Brief Report

LYMPHOID NEOPLASIA

Genetic profile of T-cell acute lymphoblastic leukemias with *MYC* translocations

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Key Points

- *MYC* translocations represent a genetic subgroup of *NOTCH1*-independent T-ALL clustered within the *TAL/LMO* category.
- *MYC* translocations are secondary abnormalities, which appear to be associated with induction failure and relapse.

MYC translocations represent a genetic subtype of T-lineage acute lymphoblastic leukemia (T-ALL), which occurs at an incidence of ~6%, assessed within a cohort of 196 T-ALL patients (64 adults and 132 children). The translocations were of 2 types; those rearranged with the T-cell receptor loci and those with other partners. *MYC* translocations were significantly associated with the *TAL/LMO* subtype of T-ALL ($P = .018$) and trisomies 6 ($P < .001$) and 7 ($P < .001$). Within the *TAL/LMO* subtype, gene expression profiling identified 148 differentially expressed genes between patients with and without *MYC* translocations; specifically, 77 were upregulated and 71 downregulated in those with *MYC* translocations. The poor prognostic marker, CD44, was among the upregulated genes. *MYC* translocations occurred as secondary abnormalities, present in subclones in one-half of the cases. Longitudinal studies indicated an association with induction failure and relapse. (*Blood*. 2014;124(24):3577-3582)

Introduction

MYC is one of the main phosphatidylinositol 3-kinase (PI3K)/ AKT targets, thus rearrangements underlying PI3K/AKT activation result in MYC overexpression. Deregulation of the PI3K/ AKT pathway plays a pivotal role in T-lineage acute lymphoblastic leukemia (T-ALL), being constitutively activated in cases with *NOTCH1/FBXW7* (50%-60%) mutations, *PTEN* (10%-30%) inactivation and *PTPN2* (6%) deletions.[1-4] These observations have identified *MYC* as a key T-ALL oncogene and an effective therapeutic target.[5] The potential role of *MYC* activation in initiating T-ALL tumorigenesis has been demonstrated in transgenic zebrafish and mouse models, where the induced over-expression of c-Myc lead to T-ALL development with high penetrance and short latency.[5-8] Moreover, in T-ALL murine models, c-Myc appeared to be critical for leukemia initiation, maintenance, and self-renewal, as its suppression, prevents leukemia development.[9-11]

We have characterized an emerging group of T-ALL with *MYC* translocations, identified as a specific subgroup of *NOTCH1*-independent *TAL/LMO*-positive leukemia, occurring in about 6% of adult and childhood T-ALL.

Study design

To assess the incidence of *MYC* translocations in T-ALL, we investigated 64 adults and 132 children (supplemental Methods, available on the *Blood* Web site). Combined interphase fluorescence in situ hybridization (CI-FISH) and/or Predictive Analysis of Microarrays[12] classified 80% of cases into groups according to distinct genetic features: *TAL/LMO* (57), *HOXA* (49), *TLX3* (31), *TLX1* (16), and *NKX2-1* (5), whose distribution into age groups reflected previous studies (supplemental Table 1). Karyotyping, CI-FISH, single nucleotide polymorphism array, and mutational analysis investigated concurrent genomic abnormalities (supplemental Methods).[12]

Results and discussion

Incidence and type of *MYC* translocations

MYC translocations were detected in 12 of 196 cases of T-ALL (6.1%) and were equally distributed between children and adults (Table 1). They involved T-cell receptor (*TCR*) loci in 6 cases and

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Table 1. Clinical, hematologic, and molecular-cytogenetic features of T-ALL with MYC translocations

