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IDH1 and *IDH2* mutations in myeloid neoplasms – Novel paradigms and clinical implications

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(Related Original Articles on pages 1668 and 1754 and related Letter on page 1797)

In the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues[1] myeloid neoplasms include myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS), myelodysplastic/myeloproliferative neoplasms (MDS/MPN), and acute myeloid leukemia (AML). In the last few years there have been major advances in our understanding of the molecular bases of these disorders, and molecular genetic data are increasingly being used for diagnosis, risk assessment and definition of treatment strategies.[2,3] These data now include information on mutations in the *IDH1* and *IDH2* genes.

IDH1 and *IDH2* encode the enzymes isocitrate dehydrogenase 1 and 2, respectively. The essential information about these genes and their products is reported in Table 1.

Somatic mutations of IDH1 *and* IDH2 *in malignant gliomas*

In 2008, though a genome-wide analysis Parsons *et al.*[4] identified somatic mutations at codon 132 of *IDH1* in approximately 12% of patients with glioblastoma multiforme, the most common and fatal type of brain cancer. In a subsequent study, these authors detected somatic mutations that affected amino acid 132 of *IDH1* in more than 70% of gliomas.[5] In most cases, arginine 132 was mutated to histidine (R132H). Some tumors without mutations in *IDH1* had mutations affecting the analogous amino acid (R172) of the *IDH2* gene, strongly indicating a role of mutations in the $NADP^+$-dependent isocitrate dehydrogenase genes in the pathogenesis of these malignancies. Overall, brain tumors with *IDH1* or *IDH2* mutations represented a distinctive subgroup of low-grade and secondary gliomas with a better outcome compared to that of tumors with wild-type *IDH* genes.

A causal relationship between acquired error in cellular metabolism and malignant transformation

Since a single copy of the gene – *IDH1* or *IDH2* – is mutated in human gliomas, Dang and co-workers[6] hypothesized that the mutations do not result in a simple loss of function. They did an elegant study to determine the impact of the *IDH1* (R132H) mutation on cellular metabolism, and showed that it resulted in the production of 2-hydroxyglutarate.[6] Since overproduction of this metabolite is associated with a high risk of brain tumors in patients with inborn metabolic errors, the authors concluded that the accumulation of excess 2-hydroxyglutarate *in vivo* contributes to the formation and malignant progression of gliomas, establishing a link between abnormal metabolism and malignancy.[7] The altered metabolic pathway associat-

ed with mutant *IDH1* has also been shown to contribute to tumor growth by activating hypoxia-inducible factor-1α.[8] These observations have important clinical implications, as patients with initial or low-grade forms of glioma may benefit from the therapeutic inhibition of 2-hydroxyglutarate production.[9]

Somatic mutations of IDH1 *and* IDH2 *in acute myeloid leukemia*

In a study of whole genome sequencing, Mardis *et al.*[10] analyzed the leukemic genome in a patient with *de novo* cytogenetically normal AML with minimal maturation. They identified 12 somatic mutations within the coding

Table 1. The genes *IDH1* and *IDH2* and their products.*

Properties	*IDH1*	*IDH2*
Official full name	Isocitrate dehydrogenase 1 ($NADP^+$), soluble	Isocitrate dehydrogenase 2 ($NADP^+$), mitochondrial
Chromosome location	2q33.3	15q26.1
Product (isocitrate dehydrogenases catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate. Five isocitrate dehydrogenases have been reported: three NAD^+-dependent isocitrate dehydrogenases, which localize to the mitochondrial matrix, and two $NADP^+$-dependent isocitrate dehydrogenases, one of which is mitochondrial and the other predominantly cytosolic).	The protein encoded by this gene is the $NADP^+$-dependent isocitrate dehydrogenase found in the cytoplasm and peroxisomes.	The protein encoded by this gene is the $NADP^+$-dependent isocitrate dehydrogenase found in the mitochondria.

