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LETTER TO THE EDITOR

Rare mutations in DNMT3A in myeloproliferative neoplasms and myelodysplastic syndromes

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Alterations of epigenetic marks are thought to play an important role in myeloid malignancies. In particular, aberrant DNA methylation is a hallmark of these diseases. DNMT3A and DNMT3B methyltransferases have predominant role in *de novo* methylation of DNA. Mutations in DNMT3A have been found in roughly 20% of acute myeloid leukemia (AML).^{1–3} The precise mechanism by which DNMT3A may affect DNA methylation is not known. The *TET2* gene encodes an enzyme that favors the transformation of 5-methylcytosines in 5-hydroxymethylcytosines. *TET2* function requires alpha-ketoglutarate (α KG). *TET2* is frequently mutated in myeloid diseases. Mutation in *IDH1* and *IDH2* changes their enzymatic activity and induces an hypermethylation of AML DNA.³ Mutated *IDH1/2* enzymes catalyze α KG into 2-hydroxyglutarate (2HG). Production of 2HG impairs *TET2* function. This explains why mutations in *TET2* and in *IDH1/2* are mutually exclusive.⁴ In contrast, mutations in *IDH1/2* are more frequent in AML cases with DNMT3A mutations.²

We searched for mutations and deletions of *DNMT3A*, *TET2* and *IDH1/2* in a series of 201 chronic myeloid diseases including 135 myeloproliferative neoplasms (MPNs) and 66 myelodysplastic syndromes (MDSs). The MPN cases comprised 33 polycythemia vera (PV) and 5 post-PV myelofibrosis (MF), 56 essential thrombocythemia (ET) and 10 post-ET MF, 25 primary myelofibrosis (PMF), 3 MPN-unclassifiable and 3 MDS/MPN cases. The MDSs comprised 5 refractory anemia (RA), 13 RA with ring sideroblasts (RARS), 7 refractory cytopenia with multilineage dysplasia, 16 RA with excess blasts (RAEB) type 1, 20 RAEB type 2 and 5 MDS-unclassifiable cases.

We determined the sequence of all exons of *TET2*, exons 4 of *IDH1* and *IDH2*, and exons 15 to 23 of *DNMT3A* (which encode the C-terminal half of the protein, including the catalytic domain, where most mutations have been found so far), as described.^{2,5} High density array-comparative genomic hybridization⁵ provided information on the status of the respective loci.

In MPNs, we found 13 mutations in *TET2* in 12 patients (2 PV, 1 post-PV MF, 3 ET, 2 post-ET MF, 2 PMF, and 2 MDS/MPN one of which had two mutations), 0 mutations in *IDH1/2*, and 2 mutations in *DNMT3A* (1 in a JAK2 V617F-positive PV, 1 in a JAK2 V617F-negative PMF) (see Table 1). The two mutations in *DNMT3A* were missense (c.2245C>T, p.Arg749Cys in the PV;

c.2644G>A, p.Arg882Ser in the PMF). All mutations were heterozygous.

In MDSs, we found 12 mutations and 1 deletion of *TET2* (all heterozygous), 5 mutations of *IDH1/2*, and 4 mutations (6%) and 1 deletion of *DNMT3A* (all heterozygous) (see Table 1). Mutations in *DNMT3A* were 1 nonsense (c.1681G>T, p.Glu561Stop), 1 frameshift (c.1872del, p.Pro625LeufsX26) and 2 missense (c.1723G>C, p.Ala575Pro; c.2141C>G, p.Ser714Cys). Mutations in *TET2*, *IDH1/2* and *DNMT3A* were all mutually exclusive. Thus, 23 MDS cases out of 66 (roughly one-third) showed one alteration (mutation or deletion) in either DNA methylation-associated gene. Strikingly, the 4 *DNMT3A*-mutated cases were 1 RA and 3 RARS. One RARS case had a trisomy 8.

DNMT3A mutations were very recently reported in two series of MDSs, including 62 RAEB cases⁶ and 150 cases of various subclasses.⁷ In the RAEB series,⁶ 3 cases (4.8%) were mutated. In the second series,⁷ 12 patients had DNMT3A mutations (8%). These results show that, in chronic myeloid diseases, *TET2* mutations are prominent, whereas *IDH1/2* and *DNMT3A* are less frequent. In MPNs, we did not find any *IDH* mutation; previous works had found that only 4% of PMF cases and few PV and ET were mutated in *IDH1/2*.^{8,9} *IDH1/2* mutations are also rare in MDSs, except in some subclasses such as MDSs with del(5q) or trisomy 8.^{5,10,11} Only six cases were mutated in *DNMT3A* in our whole series of chronic cases. Overall, *IDH1/2* and *DNMT3A* mutations are therefore more a feature of AMLs, especially primary AMLs with normal karyotype and intermediate prognosis.^{2,3} This suggests that mutations in *TET2*, *IDH1/2* and *DNMT3A*, although potentially all functionally linked to DNA methylation, may not be equivalent events in the initiation of leukemogenesis; *TET2* mutation could be more efficient in triggering the process. In our series, mutations of the three genes were mutually exclusive, whereas *DNMT3A* mutations have been found to be associated with *TET2* or *IDH1/2* mutations in AMLs.² This may just be because of a low number of mutated samples in chronic cases. However, this may also suggest that *IDH1/2* and *DNMT3A* mutations may participate, although less frequently than *TET2*, to the initial phases of the disease. This may be in collaboration with specific cooperating alterations such as trisomy 8 or del(5q).

All our *DNMT3A*-mutated MDSs were low-risk RA/RARS cases. The *DNMT3A* Arg882 amino-acid residue, which is a mutation hotspot in AMLs,^{1–3} was only mutated once in our series of MPNs (in a PMF) and it was not mutated in our series of MDSs. In the reported RAEB series,⁶ the three mutations affected the Arg882 residue. In the other published series,⁷ three out of the four Arg882-mutated MDSs were RAEB/RAEB-T cases. The *DNMT3A* mutations can occur in the various subclasses of MDS. However, the Arg882 mutation may be more specific of RAEB and/or aggressive cases, whereas mutations at the other residues may have a different function and may be associated with a different (milder?) phenotype.

Table 1 Mutations in three DNA methylation-associated genes in patients with chronic myeloid diseases

	<i>TET2</i> ^a	<i>IDH1/2</i> ^a	<i>DNMT3A</i> ^a	Total ^a
MPNs (N = 135)	12 (8.9)	0	2 (1.5)	14 (10.4)
MDSs (N = 66)	12 (18.2)	5 (7.6)	4 (6)	21 (31.8)
Total (N = 201)	24 (11.9)	5 (2.5)	6 (3)	35 (17.4)

Abbreviations: *IDH1*, isocitrate dehydrogenase 1; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.

^aPercentages are in parentheses.

Conflict of interest

The authors declare no conflict of interest.

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