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Leukemic evolution of donor-derived cells harboring *IDH2* and *DNMT3A* mutations after allogeneic stem cell transplantation

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Although allogeneic stem cell transplantation is effective for the treatment of leukemia with poor prognosis, some such treated individuals experience disease relapse at various times after transplantation. Chimerism analysis of the relapsed disease has revealed infrequent cases in which the malignant cells originate from the donor and not from the initial leukemic clones.[1,2] Such donor cell leukemia (DCL) is often refractory to further treatment, with a mean overall survival for the affected patients of only 32.8 months.[2]

We recently described a 47-year-old Japanese man with acute myeloid leukemia (AML) who underwent a transplantation of peripheral blood stem cells (PBSCs) from his HLA-matched brother.[3] Although the allogeneic transplantation was successful, AML again became apparent in the patient 27 months later and chimerism analysis revealed that the leukemia was DCL. Genomic DNA was isolated and subjected to whole-exome sequencing from specimens of the initial AML (containing 70% myeloblasts, referred to as sample P1), the first complete remission after chemotherapy (sample P2), the first relapse (containing 24% myeloblasts; sample P3), donor PBSCs (sample D1), DCL at 27 months after allogeneic transplantation (containing 6% myeloblasts, sample D2) and DCL at 36 months after transplantation (containing 71% myeloblasts, sample D3).

Exome sequencing yielded a total of ~84.7 million, ~31.6 million, ~73.5 million, ~44.3 million and ~53.2 million unique, high-quality, paired-end reads for samples P1, P2, P3, D1 and D3, respectively (Supplementary Information). Although chimerism analysis for short tandem repeats had indicated that D3 was derived from D1 clones,[3] we further examined this possibility in a genome-wide manner. As demonstrated in Supplementary Figure 1a, the allele frequency of single-nucleotide polymorphisms (SNPs) detected in our data sets was highly concordant between P1 and P2 (Pearson's correlation coefficient (r) of 0.978) as well as between P1 and P3 ($r=0.986$), suggesting that these three samples originate from a single individual. However, as expected, the concordance dropped substantially for the P1 and D3 pair ($r=0.628$). In contrast, the concordance between D1 and D3 was high ($r=0.983$), suggesting that the relapsed leukemia after transplantation was indeed derived from the donor cell. Of note, the allele frequency of SNPs showed only a low level of concordance ($r=0.285$) between P1 and a cell line (KCL22)[4] derived from an unrelated Japanese patient with chronic myeloid leukemia (Supplementary Figure 1b). The correlation coefficient of 0.628 for P1 and D3 thus indicated that the patient and donor siblings share a substantial number of SNPs.

We next searched for somatic nonsynonymous mutations among the leukemic samples. For P1 and P3, we used P2 as a paired normal control. Given that D3 was shown to be derived from D1, we used the latter as the germline control for the former. Through our computational pipeline (Supplementary Information), nine missense mutations and two out-of-frame insertions/deletions (indels) were detected for P1, two missense mutations for P3 and nine missense mutations and one out-of-frame indel for D3 (Table 1). As described previously,[3] a 4-bp deletion of *CEBPA* was present in the initial AML but absent from the DCL. Similarly,

