The t(1;12)(q21;p13) translocation of human acute myeloblastic leukemia results in a TEL-ARNT fusion

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Communicated by Jean Dausset, Centre d'Étude du Polymorphisme Humain, Paris, France, April 10, 2000 (received for review January 20, 2000)

The *TEL/ETV6* gene is located at 12p13 and encodes a member of the ETS family of transcription factors. Translocated ETS leukemia (TEL) is frequently involved in chromosomal translocations in human malignancies, usually resulting in the expression of fusion proteins between the amino-terminal part of TEL and either unrelated transcription factors or protein tyrosine kinases. We have characterized a t(1;12)(q21;p13) translocation in an acute myeloblastic leukemia (AML-M2). At the protein level, the untranslocated TEL copy and, as a result of the t(1;12) translocation, a fusion protein between TEL and essentially all of aryl hydrocarbon receptor nuclear translocator (ARNT) are expressed. The involvement of ARNT in human leukemogenesis has not been previously described. The ARNT protein belongs to a subfamily of the ''basic region helix–loop–helix'' (bHLH) protein that shares an additional region of similarity called the PAS (Per, ARNT, SIM) domain. ARNT is the central partner of several heterodimeric transcription factors, including those containing the aryl hydrocarbon (dioxin) receptor (AhR) and the hypoxia-inducible factor 1α (HIF1α). Our results show that the TEL-ARNT fusion protein is the crucial product of the translocation and suggest that interference with the activity of AhR or HIF1α can contribute to leukemogenesis.

Chromosomal abnormalities have been identified as an important step toward malignancy. Studies of solid and hematopoietic tumors have shown that chromosomal translocations usually result in the creation of chimeric genes and subsequent expression of fusion proteins. The translocated ETS leukemia (TEL) (also known as ETV6) gene, which encodes a member of the ETS family of transcription factors, is affected in more than half of the abnormalities of the short arm of chromosome 12 in various hematopoietic malignancies, and in solid tumors. Some of these abnormalities are specific for a leukemia subtype, whereas others are not. Perhaps the most intriguing characteristics of TEL-derived fusion proteins is that the contribution of TEL appears to be variable and the fusion partners are not functionally homogeneous because they encode protein tyrosine kinases or various unrelated transcription factors (for review see ref. 1).

More precisely, following the description of the fusion of TEL to the platelet-derived growth factor receptor β chain (PDGFRβ) gene, which is specific for chronic myelomonocytic leukemia (CMML) (2), the amino-terminal part of TEL has been found to be fused with other tyrosine kinases, such as ABL in atypical chronic myelocytic leukemia (aCML) and B acute lymphoblastic leukemia (ALL) (3, 4), JAK2 in T or B ALL and aCML (5, 6), and NTRK3 in acute myeloid leukemia (AML) and in congenital fibrosarcomas and renal tumors (7, 8). In those situations, either 154 or 336 amino acids of the amino-terminal part of TEL, including a powerful oligomerization domain, are fused to these tyrosine kinases. The resulting fusion proteins exhibit constitutive tyrosine kinase activity and transforming properties in both cell lines and animal models (3, 6, 9, 10).

Several examples of TEL fusion with unrelated transcription factors have been described. Among them, the MN1-TEL fusion, associated to the t(12;22)(p13;q22) observed in myeloid malignancies, is expected to result in dysregulation of TEL target genes, because the predicted important fusion protein bears the TEL DNA-binding domain (11).

The most frequent chromosomal rearrangement involving TEL known to date is the t(12;21)(p13;q22) that is specific for childhood B type ALL and observed in 25% of these cases (12–14). As a result of the t(12;21), 336 amino-terminal residues of TEL are fused to essentially all of AML1, including its DNA binding domain. AML1 encodes one of the α subunits of the core binding factor (CBF) and is known to be frequently rearranged in myeloid malignancies (15). In keeping with the recently established transcriptional repression properties of the normal TEL protein, TEL-AML1 fusion protein has been shown to exhibit dominant-negative activity with respect to normal CBF in transient transfection assays (16–18). The functional consequences of the TEL-AML1 fusion are therefore likely to be dysregulation of CBF target genes. In virtually all cases, the t(12;21) is associated with loss of expression of the untranslocated TEL copy, usually because of total or partial deletion (19, 20). Whether this loss of expression is important for the TEL-AML1 oncogenic activity per se or is more generally involved in leukemogenesis by affecting TEL-specific pathways is not established.

