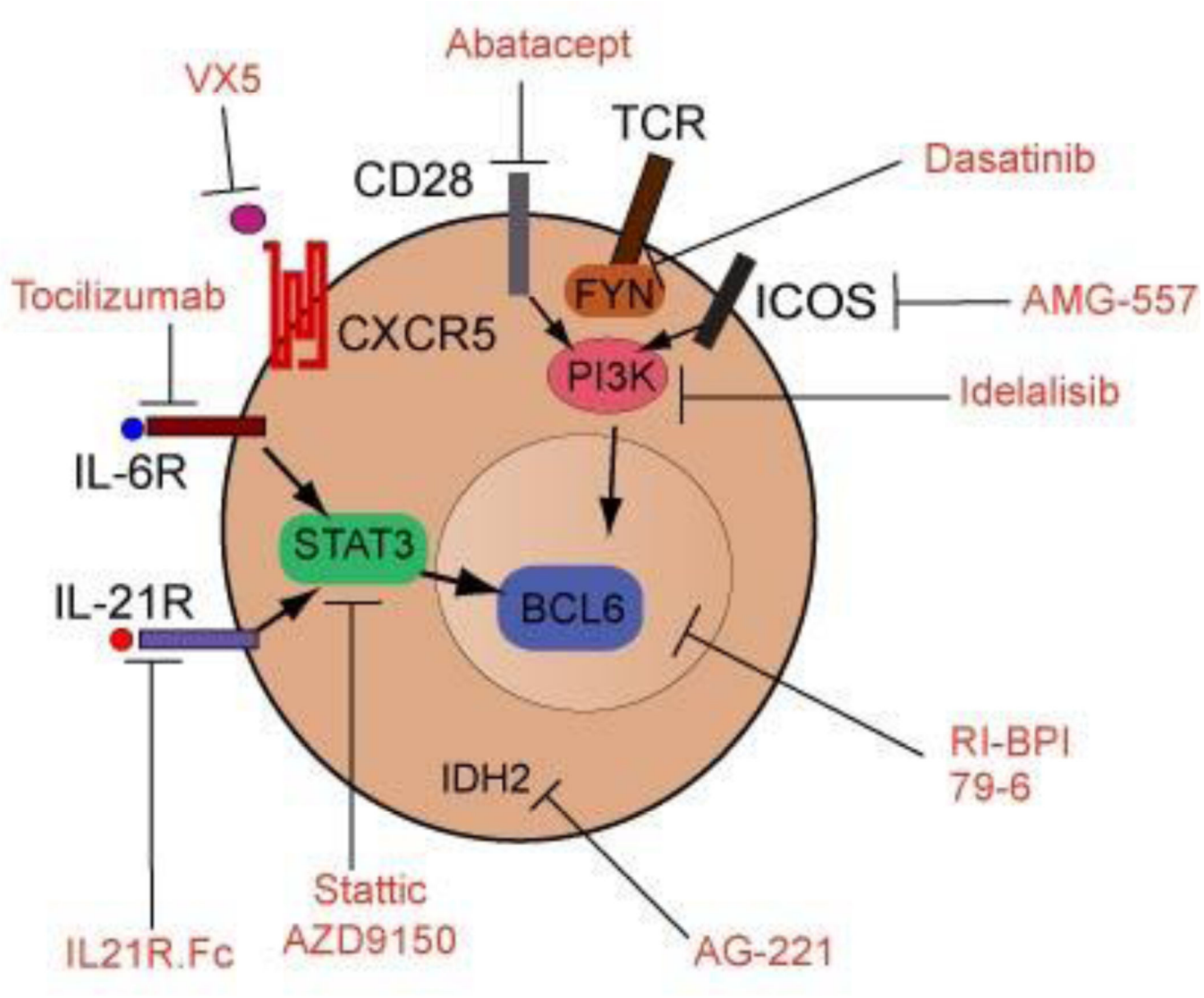


Figure 4. Targeted therapies in AITL

Schematic diagram depicting pharmacologic agents that target relevant proteins in AITL and TFH cells that could be used for personalized therapies against AITL lymphomas.