** Information is from Entrez Gene (www.ncbi.nlm.nih.gov/gene) accessed on Aug 9, 2010.*

Table 2. Recent studies on the clinical significance of somatic mutations of *IDH1* and *IDH2* in acute myeloid leukemia.

Authors	*IDH1* mutations	*IDH2* mutations	Clinical correlates
Chou *et al.*[11]	27/493 (5.5%) patients with *de novo* AML carried an *IDH1* (R132) mutation		*IDH1* mutations were associated with normal karyotype and *NPM1* mutations
Wagner *et al.*[12]	30/275 (10.9%) patients (age 17 to 60) with *de novo* CN-AML carried an *IDH1* (R132) mutation		*IDH1* single nucleotide polymorphism rs11554137 was associated with an inferior outcome in CN-AML, while *IDH1* (R132) mutations were not
Marcucci *et al.*[13]	*IDH1* mutations were detected in 49/358 (13.7%) patients (age 19 to 83) with *de novo* CN-AML (47/49 involved residue R132)	*IDH2* mutations were detected in 69/358 (19.3%) patients with *de novo* CN-AML (56/69 involving R140, and 13/69 involving R172)	*IDH2* (R172) mutations were mutually exclusive with other prognostic mutations, and were associated with distinctive genetic profiles. Overall *IDH1* and *IDH2* mutations were found in 33% of the patients, and had an unfavorable impact on the outcome of CN-AML
Ho *et al.*[14]	12/274 (4.4%) adult patients with AML carried an *IDH1* (R132) mutation		*IDH1* mutations were not detected in pediatric AML
Thol *et al.*[15]		*IDH2* mutations were found in 33/272 (12.1%) patients with CN-AML (30 in codon 140 and 3 in codon 172)	*IDH2* mutation alone or in combination with *IDH1* mutations did not influence treatment outcome in patients with CN-AML
Abbas *et al.*[16]	*IDH1* mutations were identified (age 18 to 77) in 55/893 (6.2%) patients with AML	*IDH2* mutations were identified in 97/893 (10.8%) patients with AML	*IDH1* and *IDH2* mutations were mutually exclusive except in two cases. They occurred in 25% of patients with normal karyotype, and were associated with worse outcome in those with wild-type *NPM1* without *FLT3*-ITD.
Paschka *et al.*[17]	*IDH1* mutations were identified in 61/805 (7.6%) patients (age 16 to 60) with AML	*IDH2* mutations were identified in 70/805 (8.7%) patients with AML	*IDH1* and *IDH2* mutations were mutually exclusive except in two cases, and 78% of patients with *IDH* mutations had a normal karyotype. *IDH* mutations represented a poor prognostic factor in CN-AML with mutated *NPM1* without *FLT3*-ITD.
Boissel *et al.*[18]	*IDH1* mutations were identified in 70/520 (13.5%) patients (age 15 to 70) with AML	*IDH2* mutations were identified in 15/502 (3.0%) patients with AML	*IDH1* and *IDH2* mutations were associated with normal cytogenetics and poor prognosis
Green *et al.*[19]	*IDH1* mutations were identified in 107/1333 (8.0%) young adult patients with AML		*IDH1* mutations correlated significantly with an *NPM1* mutation but not a *FLT3*/ITD. An *IDH1* mutation was an independent adverse factor for relapse in *FLT3*/ITD-negative patients.
Schnittger *et al.*[20]	*IDH1* (R132) mutations were detected in 93/1414 (6.6%) patients with AML		Mutations were prevalent in the intermediate risk karyotype group, and were associated with a trend for worse clinical outcome

**CN-AML: cytogenetically normal acute myeloid leukemia.*

sequences of genes, including *IDH1* (R132C). Interestingly, somatic mutations at codon 132 of *IDH1* were found in 15 of 187 additional AML genomes: all these mutations were heterozygous and strongly associated with normal cytogenetic status.