We report here the characterization of a t(1;12)(q21;p13) observed in a case of AML-M2. This translocation fuses TEL to the gene encoding the aryl hydrocarbon receptor nuclear translocator (ARNT) and results in the expression of a fusion protein containing the amino-terminal part of TEL and almost all of the ARNT protein.

Materials and Methods

Materials. The patient, a 5-yr-old male with AML-M2, has been previously reported (case 4, ref. 21). Karyotype was: 47,XY,t(1;12)(q21;p13),+21 (29)/46,XY (3) studied in bone marrow cell short-term cultures, and 47,XY,t(1;12) (6) in unstimulated blood cell cultures.

Two other patient leukemic samples used as control were AML-M2 without obvious rearrangement of 1q21 or 12p13 chromosomal regions. Their karyotypes were: patient A: 46,XX(21); patient B: 45,X,-X,r(8),t(8;21)(q22;q22)/46,idem,+i(22)(p10).

Cell lines have been widely described. Human cell lines are as

Abbreviations: TEL, translocated ETS leukemia; bHLH PAS, basic region helix–loop–helix Per/ARNT/SIM; ARNT, aryl hydrocarbon receptor nuclear translocator; AhR, aryl hydrocarbon receptor; HIF, hypoxia-inducible factor; EPAS1, endothelial PAS protein 1; CBF, core binding factor; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; CML, chronic myeloblastic leukemia; RT-PCR, reverse transcription–PCR; GST, glutathione *S*-transferase.

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Article published online before print: *Proc. Natl. Acad. Sci. USA*, 10.1073/pnas.120162297. Article and publication date are at www.pnas.org/cgi/doi/10.1073/pnas.120162297

follows: Kasumi, HL60 (AML-M2); NB4 (AML-M3); MUTZ3 (AML-M4); U937 (AML-M5); HEL (AML-M6); MEG (AML-M7); K562 (CML); Nalm6, 380 (ALL-B); Raji, Daudi (Burkitt); U266, RPMI8226 (plasmacytoma); BL2 (Epstein–Barr virus-transformed B lymphocyte); Jurkat, Rex, MOLT4, CEM, RPMI8402, SKW3 (ALL-T); YT (NK malignancy).

Nucleic Acid Methods. RNA was extracted from growing cell lines or from cryopreserved patients' cells by using Trizol (BRL) reagent according to the manufacturer's instructions. Anchored reverse transcription–PCR (RT-PCR) was performed essentially as described (22). Primers were TEL4.1, TEL4.2, and TEL4.3 (see below). Bispecific RT-PCR were performed starting from 100 ng of randomly primed reverse-transcribed total RNA for 40 cycles.

For basic region helix–loop–helix Per, ARNT, SIM (bHLH PAS) gene expression, RT-PCR was performed starting from 125 ng of randomly primed reverse-transcribed total RNA. PCR cycles were as follows: 94°C for 5 min, and 94°C for 45 s, 58°C for 20 s, and 72°C for 30 s for 27 cycles, 30 cycles, or 33 cycles. Primers (see below) were chosen to amplify efficiently both murine and human sequences. Specificity of the amplifications was verified by direct nucleotide sequence analysis.

Fusion cDNAs were constructed by PCR-mediated amplification of the appropriate regions of TEL and ARNT and subsequent subcloning. The amplified fragments were checked to be devoid of mutations. *In vitro* transcription/translation were performed by using the TNT kit (Promega) according to the manufacturer's instructions.