No.	Sex	Age, y	WBC mmc	Phenotype	Treatment	Relapse	Status	Follow-up, mo	Karyotype	FISH	Category*	PTEN	NOTCH1/ FBX7
Children													
1	M	14	235.600	Early	AIEOP, IR	No	Alive	107	46,XY,**t(1;8)(q32;q24)**,del(4)(p15)[13]	**MYC translocation (85%)** / del(4)(q25)/LEF1 / del(9)(p21)/CDKN2A/B / **del(10)(q23)/PTEN**	TAL/LMO	wt	wt/wt
2	F	12	43.800	Cortical	AIEOP, SR	Yes	Died	13	46,XX,**t(8;14)(q24;q11)**[3] 48,idem,+6, +7[7]	**TCRAD-MYC (60%)** / del(9)(p21)/CDKN2A.B / **Trisomy 6** / **Trisomy 7**	TAL/LMO	mut	wt/wt
3	M	10	754.800	Mature	AIEOP, HR	Yes	Died	24	n.a.	SIL-TAL1 / **MYC translocation (70%)**	TAL/LMO	mut	wt/wt
4†	M	5	112.100	Mature	AIEOP, HR	No	Alive	87	46,XY,del(6)(q16),**t(7;8)(q22;q24)**, t(11;14)(p14;q11)[6] 46,XY[6]	SIL-TAL1 / TCRAD-LMO2 / **MYC translocation (18%)** / del(6)(q16)/GRIK2 / del(9)(p21)/CDKN2AB	TAL/LMO	wt	wt/wt
5†	M	8	168.000	n.a.	UKALL2003, regimen B	No	Alive	60	46,XY,**t(8;14)(q24;q11)**[2]/46,XY[6]	TCRB-TAL2 / **TCRAD-MYC (30%)**	TAL/LMO	wt	wt/wt
6	F	9	618.000	n.a.	MRC.ALL97/99, regimen B	No	Alive	84	46,XX[14]	SIL-TAL1 / **TCRB-MYC (86%)** / **del(10)(123)/PTEN** / del(9)(p21)/CDKN2AB	TAL/LMO	wt	wt/wt
7†	M	13	79.500	n.a.	MRC.ALL97/99, regimen C	No	Alive	83	46,XY,t(11;19)(q23;p13)[10]	MLL-ENL / **MYC translocation (28%)** / trisomy 6 / trisomy 7	HOXA	mut	wt/wt
8†	F	3	650.000	n.a.	MRC.ALL97,SR	No	Alive	120	46,XX,**t(8;14)(q24;q11)**[6]/46,XX[4]	**TCRAD-MYC (10%)** / bdel(9)(p21)/CDKN2AB	Unclassified	wt	wt/wt
Adults													
9	F	25	62.700	Cortical vs mature	GIMEMA LAL 2000	Yes	Died	30	n.a.	SIL-TAL1 / TCRB-LM01 / **TCRB-MYC (62%)** / del(9)(p21)/CDKN2AB / del(6q15)/CAS8AP2	TAL/LMO	mut	
10	M	44	251.000	Cortical	NILG ALL 10/07	No	Alive	29	46,XY,**t(8;14)(q24;q11)**[13],46,XX[3]	SIL-TAL1 / **TCRA/D-YC (90%)** / **del(10)(q23)/PTEN** / del(9)(p21)/CDKN2AB / Gain 10p13/AF10	TAL/LMO	mut	wt/wt

AIEOP, Associazione Italiana Emato-Oncologia Pediatrica; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; F, female; GIMEMA, Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto protocols; HR, high risk; hyperCVAD, cyclophosphamide, doxorubicin, vincristine, prednisone, methotrexate, cytarabine; IR, intermediate risk; LAL, acute lymphoblastic leukemia; M, male; mmc, cubic millimeter; MRC, Medical Research Council protocols; mut, mutated; n.a., not available; NILG, Northen Italy Leukemia Group protocol; SR, standard risk; UKALL2003, United Kingdom acute lymphoblastic leukemia protocol; WBC, white blood cell; wt, wild type.

*The genetic category was defined by CI-FISH and/or gene expression profile.

†Cases with subclonal MYC translocations. Between brackets the percentage of cells with MYC translocation is indicated.

Table 1. (continued)

No.	Sex	Age, y	WBC mmc	Phenotype	Treatment	Relapse	Status	Follow-up, mo	Karyotype	FISH	Category*	PTEN	NOTCH1/ FBX7
11†	F	56	84.740	Cortical vs mature	CHOP,HyperCVAD	Yes	Died	8	n.a.	**MYC translocation (50%)** del(9)(p21)/*CDKN2AB* **Gain 6q23/*MYB*** **Trisomy 7** Gain Xq28/*MTCP1*	*TAL/LMO*	wt	wt/wt
12†	M	48	20.000	Cortical	GIMEMA 0904	Yes	Died	18	n.a.	*TCRAD-TLX1* **MYC translocation (8%)** del(18)(q11)/*PTPN2* del(9)(q21)/*CDKN2AB* del(12)(p13)/*3 ETV6* del(14)(q32)/*BCL11B* del(11)(p13)/*WT1*	*TLX1*	wt	mut/mut

AIEOP, Associazione Italiana Emato-Oncologia Pediatrica; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; F, female; GIMEMA, Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto protocols; HR, high risk; hyperCVAD, cyclophosphamide, doxorubicin, vincristine, prednisone, methotrexate, cytarabine; IR, intermediate risk; LAL, acute lymphoblastic leukemia; M, male; mmc, cubic millimeter; MRC, Medical Research Council protocols; mut, mutated; n.a., not available; NILG, Northen Italy Leukemia Group protocol; SR, standard risk; UKALL2003, United Kingdom acute lymphoblastic leukemia protocol; WBC, white blood cell; wt, wild type.

