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Brief report

IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma

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Mutations in isocitrate dehydrogenase 1 *(IDH1)* and isocitrate dehydrogenase 2 *(IDH2)* occur in most grade 2 and 3 gliomas, secondary glioblastomas, and a subset of acute myelogenous leukemias but have not been detected in other tumor types. The mutations occur at specific arginine residues and result in the acquisition of a novel enzymatic activity that converts 2-oxoglutarate to D-2-hydroxyglutarate. This study reports *IDH1* and *IDH2* genotyping results from a set of lymphomas, which included a large set of peripheral T-cell lymphomas. *IDH2* mutations were identified in approximately 20% of angioimmunoblastic T-cell lymphomas (AITLs), but not in other peripheral T-cell lymphoma entities. These results were confirmed in an independent set of AITL patients, where the *IDH2* mutation rate was approximately 45%. This is the second common genetic lesion identified in AITL after *TET2* and extends the number of neoplastic diseases where *IDH1* and *IDH2* mutations may play a role. (*Blood*. 2012;119(8):1901-1903)

Introduction

Heterozygous isocitrate dehydrogenase 1 and 2 (*IDH1* and *IDH2*) mutations at specific active site arginine residues occur in most low-grade gliomas, secondary glioblastomas, and in some acute myeloid leukemias (AMLs).[1-3] These mutations alter IDH enzymatic function, resulting in the conversion of 2-oxoglutarate to the rare metabolite D-2-hydroxyglutarate (D-2-HG), which accumulates to high levels in cells and tissues.[4,5] D-2-HG may act as an oncometabolite, driving tumor progression by interfering with 2-oxoglutarate–dependent enzymes that affect hypoxia signaling (prolyl hydroxylases), histone methylation, and DNA methylation (TET2).[6,7] Despite extensive genotyping, *IDH1* and *IDH2* mutations have not been identified in significant proportions of other neoplasms.[3,8,9]

Peripheral T-cell lymphomas (PTCLs) are non-Hodgkin lymphomas with a diverse presentation, histology, therapy response, and outcome.[10] Because this group of diseases has not been comprehensively assessed for the presence of *IDH* mutations, patient samples from 3 independent groups were genotyped to determine whether these mutations are present.

Methods

Patients and clinical data

Lymphoma and leukemia DNA samples from frozen tissue were provided by a multicentric T-cell lymphoma consortium (Tenomic), and the University of Hong Kong. Diagnosis was confirmed by a panel of pathologists to ensure consistent classification of PTCL according to the WHO classification.

A complementary set of DNA from 22 angioimmunoblastic T-cell lymphomas (AITLs) was provided by the University of Nebraska Medical Center (UNMC) Lymphoma Tumor Bank.[11] These AITL patients were identified by histopathologic assessment and confirmed by gene expression profiling.[11]

As there is no standard therapy for AITL, patients received heterogeneous treatment. AITL samples with greater than 50% estimated tumor cell content were prioritized (supplemental Table 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). All patients provided informed consent in accordance with the Declaration of Helsinki, and use of patient materials and information was approved by the institutional review boards of the University of Hong Kong, the UNMC, and the member institutions of the Tenomic Consortium.

IDH1 and *IDH2* genotyping

For Tenomic and University of Hong Kong patients, *IDH1* R132 and *IDH2* R172 and R140 genotypes were determined at the Analytical Genetics Technology Center at the University Health Network (Toronto, ON) using a Sequenom MassARRAY platform (Sequenom) as previously described.[5] Positive results were confirmed by Sanger sequencing of the mutated region. In the UNMC patients, *IDH1* and *IDH2* genotype was determined by Sanger sequencing of all exons and subsequently by Sequenom (Genomic Core facility, UNMC). Sequenom genotyping is more sensitive and specific than Sanger sequencing, with the ability to detect a mutation in

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Table 1. *IDH1* and *IDH2* mutation status of lymphoma samples

Disease	IDH1R132	IDH2R172	IDH2R140
Tenomic Consortium and University of Hong Kong patients			
Hodgkin lymphoma	0/66	0/66	0/66
Non-Hodgkin B-cell lymphoma	0/14	0/14	0/14
B-cell acute lymphoblastic lymphoma (ALL B)	0/32	0/32	0/32
T-cell acute lymphoblastic lymphoma (ALL T)	0/8	0/8	0/8
AML	2/8	0/8	0/8
PTCL			
PTCL not otherwise specified (PTCLnos)	0/43	0/43	0/43
Anaplastic large cell lymphoma (ALCL)	0/50	0/50	0/50
Enteropathy type T-cell lymphoma (ETL)	0/8	0/8	0/8
Cutaneous T-cell lymphoma (CTCL)	0/17	0/17	0/17
Hepatosplenic T-cell lymphoma (HSTCL)	0/10	0/10	0/10
Extranodal NK/T-cell lymphoma (NK/TCL)	0/10	0/10	0/10
AITL	0/79	15/79	1/79
UNMC patients			
AITL	0/22	10/22	0/22

10% of the input DNA, which is an advantage for samples with stromal contamination.[12]

Statistical analysis

Fisher exact text and the Wilcoxon rank-sum test were used to test for differences between IDH2wt and IDH2 mutant patients. Estimates of overall and progression-free survival were calculated using the Kaplan-Meier method and compared using the log-rank test.

Results and discussion

Lymphoma samples from the Tenomic Consortium and University of Hong Kong were genotyped to determine whether mutations were present in *IDH1* at R132 and in *IDH2* at R172 and R140 (Table 1). This set of samples included a large group of PTCLs. Although other studies have suggested that *IDH1/IDH2* mutations are not present in lymphomas and leukemias other than AML,[3,9] PTCL has not been comprehensively studied.