Primers. TEL3.1, cttgcagccaatttactgg; TEL4.1, tctgaagcagaggaaacc; TEL4.2, attcttccaccctggaaactct; TEL4.3, acagccggaggtcatact; TEL5.1, agagggtaggactcctggt; ARNT P1, gccggatccggtggcatctgcggccat; ARNT P2, cagagctctgctcatcatccga; ARNT 1F, gccargaaccacggcctacac; ARNT 1R, ctcaaggggcttgctgtgttc; HIF1αF, gcgaaaaatggaacatgatgg; HIF1αR, tggtcagctgtggtaatccac; AhRF, tacwgaagyagagctgtgca; AhRR, ctcrtacaacacagcytctcc; EPAS1F, aggggacggtcatctacaacc; EPAS1R, atggccttgccataggctgag; SIM1F, agcagagaagcctatgaraac; SIM1R, tagctgtaatctgttctcttc; SIM2F, cactgcatcgtgagtgtcaat; SIM2R, tggcygcaytccagtttgtcc; PER1F, ccagtgactttccagcagatc; PER1R, gcagttgatctgctggtagga; PER2F, aacggrtcccacgarcacct; PER2R, gctgatctgctggtaggagca; ARNT2F, aacttcagcaacagcaggca; ARNT2R, ggctgagctcatcatcttct.

Cellular Extracts. Frozen cells were thawed and washed once with RPMI 1640 medium. The pellet was resuspended in sample buffer (Laemmli 1×, 10 μl/1 million cells), disrupted by sonication, and heated for 5 min at 100°C. A total of 15 μl of the sample was loaded per well. Anti-TEL immune sera were described previously (23). Antibodies to the carboxyl terminus of ARNT were similarly generated by using a glutathione *S*-transferase (GST)-ARNT fusion protein encompassing amino acids 499–789 of human ARNT and used at 1/1000 dilution. Western blotting analyses were performed as described (6, 20).

Immunoprecipitations. The antiserum to the first 45 amino acids of human TEL protein (α M1TEL) has been described (16). Immunoprecipitations were performed as described (6, 16).

Results

Previous studies have demonstrated the involvement of TEL in the t(1;12) case studied here and located the breakpoint within the fourth intron of TEL (21). Anchored PCR techniques starting from patient material allowed us to characterize non-TEL sequences fused downstream of the fourth exon of TEL. Database searches revealed that these sequences originated from the ARNT gene, and the published location of the human ARNT locus on the long arm of chromosome 1 is in keeping with the location of the translocation breakpoint at 1q21 (24, 25). The existence of a TEL-ARNT fusion was next ascertained by RT-PCR. As shown Fig. 1*A*, both TEL-ARNT and ARNT-TEL fusion transcripts could be detected in patient material but not in the HL60 cell line, used as a negative control. Fluorescence *in situ* hybridization (FISH) analysis of patient metaphase chromosomes by using a bacterial artificial chromosome (BAC) probe corresponding to the ARNT gene confirmed the involvement of ARNT in the t(1;12)(q21;p13) at the cytogenetic level (data not shown).

ARNT encodes a member of the bHLH factors and belongs to a subset of these proteins that share an additional domain, the PAS repeat, named for the three first proteins identified in this subfamily. bHLH proteins bind as dimers to E boxes (CANNTG), with each of the subunits interacting with a half site. The bHLH PAS is a growing family of proteins that are involved in transcriptional regulation during development, signaling through nuclear receptor, stress, and circadian rhythm (see ref. 26 for review).

A scheme of normal TEL and ARNT proteins as well as the fusion products is shown Fig. 1*B*. As a result of the t(1;12), the TEL-ARNT protein is predicted to contain the 154 first amino acids of TEL, including its oligomerization domain (NCR), fused to all but the first 8 amino acids of the ARNT protein. The reciprocal product, ARNT-TEL, would consist of the 8 first amino acids of ARNT fused to the 298 carboxyl-terminal amino acids of TEL, including its ETS DNA-binding domain.