Table 1. Confirmed somatic mutations in the specimens analyzed

Specimen	*Gene symbol*	*GenBank accession no.*	*Nucleotide change*	*Amino-acid change*	*Mutation ratio (%)*				
					P1	*P2*	*P3*	*D1*	*D3*
P1	*ACSL5*	NM_016234	c.280G>A	p.V94I	40.6	0.0	30.6	0.0	0.0
	ANO4	NM_178826	c.2441C>T	p.S814L	42.3	0.0	16.7	0.0	0.0
	APOB	NM_000384	c.9175C>T	p.R3059C	32.8	0.0	7.4	0.0	0.0
	BANK1	NM_017935	c.222C>G	p.N74K	36.4	0.0	9.2	0.0	0.0
	CCDC88C	NM_001080414	c.3748G>A	p.E1250K	36.4	0.0	0.0	0.0	0.0
	FAM178B	NM_001122646	c.81G>A	p.M27I	41.2	0.0	25.0	0.0	0.0
	GABRB2	NM_021911	c.1009C>T	p.R337C	44.8	0.0	14.5	0.0	0.0
	JAK3	NM_000215	c.2570T>C	p.L857P	40.8	0.0	0.0	0.0	0.0
	SPATA31D1	NM_001001670	c.3793C>T	p.R1265C	36.6	0.0	6.7	0.0	0.0
	CEBPA	NM_004364	c.319_322delGACT	p.D107Tfs	63.6	0.0	10.0	0.0	0.0
	STAG2	NM_001042750	c.219_220insCG	p.H73Rfs	100.0	0.0	27.6	0.0	0.0
P3	*ACSL5*	NM_016234	c.280G>A	p.V94I	40.6	0.0	30.6	0.0	0.0
	NTNG2	NM_032536	c.1348G>T	p.G450C	0.0	0.0	37.5	0.0	0.0
D3	*CCDC168*	NM_001146197	c.11761G>C	p.D3921H	0.0	0.0	0.0	0.0	55.6
	GAL3ST1	NM_004861	c.1086G>T	p.M362I	0.0	0.0	0.0	0.0	32.6
	IDH2	NM_002168	c.419G>A	p.R140Q	0.0	0.0	0.0	7.1	50.0
	MYO7B	NM_001080527	c.635G>A	p.R212H	0.0	0.0	0.0	0.0	45.8
	NFATC1	NM_172390	c.736G>A	p.V246I	0.0	0.0	0.0	0.0	48.6
	PSMB8	NM_004159	c.637C>T	p.P213S	0.0	0.0	0.0	0.0	40.9
	TCAIM	NM_173826	c.668C>G	p.S223C	0.0	0.0	0.0	0.0	70.0
	TMEM132D	NM_133448	c.481G>A	p.A161T	0.0	0.0	0.0	0.0	35.3
	UBA2	NM_005499	c.419G>A	p.G140E	0.0	0.0	0.0	0.0	47.4
	DNMT3A	NM_153759	c.449delT	p.V150Gfs	0.0	0.0	0.0	8.7	61.1
	NRAS[a]	NM_002524	c.38G>A	p.G13D	0.0	0.0	0.0	0.0	18.4

[a]Below the threshold in the initial screening.

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none of the identified somatic mutations were shared between the initial AML and DCL, providing further support for the distinct nature of the two leukemias.

Given that P3 contains only 24% myeloblasts, our computational pipeline could not accurately detect all of the associated somatic mutations. Indeed, most of the somatic mutations found in P1 (such as those in *ANO4*, *APOB*, *BANK1*, *STAG2* and *CEBPA*) were still present in P3 at lower frequencies (Table 1) but were not isolated in our pipeline analysis for P3. Lowering the threshold for somatic calls, however, increased the number of pseudopositive mutations in all specimens. We therefore applied the 30% threshold for mutation calls to all analyses. Of note, our data still indicate that P3 is not completely identical to P1. Nonsynonymous mutations of *CCDC88C* and *JAK3* detected in P1 were thus absent in P3, whereas a mutation of *NTNG2* was newly apparent in P3, suggestive of a clonal evolution in P3 divergent from the original P1 clones.

Surprisingly, whereas most somatic mutations detected in D3 were not present in D1, our results suggested that IDH2(R140Q) and DNMT3A(V150Gfs) were already present in the healthy donor at a low frequency (Table 1). Polymerase chain reaction (PCR)-based cloning of the genomic fragments and Sanger sequencing for *IDH2* and *DNMT3A* from D1 indeed confirmed the presence of the corresponding mutations in 2 (2.3%) out of 87 DNA clones and 1 (1.1%) out of 93 clones, respectively (Supplementary Figure 2). Furthermore, although the mutation rate (18.4%) was below the threshold of the present study, the oncogenic mutation NRAS(G13D)[5] in D3 (Table 1) was confirmed by Sanger sequencing of the corresponding genomic DNA (Supplementary Figure 2).

We then verified these infrequent mutations by sequencing the corresponding DNA fragments at extra-high coverage (hundreds of thousand times) with the use of a next-generation sequencer. The D2 sample, which contains only 6% myeloblasts, was also examined in this analysis. We confirmed that 1.6% (5.96×10^3 mutant reads out of 3.67×10^5 total reads at the corresponding nucleotide position) and 2.1% (1.24×10^4 out of 6.01×10^5 reads) of D1 cells already harbored the IDH2(R140Q) and DNMT3A(V150Gfs) mutations, respectively (Figure 1a). These mutations were not detected in the primary AML (P1 to P3). Whereas the *NRAS* mutation was not detected in D1, it became apparent in D2 and D3 at a frequency similar to that of the *IDH2* mutation. In addition, the *JAK3* mutation present in P1 was no longer evident at the relapsed stage P3.

