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Title: GATA-3 in T-cell Lymphoproliferative Disorders

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Abstract

GATA-3 regulates the differentiation, proliferation, survival, and function of peripheral T cells and their thymic progenitors. Recent findings, reviewed here, not only implicate GATA-3 in the pathogenesis of molecularly, genetically, and clinically distinct T-cell lymphoproliferative disorders, but also have significant diagnostic, prognostic, and therapeutic implications.

Peripheral T-cell lymphoma (PTCL) [1], not otherwise specified (PTCL, NOS) and angioimmunoblastic T-cell lymphomas (AITL), while accounting for the majority of peripheral NK/T cell lymphomas in North America, are relatively rare, with incidence rates ≤0.4 per 100,000 (1). Approximately 2000 patients are diagnosed annually with PTCL, NOS or AITL in the United States (1). The rarity of these PTCL and their significant heterogeneity has hampered progress, including their classification. For example, approximately one-third of AITL/PTCL, NOS cases are reclassified following expert hematopathology review (2). Unfortunately, most patients afflicted with AITL/PTCL, NOS will ultimately succumb to their disease, as resistance to initial anthracycline-based chemotherapy regimens is common, and the responses observed with novel agents in the relapsed/refractory setting are rarely durable or complete (3-7).

Increasingly, the proper classification and determination of the cell of origin among the most common PTCL has therapeutic implications. Therefore, we will review their respective cell of origin and molecular pathogenesis, highlighting the emerging role for GATA-3 in a distinct subset of PTCL, NOS. While these advances have significant therapeutic implications, they also present future challenges that were almost unimaginable ten years ago.

AITL and PTCL, NOS: Cell of origin and classification

[1] Abbreviations: α-KG, alpha-ketoglutarate; AKT, protein kinase B; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ChIP, chromosome immunoprecipitation; CTCL, cutaneous T-cell lymphoma; CTL, cytotoxic T cell; DNMT3A, DNA methyltransferase 3A; IDH, isocitrate dehydrogenase; IκB, inhibitor of κB; ITK, IL-2 inducible T-cell kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOS, not otherwise specified; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; PTCL, peripheral T-cell lymphoma; T-ALL, T-cell acute lymphoblastic leukemia; Ten-Elevan-Translocation, TET; TFH, T follicular helper; TME, tumor microenvironment;

Improved understanding of lymphocyte development and differentiation, including the significant role played by dominant transcriptional regulators, has influenced the classification of most lymphomas, as molecularly distinct lymphoma subtypes are associated with normal lymphocyte ontogeny. The normal “cell of origin”, at least among the more common PTCL’s, is best appreciated for AITL and ontologically related PTCL’s, designated in the 2016 WHO classification as follicular T-cell lymphomas and nodal PTCL with a T follicular helper (T_{FH}) cell immunophenotype (8). Follicular helper T cells (T_{FH} cells) produce specific cytokines (e.g. IL-4, IL-21) and express cell-surface ligands (e.g. CD40L) that regulate somatic hypermutation and isotype switching during the humoral immune response. Their differentiation is orchestrated by the “master” transcriptional repressor Bcl-6, which is inducibly expressed upon ICOS costimuation. Chemokine (e.g. CXCL13) and chemokine receptor (e.g. CXCR5) expression promotes T_{FH} cell co-localization with germinal center B cells and follicular dendritic cells [reviewed in (9)]. Immunophenotyping studies examining many of these, and other (e.g. CD10, PD-1), markers led to the suggestion that malignant T cells in AITL are T_{FH} cell derived (10-17). This contention was further supported by gene expression profiling studies demonstrating that the molecular profile of AITL most closely resembles that observed in normal T_{FH} cells and is distinct from that observed in most PTCL, NOS [(18, 19), reviewed in (20)]. AITL ontogeny likely explains the classic histologic findings (e.g. expansion of germinal-center B cells and an expanded meshwork of follicular dendritic cells) and clinical characteristics of this PTCL [reviewed in (21)], and the observed enrichment in angiogenesis, B-cell, and monocyte/macrophage signatures (“tumor microenvironment”) observed in gene expression profiling studies (19).