To investigate the expression of these proteins, whole cell lysate of patient blasts cells was analyzed by Western blotting using antibodies directed against TEL or against ARNT (Fig. 1*C*). As positive control, we used *in vitro*-translated TEL-ARNT that is easily detected as a 102-kDa protein species, using either an anti-ARNT immune serum (Fig. 1*C*, lane 1) or an immune serum specific for the amino-terminal part of TEL (anti-NTEL; data not shown). A strong signal of similar size was seen in patient material when either the anti-ARNT immune serum (Fig. 1*C*, lane 2) or the anti-NTEL immune serum (Fig. 1*C*, lane 3) was used, indicating that the fusion TEL-ARNT protein is expressed at high level in patient blast cells. A weaker signal corresponding to the size of normal ARNT could also be detected in patient material by using anti-ARNT immune serum (see Fig. 1*C*, lane 2). Similar experiments using an immune serum reacting specifically with the ETS domain of TEL (anti-CTEL) failed to unambiguously detect a protein species corresponding to the ARNT-TEL reciprocal product (compare lanes 4 and 5 in Fig. 1*C*). Therefore, very small amounts, if any, of the ARNT-TEL protein are expressed in blast cells. In contrast, normally sized TEL proteins could be easily detected by using either of the immune sera against TEL. This observation is in keeping with fluorescence *in situ* hybridization data, showing conservation of the untranslocated TEL copy, and RT-PCR amplification of normal TEL transcript (ref. 21, and data not shown).

It has been reported that the so-called NCR, *pointed* or B domain, located within the amino-terminal part of TEL (amino acids 54–119) mediates oligomerization and repression properties of TEL and TEL-derived fusion proteins (3, 6, 9, 16, 18). To analyze whether this domain is functional in TEL-ARNT, we first checked for the capacity of TEL-ARNT to oligomerize with itself. The first two in-frame AUGs present in the TEL mRNA are known to be active as translational start sites (23). Analysis of the translation of a carboxyl-terminally truncated form of TEL-ARNT showed that both AUGs are also active in the TEL-ARNT context and that both species (M1 and M43) can be discriminated as doublet by SDS/PAGE (Fig. 2*A*). Taking advantage of this situation, we immunoprecipitated *in vitro*-