On the basis of the genetic mutation profiles identified in the present case, we propose the following scheme for disease progression (Figure 1b). Given the high frequency of *STAG2* and *CEBPA* mutations in the primary AML, the 2-bp insertion in *STAG2* on the X chromosome (with there being only one copy of *STAG2* per cell in the male patient) as well as the heterozygous 4-bp deletion in *CEBPA* may characterize the founding clone of the original leukemia, with subsets of this clone subsequently acquiring additional oncogenic hits such as JAK3(L857P). The disappearance of *JAK3* and *CCDC88C* mutations in P3 suggests that the leukemic subclones harboring these mutations were sensitive to the initial chemotherapy.

The molecular pathogenesis of DCL has been unclear and may differ among cases. For instance, germline predisposition to cancer, such as the Li-Fraumeni syndrome or Bloom syndrome, may be shared between recipients and related donors.[6] However, in the present case, mutations in *IDH2* and *DNMT3A* were detected only in the donor, not in the primary AML, rendering this scenario unlikely. Alternatively, occult leukemia may already be present in the donor blood system and is inadvertently transmitted to the recipient.[7] In such cases, however, leukemia usually emerges in the donor soon after transplantation. Our donor, in contrast, has not developed any hematologic malignancy at 10 years after the donation of his PBSCs.

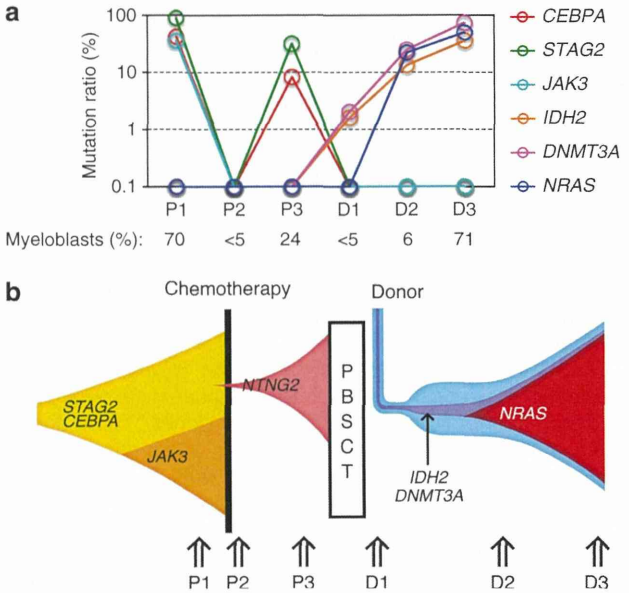

Figure 1. Genomic analysis of AML samples and donor PBSCs. (**a**) Genomic mutations corresponding to CEBPA(D107Tfs), STAG2(H73Rfs), JAK3(L857P), IDH2(R140Q), DNMT3A(V150Gfs) and NRAS(G13D) were examined by targeted deep sequencing in genomic DNA prepared from samples P1, P2, P3, D1, D2 and D3. The ratio of mutant reads to all reads at the corresponding position is shown as a percentage, with mutation frequencies of $<0.1\%$ being considered as 0.1% in the graph. The percentage of myeloblasts in each sample is indicated below the graph. (**b**) Founding clones of the primary AML harbored nonsynonymous mutations of *STAG2* and *CEBPA* and gave rise to subclones harboring a *JAK3* mutation. Whereas the latter cell population was sensitive to the initial chemotherapy, a subclone positive for an *NTNG2* mutation emerged from the former population and gave rise to relapse. All of these leukemic clones were successfully eradicated by peripheral blood stem cell transplantation (PBSCT). PBSCs of the donor, however, contained a small clonal population of cells positive for *IDH2* and *DNMT3A* mutations that eventually gave rise to AML on acquisition of additional mutations including NRAS(G13D).

Our present data therefore strongly suggest that apparently healthy individuals may harbor preleukemic subclones in their blood system (Figure 1b). Indeed, somatic mutations of *TET2* and *DNMT3A* were recently identified in clonal blood cells from one healthy elderly individual.[8] Furthermore, the *IDH2* and *DNMT3A* mutations identified in the present study may have had a specific role in the initiation of leukemia, given that mutations in the epigenetic modifiers including TET1/2, IDH1/2 and DNMT3A have been identified as early genetic events in AML progression.[9,10] Such mutations are indeed among the most frequently detected somatic alterations in AML.[11] These observations raise an important concern as to how 'appropriate' donors should be chosen, especially given that the incidence of DCL is increasing with the prevalence of molecular analysis for donor/recipient chimerism.[2] Prospective studies of whether and how examination of preleukemic subclones should be incorporated into the donor selection process for stem cell transplantation are thus warranted.