*The genetic category was defined by CI-FISH and/or gene expression profile.

†Cases with subclonal *MYC* translocations. Between brackets the percentage of cells with *MYC* translocation is indicated.

new partners in the other 6. The 8q24 breakpoints clustered within the telomeric region of *MYC* in all *TCR* translocations, whereas in the non-*TCR* translocations the 8q24 breakpoints mapped both telomeric and centromeric to *MYC* (supplemental Figure 1) mirroring non-*IGH* *MYC* translocations in B-cell ALL.[13]

Here, non-*TCR* translocation partners were assessed in 4 cases. *CDK6*/7q21.2, rearranged in T-ALL with t(5;7)(q35;q21) and TLX3 overexpression,[14] was involved in cases 3 and 4. Hitherto-undescribed breakpoints involved 1q32.1, in case 1, within a long intergenic noncoding RNA, about 300 kb downstream of *PTPRC* and Xq25, in case 7, in a no-gene region 5 kb upstream of *SH2D1* (supplemental Figure 2). Whatever the partner, *MYC* translocations resulted in *MYC* overexpression (Figure 1B). Remarkably, common to all cases was *MYC* relocation close to genes which are transcriptionally active in T lymphocytes (supplemental Figure 2).

In T-ALL, high *MYC* expression is mainly caused by molecular mechanisms acting at the transcriptional or posttranscriptional level.[15] In this study, we have shown that other genes/regions besides *TCR* may be involved in *MYC* translocations and that the incidence of *MYC* translocations in T-ALL is higher than previously reported.

Genetic profile of T-ALL with *MYC* translocations

Similar to other type B abnormalities, *MYC* translocations were not seen as isolated changes. In-depth molecular-cytogenetic characterization revealed from 2 to 9 abnormalities per case (median, 3.7) (Table 1; supplemental Table 2). T-ALL with *MYC* translocations clustered within the *TAL/LMO* category (Pearson χ^2, $P = .018$) (Figure 1C). Complete or partial trisomies of chromosomes 6 (3 of 12, 25%) (χ^2, $P < 0.001$) and 7 (3 of 12, 25%) (χ^2, $P < .001$) were significantly associated with *MYC* translocations and occurred together in all cases (2, 7, and 11 from Table 1). Other cooccurring abnormalities were *CDKN2A/B* deletions (*CDKN2AB*[del]) (75%) and *PTEN* inactivation, resulting from deletion or mutation (*PTEN*[del/mut]) (58%). Similar results were found in the MOLT-16 and SKW-3/KE-37 cell lines with t(8;14)(q24;q11)/*TCRAD-MYC*. In fact, they both carry *SIL-TAL1* and/or *LMO2* translocations as primary abnormalities, and *CDKN2AB*[del] and *PTEN*[del/mut] as additional hits (supplemental Table 3). *PTEN* inactivation in primary samples as well as cell lines reflect results from experimental mouse models, which have shown that c-Myc rearrangements and Pten[del] exert a synergistic effect in the development of T-ALL, appearing to replace the function of Notch1.[8,16] Interestingly, *PTEN*[del/mut] and *NOTCH1* mutations were mutually exclusive in our cases, confirming that they arise in different T-ALL subgroups.[17] In a unique *TLX1*-positive case (no. 12), the *MYC* translocation was associated with *PTPN2* loss. The 2 *PTEN*- and *PTPN2*-negative regulators of PI3K/AKT signaling[18] were inactive in ~65% of our cases, suggesting that constitutive PI3K/AKT pathway activation is a critical synergistic hit in this T-ALL subgroup.