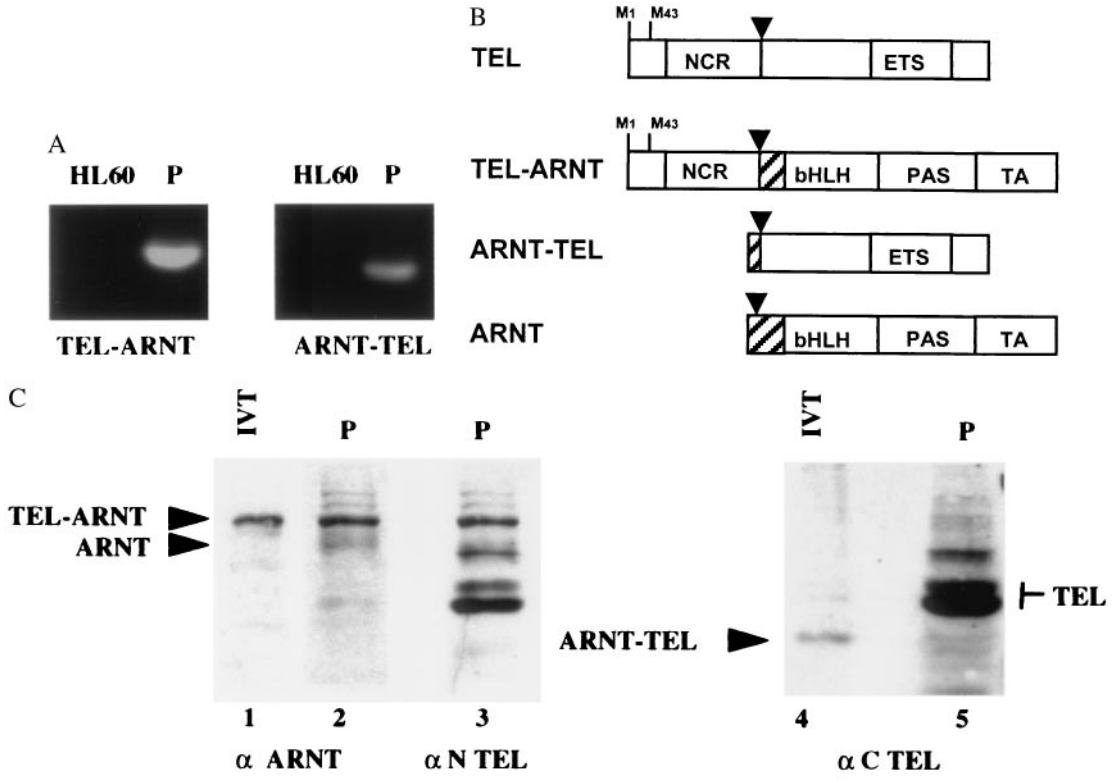

Fig. 1. Molecular analysis of the t(1;12)(q21;p13). (*A*) RT-PCR detection of TEL-ARNT and ARNT-TEL fusion transcript. TEL-ARNT (TEL 3.1-ARNT P2: 523 bp) and ARNT-TEL (ARNT P1-TEL 5.1: 283 bp) fragments were PCR amplified starting from patient cDNA but not from control (HL60) cDNA. (*B*) Schematic of normal and fusion TEL and ARNT proteins. The fusion points are indicated by arrows. Identified protein domains are indicated. M1 and M43 mark the two in-frame AUGs of the TEL mRNA (23). Size of normal TEL protein is 452 amino acids and of normal ARNT, 789 amino acids. (*C*) Western blot analysis of normal and fusion TEL and ARNT proteins in the patient's cells. The expected proteins are indicated by an arrowhead: TEL, 60–50 kDa; ARNT, 86 kDa; TEL-ARNT, 102 kDa; ARNT-TEL, 36 kDa. Note that TEL is detected as several protein species because of alternative translation start sites and posttranslational modifications.

translated TEL-ARNT by using an immune serum that is directed against the first 45 amino acids of TEL (α M1TEL). This immune serum has been previously proven to react specifically with the large species of TEL (M1) but not the smaller species (M43) (16). As shown in Fig. 2*A*, both TEL-ARNT species were immunoprecipitated by this immune serum, showing that the M1 and M43 isoforms of TEL-ARNT self-associate. To analyze whether TEL-ARNT is still able to interact with TEL, we carried out immunoprecipitation experiments on *in vitro* cotranslated TEL-ARNT and TEL proteins. As shown in Fig. 2*B*, TEL-ARNT efficiently interacts with TEL (see Fig. 2*B*, lanes 1–6 and 13–15), whereas TELΔNCR-ARNT, a fusion protein lacking the