Furthermore, in our case, the oncogenic mutation NRAS(G13D) was likely a driver for leukemia progression, given that the frequency of this mutation was almost identical to that of the *IDH2* mutation in the D2 and D3 specimens. In contrast to the absence of leukemia in the donor, DCL rapidly developed in the recipient after transplantation in association with the accumulation of additional genetic hits, possibly as a result of a growth-promoting condition of the bone marrow after transplantation and due to a

defective immune surveillance resulting from the immunosuppressive treatment to control graft-versus-host disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Cytogenetics and outcome of infants with acute lymphoblastic leukemia and absence of *MLL* rearrangements

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Acute lymphoblastic leukemia (ALL) in infants less than 1 year of age is rare and the biological features are different from ALL in older children.[1] Infant ALL is characterized by a high frequency of rearrangements of the *MLL* gene (*MLL*-R) and heterogeneous outcome. However overall, their event-free survival (EFS) is much worse than older children with ALL.[1–5] A large collaborative trial, Interfant-99, demonstrated improved outcome, while characterizing definitively the independent prognostic variables in infant ALL.[6] While cytogenetic data are reported within individual infant ALL clinical trials, the numbers are typically small and many reports are less detailed for those patients without *MLL* gene rearrangements (*MLL*-G). However, it was previously suggested that *MLL*-G had an important predictive influence on outcome.[7,8] These observations were later confirmed in Interfant-99,[6] in which *MLL*-G patients showed a threefold reduced risk of an event compared with *MLL*-R patients, although all *MLL*-G patients were grouped together into a single category. To better understand the association of different chromosomal abnormalities and outcome among *MLL*-G infants, here we have carried out detailed cytogenetic investigation of two infant ALL trials: Interfant-99 and Children's Oncology Group (COG)-P9407.

Patients were 365 days old or less with newly diagnosed ALL without a rearrangement of the *MLL* gene enrolled to Interfant-99 (May 1999–December 2005; $n = 110$) and COG-P9407 (June 1996–October 2006; $n = 52$).[6,9] Individual study groups obtained ethical approval, and treating physicians obtained informed consent from parents or guardians. The presence of *MLL* gene rearrangements was excluded using fluorescence *in situ* hybridization (FISH), reverse transcription (RT)-PCR and/or Southern blotting, as previously reported.[6] Each national study group provided patient data, including cytogenetics, FISH and molecular results. EFS and overall survival (OS) were calculated from the date of trial enrolement to the date of the first event (induction failure, relapse, second malignancy or death) or last follow-up. Median follow-up time was 7 years.

Among 162 *MLL*-G patients, no cytogenetic data were available for 34 (21%), resulting in a success rate of 79%. An abnormal karyotype was detected in 90/128 (70%) patients with a successful cytogenetic result (Supplementary Table 1) with the remainder classified as normal based on the presence of at least 10 (but usually 20) normal metaphases. They were categorized according to cytogenetic risk group as previously defined for childhood ALL.[10] Compared with childhood ALL (1–18 years) using data from the UKALL97/99 treatment trial,[10] the frequency of good risk cytogenetic abnormalities among *MLL*-G infants was significantly lower (12 vs 60%, $P < 0.01$), whereas the frequency of poor risk abnormalities (excluding *MLL* translocations) was similar (8 vs 10%). Although *ETV6–RUNX1* fusion is present in 25% of childhood ALL, we found no *ETV6–RUNX1* cases among the 75 patients tested by FISH or RT-PCR. High hyperdiploidy (HeH) was the most

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Recurrent *CDC25C* mutations drive malignant transformation in FPD/AML

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Familial platelet disorder (FPD) with predisposition to acute myelogenous leukaemia (AML) is characterized by platelet defects with a propensity for the development of haematological malignancies. Its molecular pathogenesis is poorly understood, except for the role of germline *RUNX1* mutations. Here we show that *CDC25C* mutations are frequently found in FPD/AML patients (53%). Mutated CDC25C disrupts the G2/M checkpoint and promotes cell cycle progression even in the presence of DNA damage, suggesting a critical role for CDC25C in malignant transformation in FPD/AML. The predicted hierarchical architecture shows that *CDC25C* mutations define a founding pre-leukaemic clone, followed by stepwise acquisition of subclonal mutations that contribute to leukaemia progression. In three of seven individuals with *CDC25C* mutations, *GATA2* is the target of subsequent mutation. Thus, *CDC25C* is a novel gene target identified in haematological malignancies. *CDC25C* is also useful as a clinical biomarker that predicts progression of FPD/AML in the early stage.

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