Despite the significant advances achieved in understanding AITL, including improved understanding of the cell of origin and genetic landscape, PTCL, NOS heterogeneity has hampered progress. The classification of these PTCL has been challenging, and PTCL, NOS, remains a diagnosis of exclusion. The largest gene expression profiling study conducted to date included 372 PTCL cases that were reviewed by a panel of expert hematopathologists (19). After expert hematopathology review, 150 cases were histologically classified as PTCL, NOS. However, among these cases, 37% were molecularly reclassified when subtype-specific molecular classifiers were applied. The majority (69%) of cases were molecularly reclassified as either AITL or ALK- ALCL. Among those cases reclassified as ALCL, further pathologic assessment of those cases demonstrated a morphology consistent with ALCL, high-level CD30 expression, and high-level expression of cytotoxic markers, thus supporting the molecular classification on morphologic grounds. Conversely, ~25% of morphologically classified AITL were molecularly reclassified as PTCL, NOS. These findings highlight both the diagnostic challenges posed by the more common PTCL's and the potential diagnostic utility of gene expression profiling in these PTCL (20).

AITL: Molecular pathogenesis

Epigenetic dysregulation due to recurrent mutations in tumor suppressor genes that regulate DNA methylation is an emerging hallmark of T_{FH}-derived malignancies. Ten-Eleven-Translocation (TET) 2 promotes DNA demethylation by catalyzing the hydroxylation of 5-methylcytosine. Recurrent loss-of-function mutations effecting its catalytic domain are observed

in the majority (~75%) of AITL. The mitochondrial protein isocitrate dehydrogenase (IDH) 2 catalyzes the decarboxylation of isocitrate to α-ketoglutarate (α-KG) in the tricarboxylic acid cycle and thus indirectly regulates α-KG dependent dioxygenases, including TET2. IDH2 is recurrently mutated at arginine-172 in approximately one-third of AITL, and in contrast to myeloid malignancies, is not mutually exclusive with TET2 mutations, as most AITL harboring this mutation are also TET2 mutated. The $IDH2^{R172}$ mutation confers neomorphic activity such that α-KG is converted to the R-enantiomer of 2-hydroxyglutarate, an oncometabolite that antagonizes TET2 and histone demethylases. AITL cases harboring concurrent TET2 and IDH2 mutations have distinct gene expression and epigenetic profiles, including upregulation of T_{FH}-associated genes and promoter and histone hypermethylation (22). Loss-of-function mutations in the DNA methyltransferase DNMT3A are also observed, and usually occur with TET2 mutations, in approximately one-third of AITL cases.

TET2 and DNMT3A mutations are observed in hematopoietic stem and progenitor cells in patients with clonal hematopoiesis (23-25). Therefore, these genetic alterations are not restricted to malignant T cells in AITL, but are also present in progenitor cells and constituents of the tumor microenvironment. This is suggested by the higher variant allele frequencies (VAF) observed for these mutations in AITL relative to other recurrent mutations (e.g. RhoA, IDH2) (26), and is convincingly demonstrated by recently performed microdissection studies demonstrating the presence of TET2-mutated B cells in AITL biopsies (27, 28). In these studies, TET2 (and/or DNMT3A) mutations were observed in both microdissected B cells and malignant T cells, whereas other mutations (RhoA, IDH2) were restricted to malignant T cells (27). These observations have at least two implications. First, mutations present within non-malignant

constituents of the tumor microenvironment may promote lymphomagenesis in a non-cell-autonomous manner. For example, TET2 deficiency in lymphoma-associated macrophages or B cells may promote their functional polarization (29) and/or proliferative potential (30), and thus indirectly promote AITL pathogenesis. Finally, TET2 and/or DNMT3A mutations are likely early events in disease pathogenesis that promote the malignant transformation of T cells that acquire additional genetic hits, including mutations involving RhoA and IDH2. Both the cooperativity between TET2 and DNMT3A, and their insufficiency to fully drive the malignant transformation of $CD4^+$ T cells, has been demonstrated in a murine bone marrow transplant model in which recipient mice were serially transplanted with DNMT3A mutated and TET2 deficient hematopoietic stem cells (30). A subset of these mice, after the first transplantation, developed AML or T-ALL within 8 months of transplant. However, a majority (9 out of 12) of new recipients developed a T-cell lymphoproliferative disorder resembling AITL following serial transplantation into new recipients, albeit with a latency of ~1-1.5 years. The very few AITL observed in primary recipients, and the relatively prolonged latency appreciated following 1-2 additional rounds of serial transplantation, suggest that T cells must acquire other epigenetic or genetic alterations prior to their malignant transformation. For example, the overexpression of Notch1 observed in this model, in conjunction with its apparent widespread activation in 86% of AITL (31), may implicate Notch in AITL pathogenesis.