MYC translocations identify a subgroup within the *TAL/LMO* category

Within the set of 51 pediatric patients with *TAL/LMO*-positive T-ALL, the 6 with *MYC* translocations belonged to the group with the highest *MYC* expression, defined as the fourth quartile (Q4) based on *MYC* expression. Supervised gene expression profiling analysis of the Q4 group showed that patients with and those without *MYC* translocations clustered separately (Figure 1D). A Shrinkage *t* test revealed 148 genes differently expressed between the 2 groups (supplemental Table 4). Namely, 77 were significantly upregulated and 71 genes downregulated (local false discovery rate <0.05) in the
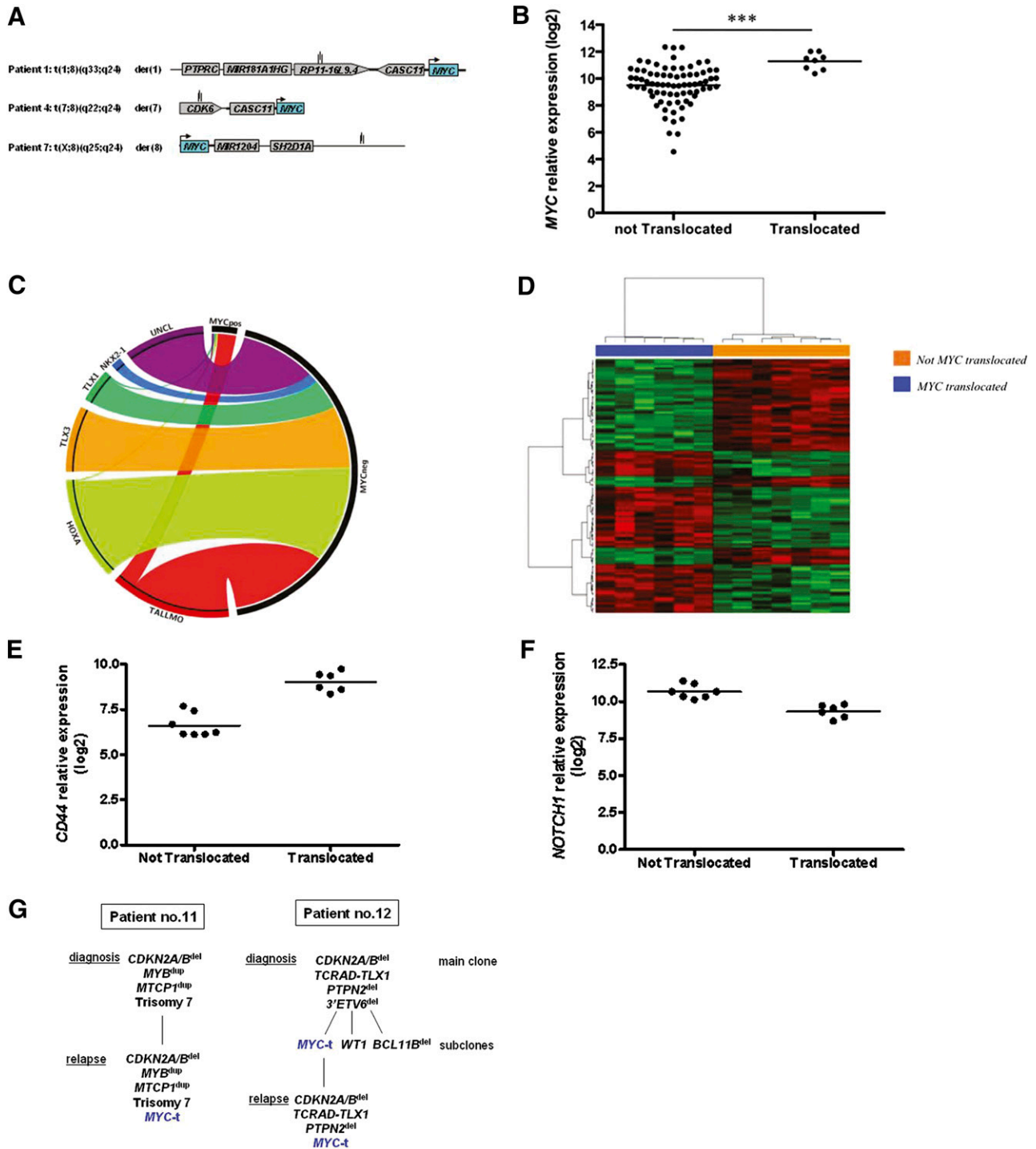
Figure 1. (A) Non-*TCR* partners of 3 cases of T-ALL (nos. 1, 4, and 7 from Table 1) with *MYC* translocations. Mapping of superenhancers at 1q32, 7q21, and Xq25 were indicated with 3 vertical thin bars. (B) *MYC* expression in 83 cases of pediatric T-ALL and in 8 *MYC* translocation–positive T-ALL (nos. 1-4, 9-12 from Table 1). Cases with translocations had a significantly higher *MYC* expression. (C) Circos plot shows distribution of *MYC* translocations according to genetic categories. *MYC* translocation–positive T-ALL clustered into the *TAL/LMO* category; (D) Supervised gene expression profiling analysis of 13 *TAL/LMO*-positive T-ALL with high *MYC* expression at diagnosis (Q4): 6 cases with *MYC* translocations (nos. 1-4, 9, 10; Table 1) clustered together and separated from the 7 cases without. (E) Q4 *TAL/LMO*-positive T-ALL: CD44 expression was higher in T-ALL cases with *MYC* translocation compared with cases without. (F) *NOTCH1* expression was significantly lower in cases with *MYC* translocations compared with cases without. (G) Longitudinal FISH studies in 2 cases: in case no. 11 the clone with *MYC* translocation was not detected at diagnosis but only at relapse (left); in case no. 12, the small subclone (~8%) with the *MYC* translocation present at diagnosis was found in 100% of leukemic blasts at relapse. Q4, fourth quartile.