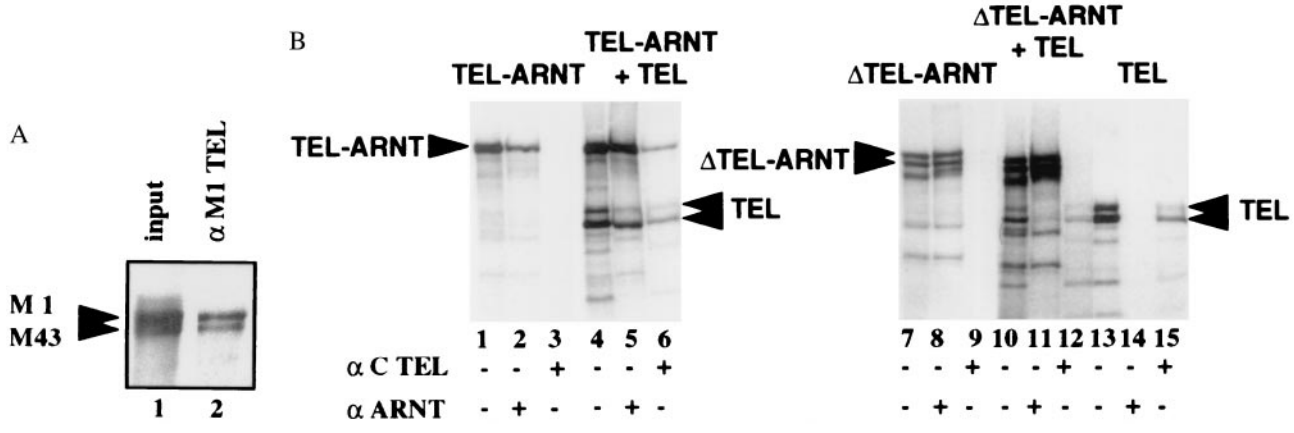

Fig. 2. Interaction between TEL and TEL-ARNT proteins. (*A*) Self-association of TEL-ARNT. (*B*) TEL and TEL-ARNT interaction depends on the TEL oligomerization domain. Note the presence of several protein species in some lines is because of multiple translational start sites. TEL-ARNT (input lane 1) and ΔTEL-ARNT (input lane 7) are specifically immunoprecipitated by anti-ARNT (lanes 2 and 8) but not anti-CTEL (lanes 3 and 9). TEL (input lane 13) is specifically immunoprecipitated by anti-CTEL (lane 15) but not anti-ARNT (lane 14). When cotranslated, TEL and TEL-ARNT proteins (input lane 4) are coimmunoprecipitated (lanes 5 and 6), demonstrating interaction. TEL and ΔTEL-ARNT proteins do not interact (lanes 10–12).

Table 1. RT-PCR analysis of expression of several bHLH PAS genes in malignant cell line samples

Cell line	ARNT	AhR	HIF1α	EPAS1
Kasumi	+	−	+	−
HL60	+	+	+	−
NB4	+	+	+	−
MUTZ3	+	+w	+	−
U937	+	+	+	−
HEL	+	−	+	+w
MEG01	+	+	+	+
K562	+	−	+	−
Nalm6	+	−	+	−
380	+	−	+	−
Raji	+	−	+	−
Daudi	+	−	+	−
U266	+	−	+	−
RPM18226	+	−	+	−
BL2	+w	−	+	−
Jurkat	+	−	+	−
Rex	+	−	+	−
MOLT4	+	−	+	−
CEM	+	−	+	−
RPM18402	+	−	+	−
SKW3	+	−	+	−
YT	+	+	+	−
HeLa	+	+	+	−
32Dcl3	+	−	+	−
Ba/F3	+	−	+	−
WEHI-3	+	−	+	−

A − indicates negativity after 33 PCR cycles of amplification of the sample; a + indicates positivity after 27 cycles of amplification; +w indicates positivity after 30 cycles of amplification.

TEL oligomerization domain (Fig. 2, lanes 7–12) or ARNT alone (data not shown), failed to interact with TEL.

In summary, our data suggest that the important product of the t(1;12) is the TEL-ARNT fusion protein and that this protein retains the properties of TEL to self-associate and might interact with the normal TEL protein expressed from the remaining normal untranslocated TEL copy.

ARNT is the common subunit of several dimeric transcriptional complexes. ARNT has been demonstrated to interact with HIF1α and the related endothelial PAS1 (EPAS1) protein, that are involved in the cellular response to hypoxia, with the aryl hydrocarbon receptor (AhR) involved in the response to xenobiotics, and with SIM, involved in neurogenesis. ARNT has been demonstrated to interact *in vitro* with the *Drosophila* Per protein, a PAS-only protein involved in the control of circadian rhythm. Because no specific analyses of the expression of the genes encoding putative ARNT partners within the hematopoietic system were available, we used RT-PCR techniques to investigate the expression of HIF1α, EPAS1, AhR, Sim 1, Sim 2, Per 1, and Per 2 in a series of human and murine malignant hematopoietic cell lines (see *Materials and Methods*). Expression of the ARNT2 gene, whose product is very similar to the ARNT protein, but whose expression is reported to be restricted to the central nervous system, was also investigated. These results are summarized in Table 1. To avoid overamplification, a limited number of PCR cycles were performed.

In all hematopoietic cell line samples, ARNT and HIF1α were detected after a 27-cycle amplification (data not shown). In contrast, AhR was not detected in lymphoid cell lines and in a subset of myeloid cell lines, even after 33 cycles of amplification. AhR was detected in only four AML cell lines (HL60, NB4, U937, Meg01) and was somewhat weaker in the Mutz3 cell line sample. EPAS1 was detected only in two cell lines representative of the erythro/megakaryocytic pathway, Meg01 at 27 cycles and HEL at 30 cycles (data not shown). The SIM, PER, and ARNT2 genes were not detectably expressed in our samples. Only the murine 32Dcl3 cell line was repeatedly found to express ARNT2.