Conventional T cell proliferation, survival, differentiation, and effector functions are dependent upon the integration of both antigen-dependent and antigen-independent (e.g. costimulation and cytokine-dependent) signaling. Therefore, these signaling pathways, activated either in response to endogenous ligands provided within the tumor microenvironment or upon

the acquisition of gain-of-function mutations in relevant receptors or downstream signaling intermediates, are prime candidates for the "second hits" that promote T-cell transformation. The constellation of mutational profiling and next-generation sequencing studies completed to date generally support this contention [reviewed in (32)].

PTCL, NOS: Molecular pathogenesis and the emergent role of GATA-3

The differentiation of conventional $CD4^+$ T-cell subsets (i.e. Th1, Th2, etc…), from which many PTCL, NOS are derived, is controlled by a number of critically important ("master") transcription factors. For example, the zinc-finger transcription factor GATA-3 regulates the homeostatic survival, proliferation, differentiation, and function of developing and mature T-cell subsets, but is classically associated with Th2 differentiation [reviewed in (33)]. A biased interrogation of these transcription factors and a limited number of their respective gene targets led to the observation that a majority of morphologically classified PTCL, NOS cases are characterized by the expression of the transcription factors T-bet or GATA-3 and their respective gene targets (34). Among the PTCL, NOS cases examined, ~50% expressed GATA-3 by immunohistochemistry, and were enriched for Th2-associated cytokines (e.g. IL-4, IL-5, IL-13). Hypereosinophilia, a harbinger of Th2-biased immunity, was significantly associated with GATA-3 expression in this series. In addition, GATA-3 expression was associated with dismal survival, as no long-term disease free survivors were observed in this cohort. The adverse outcomes observed in GATA-3^+ PTCL, NOS have been attributed to GATA-3-dependent cell-autonomous effects. Using integrated GATA-3 ChIP and loss-of-function strategies, we have demonstrated

that GATA-3 drives the expression of relevant gene targets regulating the tumor microenvironment, cell trafficking, and survival in TCL. For example, GATA-3 dependent cytokines, including IL-13, directly promote the growth and survival of malignant T cells (35). These GATA-3 target genes, likely in collaboration with the additional loci it regulates, promote a particularly malignant and treatment resistant phenotype (34, 36).

In addition, GATA-3 dependent cytokines regulate constituents of the tumor microenvironment and thus promote chemotherapy resistance in a non-cell-autonomous manner (34, 37, 36). Normal T-cell ontogeny – including thymic selection and peripheral antigen-dependent activation/differentiation – depends upon antigen-presenting cells that regulate T-cell growth and survival. Malignant T cells apparently retain this dependence upon antigen-presenting cells, including lymphoma-associated macrophages (LAM), which are most abundant within the tumor microenvironment (38, 39, 36). These observations are concordant with those in many B-cell lymphomas, where gene expression by LAM and their density within the tumor microenvironment explain their variable natural history (40-42). GATA-3 dependent cytokines, including IL-4/IL-13 and IL-10, promote the pro-tumoral functions of LAM (34). The survival of tissue resident macrophages, historically conceived as quiescent cells that fail to proliferate or expand, are dependent upon macrophage-colony stimulating factor (MCSF, or CSF1). Consequently, CSF1R antagonism has emerged as a therapeutic strategy to deplete tumor-associated macrophages, and has been investigated in many tumor models [reviewed in (43, 44)]. However, studies performed in selected tumor models demonstrate that inhibition of CSF1R alone may be insufficient to deplete tumor-associated macrophages, presumably due to the presence of hematopoietic and inflammatory cytokines within the tumor microenvironment

that promote their survival. Consistent with these observations, it is now appreciated that tissue resident macrophages proliferate locally in an IL-4 dependent manner (45, 46). Collectively, these findings, in conjunction with the observed association between GATA-3 expression and macrophage polarization and density in PTCL, NOS (34, 37), suggest that GATA-3 promotes the alternative polarization and expansion of LAM. While GATA-3-dependent IL-5 production undoubtedly explains the hypereosinophilia frequently observed in GATA-3$^+$ PTCL, NOS (34), the potential role of eosinophils in PTCL pathogenesis is unknown and largely unexplored (47).