In the last few months, several studies have been published on somatic mutations of *IDH1* and *IDH2* in AML, and their main findings are summarized in Table 2.[11-20]

Based on data reported in Table 2, it can be concluded that:

(i) somatic mutations of *IDH1* and *IDH2* are found mainly, although not exclusively, in cytogenetically normal AML, in which they are – with a few exceptions - mutually exclusive. On average, about 30% of patients with cytogenetically normal AML carry a mutant *IDH1* or *IDH2* gene, and in this category *IDH2* mutations are more common that *IDH1* mutations;

(ii) the vast majority of somatic mutations of *IDH1* and *IDH2* involve residues R132 of *IDH1*, and R140 or R172 of *IDH2*. This allows a quick and sensitive screening for *IDH1* and *IDH2* mutations,[21] providing clinicians with an important diagnostic instrument;

(iii) the prognostic significance of somatic mutations of *IDH1* and *IDH2* in AML is currently under investigation, but the available evidence indicates that they may be associated with an intermediate to high genetic risk.

Metabolic abnormalities in acute myeloid leukemia associated with somatic mutations of IDH1 *and* IDH2 *and potential novel therapeutic perspectives*

Two recent studies showed that AML cells bearing heterozygous *IDH1* or *IDH2* mutations accumulate 2-hydroxyglutarate.[22,23] This finding suggests that 2-hydroxyglutarate is an onco-metabolite that plays a role not only in the pathogenesis of gliomas but also in leukemic transformation, and might have therapeutic implications for the treatment of AML. In fact, blocking the accumulation of 2-hydroxyglutarate through the inhibition of mutant IDH enzymes could represent a therapeutic goal: for detailed information about this issue, the reader is referred to a very comprehensive review article by Dang *et al.*[9] A few small molecules capable of inhibiting IDH enzymes have already entered preclinical studies or clinical development.

Somatic mutations of IDH1 *and* IDH2 *in myeloproliferative neoplasms, myelodysplastic syndromes and secondary acute myeloid leukemia*

Green and Beer[24] searched for mutations in *IDH1* and *IDH2* in patients with AML that had evolved from *JAK2*-mutated MPN, and found somatic mutations in five of 16 patients: three involved *IDH1* (R132) and two *IDH2* (R140). These mutations were not present in 180 unselected patients with polycythemia vera or essential thrombocythemia in chronic phase. Pardanani *et al.*[25] detected *IDH1* (R132) or *IDH2* (R140) mutations in seven of 34 patients with blast-phase MPN, and in three of 166 patients with chronic-phase MPN (these latter patients had primary myelofibrosis). In a study reported in this issue of Haematologica, Andrulis *et al.*[26] investigated bone marrow samples from 160 patients with chronic MPN using an antibody highly specific for the *IDH1* (R132H) mutation, and found three positive patients. The mutation could be confirmed by DNA sequencing in only one of these three individuals, which may have been because of a low mutant allele burden. This underscores the need for sensitive assays to detect *IDH1* or *IDH2* mutations in patients with