No mutations were observed in lymphoma subtypes, including 46 B-cell lymphomas and 66 Hodgkin lymphomas, except for AITLs, where 16 of 79 (20%) samples from the Tenomic Consortium carried an *IDH2* mutation. This is the second common mutation to be identified in AITL after *TET2*[13] and makes AITL the third disease where *IDH1/IDH2* mutations have been identified in a significant proportion of patients. As has been observed in glioma and AML, all mutations were heterozygous. However, the spectrum of mutations observed in AITL was different. Unlike in glioma and AML, no *IDH1* mutations were identified, and the *IDH2* mutations were largely confined to alterations resulting in an R172 substitution (12 R172K, 2 R172G, 1 R172T, and 1 R140G).

To further validate these results, 22 AITL patients from UNMC were genotyped (Table 1). None of the patients carried *IDH1* mutations, and in 10 of 22 cases (45%) *IDH2* mutations were identified, confirming the results of the Tenomic data. Although this was an independent set of patients, and mutation detection was performed using Sanger sequencing of all exons, the mutation spectrum was consistent with that of the Tenomic patients, with the *IDH2* mutations detected at R172 (4 R172K, 4 R172S, 1 R172T, and 1 R172G). There were no other mutations found in *IDH1* or *IDH2*. The higher rate of mutation in this smaller set of patients may reflect differences in patient selection defined by a gene expression signature,[11] which may identify a more homogeneous group of patients whoshare the *IDH2* mutation at higher frequency.

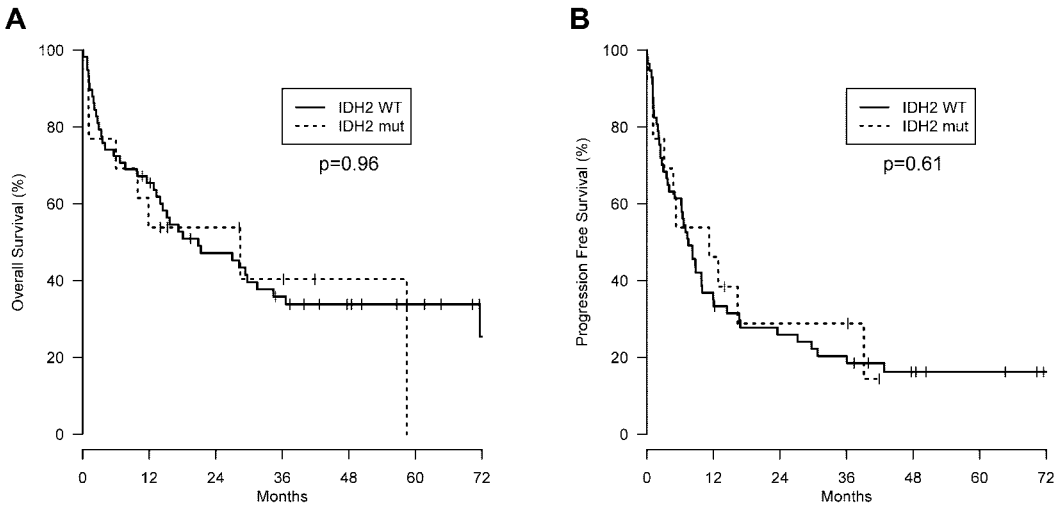

Figure 1. Survival. (A) Overall survival and (B) progression-free survival of AITL patients with wild-type (n = 61) or mutant *IDH2* (n = 16) from the Tenomic Consortium dataset. Wild-type *IDH2* patients were not significantly different from *IDH2* mutant patients for either parameter.

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AITL is 1 of the 3 most common PTCL subtypes, along with anaplastic large cell lymphoma and PTCL not otherwise specified.[14] It normally presents as a systemic disease, with polyadenopathy and a variety of immunologic abnormalities, and carries a poor prognosis.[15] Based on molecular marker expression (CD4, CD10, BCL6, PD1, and CXCL13) and microarray profiling, AITL is thought to arise from follicular T-helper cells normally present in germinal centers.[11,16,17] The molecular pathogenesis and underlying genetic events driving AITL are largely unknown.

The clinical features of *IDH2* wild-type and mutant AITL patients were assessed. Although all clinical parameters were not available for each patient, there were no significant differences between the 2 groups in the Tenomic patients, except that the Direct Coombs test was less frequently positive in *IDH2* mutant patients (supplemental Table 1). These results were consistent with the smaller UNMC patient group (data not shown). On review, there were no pathologic differences between the groups. Furthermore, *IDH2* status had no effect on progression-free or overall survival (Figure 1). This is at odds with the findings in glioma, where *IDH1/IDH2* mutations predict for improved survival, but more consistent with AML, where there is no overall independent impact on outcome, although some studies show prognostic value when specific *IDH* mutations are combined with other prognostic markers.[18] Prognostic impact may be difficult to detect in AITL, as patients are acquired from multiple centers and receive heterogeneous treatment.

Although the current results suggest that *IDH2* may not provide prognostic information in AITL, a better understanding of the mechanisms underlying IDH1/IDH2-driven tumor progression may lead to new opportunities for AITL treatment. Future measurement of D-2-HG, the metabolite produced by these mutant enzymes, may provide a useful biomarker of disease progression and response to therapy. In addition, small-molecule inhibitors specific for the mutant IDH2 enzymes could represent important tools in the future management of AITL.

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Authorship

Contribution: R.A.C., J.I., L.X., L.C.C., W.-C.C., P.B., P.G., and T.W.M. designed the research; R.A.C., J.I., C.K., L.d.L., M.P., F.L., L.X., and A.M. performed research and collected and analyzed the data; F.L., J.-P.J., and J.I. performed statistical analysis; and R.A.C. wrote the manuscript.

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