Given the cell-autonomous and non-cell-autonomous roles of GATA-3 in PTCL, the relatively high rate of primary refractory disease, exceeding 50%, among GATA-3$^+$ PTCL, NOS receiving anthracycline-based induction chemotherapy may not be surprising (36). The adverse prognostic implications associated with GATA-3 expression were independently validated in two subsequent studies (48, 37). In the large gene expression profiling study conducted by Iqbal et. al., an “unbiased” approach was adopted. After excluding molecularly reclassified cases, they observed that most PTCL, NOS cases highly expressed either GATA-3 and its gene targets (33% of cases) or TBX21 (T-bet) and its gene targets (49% of cases). Poor overall survival was similarly observed in the GATA-3 subgroup. A subset of the T-bet subgroup highly expressed CD8$^+$ cytotoxic T-cell associated genes and was associated with poor survival, consistent with previous findings (49). Enrichment of c-myc and PI3K/mTOR related gene signatures were observed in GATA-3 PTCL, whereas interferon-γ and NF-kB related gene signatures were enriched in T-bet PTCL. Collectively, these findings suggest that GATA-3 PTCL may be Th2-derived, whereas T-bet PTCL are heterogeneous, including Th1 and cytotoxic T-cell (CTL)-derived lymphomas.

Recently performed studies have clarified the relationship between the genetic landscape in PTCL, NOS and the putative cell of origin in PTCL, NOS. As in AITL, TET2 mutations are also observed in PTCL, NOS, but are less prevalent (~45%) (22), with no obvious difference in prevalence between GATA-3 and T-bet subsets. DNMT3A and RHOA mutations are similarly observed, whereas IDH2 mutations are rare in PTCL, NOS (22). Whether TET2 and DNMT3A mutations are also present within nonmalignant cells within the tumor microenvironment, as observed in AITL, and the mechanism by which these mutations may foster lymphomagenesis in a non-cell-autonomous manner in that context remains an open question. In contrast to the mutational landscape in these epigenetic regulators, significant differences in clinically relevant chromosomal copy number alternations have been observed between GATA-3 and T-bet PTCL. For example, genomic losses (usually heterozygous) that include relevant tumor suppressor genes, including p53, PTEN, and CDKN2A/B, are observed in ~40-50% of GATA-3 PTCL, while genomic losses generally were infrequently observed in T-bet PTCL (50). Genomic gains involving c-myc were observed in ≈40% of GATA-3 PTCL, and are concordant with the enriched expression of c-myc target genes previously observed in this subset (19). The loss of relevant tumor suppressor genes, including p53, and amplification of c-myc, may further contribute to the high rate of primary refractory disease observed in GATA-3 PTCL. A genomic gain involving chromosome 17q, which includes STAT3, was frequently observed in GATA-3 PTCL, whereas this region was focally deleted in T-bet PTCL. A focal gain that includes the BCL11B gene was observed in 17% of T-bet PTCL. This is notable, as Bcl11b is a GATA-3 binding partner that inhibits GATA-3-dependent transcription of Th2-associated cytokines (51). The striking differences observed in the genetic landscape between GATA-3 and

T-bet PTCL provide further evidence that these are truly distinct T-cell lymphomas. These findings have significant therapeutic implications [see commentary (52)], including the development of targeted, and potentially subset-specific, therapies.

Beyond PTCL: GATA-3 in other T-cell lymphoproliferative disorders

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of extranodal lymphomas, many of which highly express GATA-3 (34, 53), and its target genes (34), and are resistant to conventional chemotherapeutic agents (54), much like GATA-3 PTCL. The chemokine receptor CCR4 is a GATA-3 target gene (unpublished data) that is preferentially expressed by Th2 and Treg cells and plays an important role in T-cell trafficking to the skin (55), and likely contributes to the primary cutaneous localization of CTCL and secondary cutaneous involvement observed in ≈50% of patients with GATA-3 PTCL (unpublished observation). In addition to its role in T-cell trafficking, CCR4 may also promote cell growth and survival, and is subject to gain-of-function mutations in PTCL subsets. Furthermore, Th2-associated cytokines (IL-4/IL-13) promote the alternative polarization of lymphoma-associated macrophages, which are an abundant source of the CCR4 ligands CCL17 and CCL22. The CCL17/CCL22 and CCR4 axis is further maintained in CTCL by the aberrant loss of CD26, a dipeptydil peptidase that inactivates CCR4 ligands (55).