group with *MYC* translocations compared with the group without. Specifically, a >1.3-fold change in *CD44* expression was observed in patients with *MYC* translocations, whereas *NOTCH1* and genes associated with *NOTCH1* activation (*PTCRA, NOTCH3, HES4,*

and *CR2*) were significantly downregulated (Figure 1E-F). In support of these results, gene set enrichment analysis confirmed enrichment of genes in the *NOTCH1* pathway in the group without *MYC* translocations (*q* value = 0.06; NES, 1.71) (supplemental

Figures 3 and 4A). Gene set enrichment analysis further indicated significant enrichment of cell death and apoptosis pathway genes in patients harboring *MYC* translocations (supplemental Figure 4B-C).

MYC-positive subclones are associated with relapse/induction failure

In case 12 (Table 1), paired diagnostic and relapse bone marrow samples showed that the size of the subclone with *MYC* translocations increased at relapse, rising from 8% to 100%, whereas other abnormalities, which were present either in the main clone, that is, $ETV6^{del}$, or in diverse subclones, such as $WT1^{del}$ and $BCL11B^{del}$, disappeared at relapse (Figure 1G). These findings are in line with results from xenograft models[19] which showed that *MYC* confers a proliferative advantage and resistance to drug toxicity. It is noteworthy that in mice c-Myc plays a crucial role in maintenance and self-renewal of leukemia-initiating cells, which are thought to be resistant to chemotherapy and mediate relapse.[11] In case 11, the *MYC* translocation, present at relapse, was not detected at diagnosis, implicating that it was acquired during disease progression (Figure 1G). Taken together, these data suggest that identification and possible eradication of small *MYC*-positive subclones at diagnosis and/or during the early stages of treatment may assist in prevention of disease progression. Notably, *MYC* translocations were found in subclones of variable size (range, 8%-62%) in 4 additional cases (Table 1).

Clinical and hematologic characteristic of T-ALL with *MYC* translocations

MYC translocation–positive T-ALL is characterized by leukocytosis and cortical/mature differentiation arrest in the majority of cases. It was not possible to evaluate the prognostic implications of *MYC* translocations in this retrospective study including children and adults belonging to different treatment protocols. However, poor prognostic markers, such as high *CD44* expression and *PTEN* inactivation, appeared to be strongly associated with this leukemia subgroup.[20-23] Moreover, although determination of minimal residual disease, the most powerful criteria used for risk stratification of pediatric ALL, classified case 2 into

the standard-risk group, this patient failed induction therapy and died in disease. Similar to B-lineage ALL and acute myeloid leukemia,[24,25] in which disease relapse has been related to minor leukemic subclones rather than to the predominant clone at diagnosis, subclones with *MYC* translocations in T-ALL may be more resistant to therapy and thus sustain relapse.

Authorship

Contribution: R.L.S. and C. Mecucci conceived and designed the study; C.S., C.J.H., A.L., G.C., S.C., and G. Basso provided study materials or patient samples; C. Matteucci and A.G.L.F. provided mutational analyses; R.L.S., C.B., G. Barba, V.P., G.t.K., and C. Mecucci analyzed and interpreted data; R.L.S. and C. Mecucci wrote the manuscript; and all authors gave final approval of the manuscript.

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