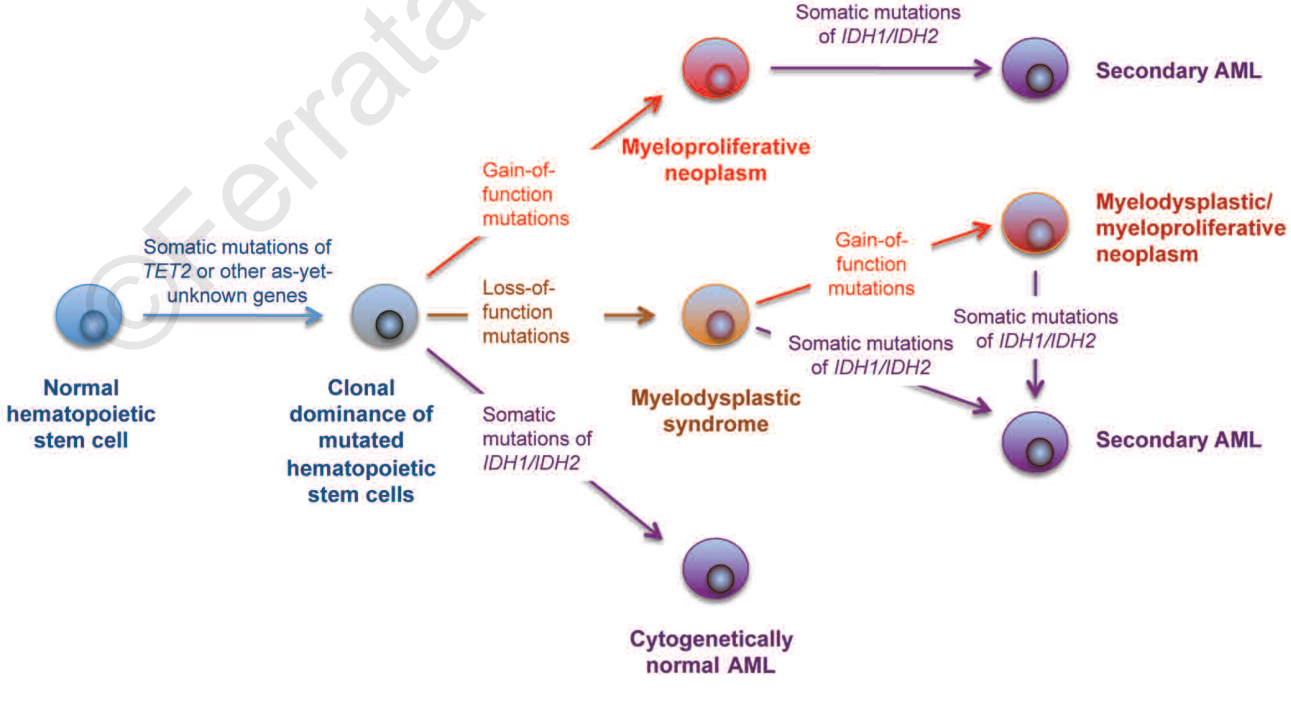

Figure 1. Schematic representation of the molecular bases of myeloid neoplasms and hypothesized role of *IDH1/IDH2* mutations.

low mutation loads.

Also in this issue of *Haematologica*, Thol *et al.*[27] report findings of a study on *IDH1* or *IDH2* mutations in patients with MDS or AML arising from MDS. Among 193 MDS patients, seven (3.6%) had a heterozygous mutation in *IDH1* codon 132, while no *IDH2* mutation was detected in any subject. Patients carrying mutated *IDH1* had a high rate of leukemic transformation and a poor event-free and overall survival. Among 53 AML patients with a previous history of MDS, four patients had mutations in codon 132 of *IDH1* and four had mutations in codon 140 of *IDH2*: thus, 15% of cases of AML arising from MDS had *IDH1* or *IDH2* mutations. Kosmider *et al.*[28] recently reported findings of a study on *IDH1* and *IDH2* mutations in early and accelerated phases of MDS and MDS/MPN. The frequencies of these mutations were 5% in MDS, 8.8% in MDS/MPN and in 9.7% in secondary AML.

Thus, the available evidence suggests that somatic mutations in *IDH1* and *IDH2* may represent a mechanism of progression to AML in MPN and MDS as schematically represented in Figure 1, although this awaits prospective validation. Other recently identified mechanisms of disease progression in these disorders include somatic mutations of *ASXL1*,[29] inactivating mutations of the histone methyltransferase gene *EZH2*,[30,31] and deletion of the *IKZF1* gene.[32]

Conclusions

The remarkable achievements described in this perspective article have been made in the last 2-3 years, which indicates how fast our understanding of the molecular bases of myeloid neoplasms is evolving. It is to be hoped that these achievements will not only make a molecular classification of myeloid neoplasms feasible, but will also allow novel targeted therapies to be developed.