In contrast to PTCL/CTCL, which are derived from post-thymic (“peripheral”) T cells, T-cell acute lymphoblastic leukemias (T-ALL) are derived from T-cell precursors (including early thymic or thymic progenitors) at various stages of development. Much like their mature

counterparts, T-ALL are characterized by significant genetic and molecular heterogeneity, and account for ≈25% of ALL in adults in North America (56). While therapeutic advances and improved outcomes have been achieved in pediatric T-ALL, outcomes in adult T-ALL have languished, and outcomes remain poor, particularly in the relapsed/refractory setting, due to the emergence of chemotherapy-resistant disease (57). While GATA-3 plays an important role regulating the differentiation of T-cell progenitors [reviewed in (58, 33)], and its expression is regulated by oncogenes (i.e. Notch1) with an established role in T-ALL pathogenesis, its role in T-ALL is largely unexplored, despite the observation that GATA-3 is highly expressed in most T-ALL cell lines and primary specimens [unpublished data and (59)]. Notch1 has a well-established role in T-ALL pathogenesis, and GATA-3 is an important Notch1 target gene (60, 58). While its role in T-ALL pathogenesis is largely unexplored, it is intriguing that the transgenic overexpression of GATA-3 in T-cell progenitors leads to the development of T-ALL in ≈50% of transgenic mice (61). Therefore, GATA-3's role in T-cell lymphoproliferative disorders may not be limited to peripheral or cutaneous T-cell lymphomas.

Therapeutic Opportunities

Despite treatment with anthracycline-based chemotherapy, most patients afflicted with PTCL will ultimately succumb to disease progression within a few years of diagnosis. Despite initial uncertainty as to the benefit of anthracycline-based therapy (3), most recent series (5), including a large prospective study (62), demonstrate an overall survival benefit with the inclusion of an anthracycline. Unfortunately, disease progression during initial anthracycline-based therapy is

observed in ≈10-20% of patients (5, 62, 63), and is associated with dismal outcomes (7). Therefore, resistance to conventional chemotherapeutic agents remains a challenge and a common reason for treatment failure and mortality in these patients. Despite the availability of multiple novel agents, a median overall survival ≤6 months is anticipated in the setting of relapsed/refractory disease (4, 6), as responses with novel agents, with only a few exceptions, are modest, rarely durable, and have not led to a discernable improvement in overall survival since their approval. Therefore, future studies should seek to interrogate biomarkers, including the cell of origin, that will not only discriminate “low risk” from “high risk” patients, but also identify those who are most likely to benefit from currently available or investigational therapies.

Selected GATA-3 target genes, for example, are attractive therapeutic targets. Mogamulizumab, a CCR4 specific monoclonal antibody that mediates antibody-dependent cell-mediated cytotoxicity, depletes CCR4-expressing cells (55). Given its significant clinical activity in phase I/II studies, mogamulizumab was compared with vorinostat in a randomized, phase III study (MAVORIC) in CTCL and was associated with a significant improvement in progression-free survival (64). Nonetheless, its utility in PTCL expressing GATA-3 (and CCR4) remains an open question.

The genetic landscape observed in GATA-3 PTCL is distinct and presents novel therapeutic opportunities. For example, c-myc is highly expressed in GATA-3 PTCL, and its stability is regulated in a proteosome-dependent manner, as multiple phosphorylation-dependent ubiquitin ligases tag c-myc for ubiquitination and degradation. For example, Polo-like kinase 1 (PLK1) was recently identified in an shRNA-based “Achilles heel” screen in CTCL (65). PLK1 phosphorylates and stabilizes c-myc, and its pharmacologic inhibition led to the loss of

detectable c-myc, and induced apoptosis in malignant T cells. PLK1 activation is regulated by phosphorylation of a threonine residue within its kinase domain, phosphorylation of which is mediated by Aurora A kinase (AAK). Therefore, AAK inhibition has emerged as an attractive therapeutic strategy in the T-cell lymphomas [reviewed in (66)]. In fact, the AAK inhibitor alisertib is associated with an overall response rate ≈30% in PTCL, which rivals the anticipated response rates observed with currently available agents (67). The extent to which the AAK/PLK1 axis, GATA-3 itself, and/or c-myc are predictive biomarkers for response to alisertib is unknown.