To investigate the expression of these genes in patient material, similar experiments were performed starting from leukemic cells from the t(1;12) patient and, as control, that of two other patients with AML-M2 but devoid of known 1q21 chromosomal abnormality (A and B, see *Materials and Methods*). ARNT and HIF1α were detected after 27 cycles. In these conditions, AhR was found clearly positive in control samples (Fig. 3, lanes 7 and 8) but was barely detectable in the t(1;12) leukemic cells (Fig. 3, lane 6). AhR was, however, unambiguously positive in patient material after 30 cycles (Fig. 3, lane 10). EPAS1 was not detectable in our samples after 27 or 30 cycles. With 33 cycles, it remained negative in control samples (Fig. 3, lanes 12 and 13), whereas an EPAS1-amplified cDNA was observed in the lane corresponding to the t(1;12) patient sample (Fig. 3, lane 14). Because of the high number of cycles used to detect EPAS1 expression in the t(1;12) sample, one cannot be sure that EPAS1 is expressed in blast cells. Therefore, HIF1α and AhR can be regarded as TEL-ARNT partners in the patient's leukemic cells.

Discussion

In tumor-associated chromosomal translocations, TEL has been shown to be fused to several partner genes, most of them distributed in two large families, namely those encoding protein tyrosine kinases and those encoding transcription factors (1). Although the breakpoints are variously located in the different translocations, most of the resulting fusion proteins include the amino-terminal oligomerization domain of TEL. We report here the characterization of a t(1;12)(q21;p13) translocation in a patient with AML-M2 that rearranges the TEL gene on 12p13 with the ARNT gene on 1q21.

Two fusion proteins are predicted from the structural analysis of this translocation. The ARNT-TEL protein that consists of 8 amino acids of ARNT fused to the 298 carboxyl-terminal amino acids of TEL. This protein should not play an important role in

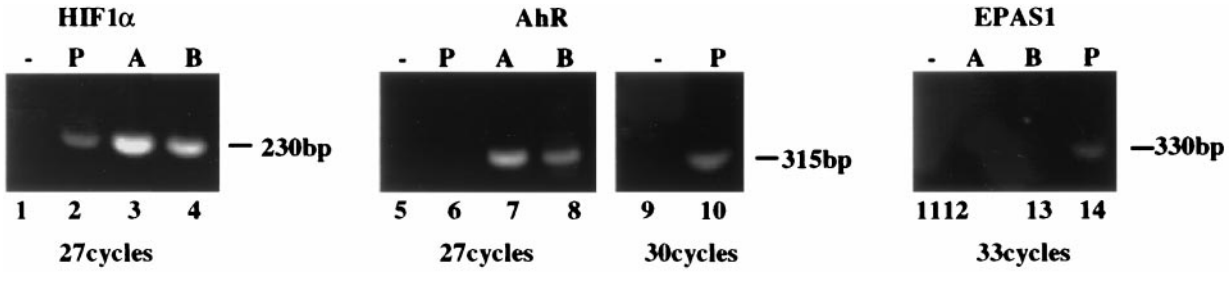

Fig. 3. RT-PCR detection of HIF1α, EPAS1, and AhR in patient blast cells.

the oncogenic process because it is expressed at very low level, if at all. Furthermore, although it retains one of the repression domains of TEL, it lacks the TEL oligomerization domain, which is indispensable for the repressor activity of the protein (16, 18). In contrast, the TEL-ARNT protein that contains the amino-terminal oligomerization domain of TEL and almost all of the ARNT protein is highly expressed in the leukemic cells of the patient, suggesting that interference with normal ARNT function is central to this leukemic process.

ARNT has been shown to interact with at least three bHLH PAS protein partners, SIM proteins involved in neurogenesis, AhR, induced by polycyclic hydrocarbons, and HIF1α following several extracellular stimuli such as hypoxia. Interaction with the *Drosophila* Per protein, a component of the circadian regulation loop, has also been reported (26).