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CD30⁺ lymphoproliferative disorders

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(Related Original Article on page 1697)

CD30 antigen, originally identified as a cell surface marker of the malignant Hodgkin and Reed-Sternberg (HRS) cells in Hodgkin's lymphoma by the use of the Ki-1 monoclonal antibody, is a transmembrane glycoprotein member of the tumor necrosis factor (TNF) receptor superfamily.[1] In lymphoid cells, CD30 is an activation marker inducible *in vitro* by mitogenic signals and viral stimulation, and its expression is detected in a small number of immunoblasts in benign lymphatic tissues.[2] In pathological conditions, CD30 is found at variable levels in different lymphomas of B-cell or T-cell derivation, and in several reactive conditions (Table 1). However, strong and homogeneous CD30 expression in most neoplastic cells is restricted to fewer entities, mainly three groups of lymphoid neoplasms: (i) classical Hodgkin's lymphoma, (ii) anaplastic large cell lymphomas (ALCL), and (iii) primary cutaneous CD30⁺ T-cell lymphoproliferative disorders.[3] For diagnostic purposes, the detection of CD30 is of particular value as a hallmark feature, albeit not specific, for the identification of these entities.

The disorders most characteristically associated with CD30 are distinct clinico-pathological entities - interestingly with some morphological similarity, as 'Hodgkin's-like' features may be encountered in both ALCL and primary cutaneous CD30⁺ lymphoproliferative disorders. Although there has been a lot of speculation in the past about the relationship and possible overlap between classical Hodgkin's lymphoma and ALCL, it is now clear that these are biologically distinct entities of different cellular derivation (B-cell *versus* T-cell, respectively). Historically, CD30 was instrumental in identifying ALCL as lymphomas composed of large cells showing homogeneous expression of CD30 at high levels, and characterized by cohesive growth and peculiar 'anaplastic' cytomorphological features.[4] Among these, a small subset of cases of B-cell derivation represent variants of diffuse large B-cell lymphoma. Nowadays, the designation ALCL is restricted to cases of T-cell derivation. These overall infrequent neoplasms involving lymph nodes and/or extranodal sites comprise so-called typical 'hallmark cells' - characterized by an eccentric horseshoe-shaped nucleus and a prominent eosinophilic Golgi region. Anaplastic lymphoma kinase (*ALK*) gene status was found to be another critical parameter to characterize two subsets of ALCL.[5] Molecularly defined ALK-positive ALCL is mostly a disease of children and young adults, carries a relatively good prognosis and comprises a morphological spectrum including variants deviating from the common type by the presence of only occasional 'hallmark' tumor cells and/or an associated reactive background. Conversely, ALK-negative ALCL affects older individuals and is associated with a worse prognosis, closer to that of peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS).[6] The view of ALK-positive and ALK-negative ALCL as two variants of the same entity evolved towards the concept of two separate disease entities in the current WHO classification of hematologic malignancies.[3] Although the majority of ALCL occur as primary systemic disorders, a subset of ALK-negative ALCL – referred to as primary cutaneous ALCL - occurs primarily as single or multifocal tumor lesions in the skin, usually remains localized to the skin, may undergo spontaneous regression and generally has a favorable prognosis. Because of overlapping clinical and pathological features with lymphomatoid papulosis, a clinically benign recurring skin lymphoproliferative disease composed of large atypical 'anaplastic' CD30⁺ cells admixed with an inflammatory background, both primary cutaneous ALCL and lymphomatoid papulosis are considered within the spectrum of primary cutaneous CD30⁺ T-cell lymphoproliferative disorders. Figure 1 provides a synoptic view of CD30⁺ lymphoproliferations of T-cell derivation.

A peculiar feature of ALCL is that, despite the presence of monoclonal T-cell receptor (*TCR*) gene rearrangement indicative of T-cell lineage derivation, its manifestations of a T-cell immunophenotype are usually limited. Indeed, ALCL tumor cells usually show reduced or absent expression of one or more T-cell antigens or