Cancers originating from a specific lineage or stage of development may continue to require growth and survival signals provided by cell- or development-specific pathways (e.g. estrogen receptor in breast cancer). Successful rearrangement of T-cell receptor (TCR) genes and the expression of a functional TCR is required for the generation of mature T cells within the thymus and for their sustained homeostatic survival and function in the periphery. Most AITL and PTCL, NOS retain TCR (and CD3) expression, while expression of many other T-cell specific antigens is lost, and gain-of-function mutations in signaling intermediates that are required for TCR signaling are prevalent in many of these T-cell lymphomas (32). Therefore, we examined the extent to which TCR engagement promotes the growth and survival of malignant T cells. TCR activation in primary malignant T cells *ex vivo* led to dramatic changes in gene expression that are associated with chemotherapy resistance (36). Many of these observed effects, including NF-κB activation and chemotherapy resistance, are dependent upon activation of the Tec family kinase IL-2 inducible T-cell kinase (ITK). Upon activation, ITK is autophosphorylated and phosphorylates PLC-γ1, thus promoting PKC-Θ/NF-κB and

Ras/Raf/MAPK activation, and is required for the proper spatiotemporal localization of the TCR signalosome (68). Therefore, Tec family kinases, including ITK, are novel and largely unexplored therapeutic targets in the T-cell lymphomas (36). GATA-3 is expressed in a TCR- and NF-κB-dependent manner in subsets of conventional T cells, where it promotes their homeostatic survival (69). Concordant with its role in conventional T cells, GATA-3 expression was upregulated in malignant T cells following engagement of the TCR and was shown to confer resistance to chemotherapy in a cell-autonomous manner (36). Proteasomal inhibition indirectly inhibits NF-κB by impairing IkBα degradation, and was observed to impair GATA-3 expression in pre-clinical studies and in an exceptional responder (with PTCL, NOS) in a small phase II study (70). Engagement of the TCR unleashes a signaling barrage that activates a number of pathways providing therapeutic opportunities, many of which are the subject of ongoing or planned clinical trials.

A reciprocal and symbiotic relationship exists between a malignant T cell and its environment, as the repertoire of chemokines/cytokines malignant T cells secrete is subtype specific (e.g. T_{FH}-related cytokines in AITL) and regulates the recruitment, retention, and functional polarization of non-malignant constituents of the TME. Conversely, both lymphoid- and myeloid-derived constituents of the TME promote T-cell lymphomagenesis both directly, by providing factors that foster the growth and survival of malignant T cells, and indirectly, by suppressing host anti-tumor immunity [reviewed in (32)]. Despite this interdependence, the relationship between the genetic landscape, particularly in T-bet and GATA-3 PTCL, and the TME remains obscure, but is an area that is ripe for discovery and therapeutic exploitation.

The genomic losses prevalent in GATA-3 PTCL, particularly those involving p53, CDKN2A/B, and PTEN, have significant implications for the TME, as these tumor suppressors may function in a non-cell-autonomous manner to regulate the TME. For example, p53 has been shown to promote classical (and anti-tumoral) polarization of tumor-associated macrophages in a non-cell-autonomous manner (71). In addition, p53 directly induces the expression of miR-34 which impairs the expression of PD-L1 and may thus license malignant cells with intact p53 for cytotoxic T-cell (CTL) mediated elimination (72, 73). Whether p53 (and/or CDKN2A/B) deleted GATA-3 PTCL highly express PD-L1, as has been observed in p53-deficient solid tumors, and the extent to which this may confer sensitivity to PD-L1/PD-1 checkpoint blockade are unknown (38, 74). As PD-L1 expression is tightly regulated post-transcriptionally in a PI3K/AKT-dependent manner, PTEN-deficient tumors also highly express PD-L1 (9, 75). Collectively, these observations might suggest that GATA-3 PTCL may be particularly susceptible to immunotherapeutic strategies, including checkpoint blockade.

Future Challenges

Improved understanding of PTCL pathogenesis and increasing appreciation of their genetic and molecular heterogeneity has spawned a smorgasbord of novel agents and an expanding list of potential therapeutic targets, yet PTCL's account for only ~10% of NHL in North America, and the pool of patients who may benefit from novel therapies remains relatively small. Therefore, completion of the clinical trials needed to evaluate the rapidly expanding pool of novel therapies, either as single agents or in combination with those that are currently approved, is an

increasingly significant challenge that must be met if we are to select the “right treatment” for the “right patient” and improve outcomes for these patients.

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Conflict of Interest

None of the authors have any potential conflict of interest related to this manuscript.

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