Of the several ARNT partners known to date, AhR and HIF1α were found to be expressed in the leukemic blasts of the t(1;12) patient and of two other AML-M2 samples and, more generally, in human myeloid cell lines. In contrast, Sim 1, Sim 2, Per 1, and Per 2 were not expressed in hematopoietic cell lines. TEL is an active repressor of transcription, and the TEL-AML1 fusion protein has been suggested to exert its oncogenic properties through a dominant-negative effect on normal AML1 function (16, 18). These repressor activities are dependent on the integrity of the TEL oligomerization domain and on its self-association properties. In that respect, the oligomerization domain of TEL remains active in the context of the TEL-ARNT fusion, and the fusion of TEL sequences is expected to convert ARNT from a transcriptional activator into a repressor.

The AhR/ARNT complex is involved in transcriptional activation of several detoxification enzymes encoding genes, such as phase I cytochromes P 450 (CYP) and phase II GST. Genetic polymorphisms of the CYP and GST genes have been linked to increased susceptibility to solid tumors (see ref. 27 for review) and ALL (28) development. There is also some strong evidence linking high exposure to benzene with increased risk of developing AML (29). Dysregulation by TEL-ARNT of key genes, normally regulated by the AhR/ARNT heterodimer, could imbalance catabolic pathways and thereby raise the level of some metabolic intermediates. Because some of these intermediates are known to be powerful mutagenic agents, this could favor evolution of cells toward malignancy.

HIF1α is a highly unstable protein that is stabilized in response to several extracellular stimuli, such as hypoxia or low glucose levels (30). The HIF1α/ARNT (HIF1) complex has been proposed to be required extrinsically to control proliferation of hematopoietic progenitors during mouse embryogenesis (31). An important transcriptional target of the HIF1α/ARNT (HIF1) complex is the vascular endothelial growth factor (vEGF) gene. In von Hippel–Lindau (VHL) patients, a direct link has been established between the constitutive activation of HIF1α/ARNT, expression of vEGF, and extensive angiogenesis (32, 33). vEGF-stimulated neovascularization is an important step in the establishment of solid tumors that has been suggested to require HIF1α activity (34, 35). However, other studies have shown that loss of hypoxia response and subsequent apoptosis, acting on the tumor cell itself, could favor tumor growth (36). The study of the properties of TEL-ARNT, a natural ARNT mutant, will allow more light to be shed on these mechanisms.

HIF1 is also involved in the transcriptional regulation of genes encoding several glycolytic enzymes. Recent studies have suggested a role of the c-*myc* protooncogene in the transcriptional control of several genes whose products are involved in cellular metabolism, including glycolysis. c-*myc*- and HIF1α/ARNT-induced leukemogenesis may share a common pathway leading to dysregulation of glycolysis (37, 38).

Further studies are needed to determine the exact role of TEL-ARNT in the leukemic process, but we favor the hypothesis that it impairs the cellular response to extracellular stimuli, such as hypoxia, that are thought to be important for embryonic hematopoiesis (31). In this respect, extensive analysis will be needed to establish the incidence of ARNT mutations in human hematopoietic disorders and its real significance.

Finally, the role of the deletional inactivation of the untranslocated TEL copy in the context of the t(12;21) has been proposed to play a role in t(12;21)-mediated leukemogenesis. Although very closely associated to the t(12;21), the inactivation of TEL has been suggested to be a secondary event (13, 14, 19, 39–41). In the t(1;12) described here, TEL is expressed from the untranslocated copy of the gene. The TEL-ARNT fusion protein retains the oligomerization properties of TEL and can interact with the TEL protein. The relevance of this interaction to the leukemic process in the context of the t(1;12) remains to be determined.

We thank Dr. G. L. Semenza, C. A. Bradfield, O. Hankinson, and Y. Fujii-Kuriyama for the generous gift of plasmids. F.S.N. is supported by a fellowship from the Ligue Nationale Contre le Cancer. This work was partially supported by l'Association de Recherche sur le Cancer.

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