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Mini Review

ETV6 (TEL1) in Blood Cell Development and Malignancy

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Abstract

The *ETV6* (*TEL1*) gene encodes a member of the ETS family of transcriptional regulators. It represents one of the most frequently disrupted genes in haematological malignancies, with over 50 different translocations described. Moreover, deletion, silencing or truncating mutations have also been reported, suggesting a potential tumor suppressor function. Recent studies have shown that ETV6 plays a broad and complex role in early hematopoiesis, impacting on the development of multiple lineages, providing new insights into how its perturbation contributes to disease.

Keywords: ETV6; TEL1; ETS; Hematopoiesis; Leukemia

Abbreviations

AML: Acute Myelogenous Leukemia; AEL: Acute Eosinophilic Leukemia; ALL: Acute Lymphocytic Leukemia; Bc: Blastic crisis; BP: Blastic Phase; CIM: Chronic Idiopathic Myelofibrosis; CML: Chronic Myelogenous Leukemia; CMML: Chronic Myelomonocytic Leukemia; CP: Chronic Phase; ETS: E26-Transforming Specific; ETV: ETS Variant; HDAC: Histone Deacetylase; HLH: Helix-Loop-Helix; MDS: Myelodysplastic Syndrome; MPN: Myeloproliferative Neoplasm; Ph: Philadelphia chromosome; PNT: Pointed; PV: Polycythemia Vera; RA: Refractory Anemia; RAEB: Refractory Anemia with excess of Blasts; TCL: T Cell Leukemia; TEL: Translocating E26 transforming-specific Leukemia

Introduction

ETV6 (ETS variant 6) also known as TEL1 (Translocating E26 transforming-specific leukemia 1) and the related ETV7 or TEL2 are members of the evolutionarily-conserved ETS (E26-transforming specific) family of transcription factors, which have been implicated in a variety of cellular development and differentiation processes [1,2]. All ETS proteins share an extensively conserved domain of about 85 amino acids, which binds to purine-rich sequences within the promoters or enhancers of target genes, utilizing a GGAA/T sequence that is flanked by 5-8 nucleotide, thus determining the specificity of each family member [3,4]. This so-called ETS domain represents a winged helix-turn-helix domain composed of 3 α-helixes and 4 β-sheets arranged in the order α1-β1-β2-α2-α3-β3-β4 [5]. Another evolutionary conserved domain shared by a subset of ETS family members is the Pointed (PNT) domain, which is in the form of a modified Helix-Loop-Helix (HLH) structure for mediating protein-protein interactions [6]. Although some ETS family members are expressed ubiquitously, others are predominantly expressed in a tissue-specific manner [7], including in hematopoietic cells where they regulate blood cell development [8].

ETV6 gene and protein structure and function

The human *ETV6* gene spans a region of over 240 kb on the short (P) arm of chromosome 12 at band 13.1 and consists of 8 exons [9]. There are two isoforms of ETV6 (57 kDa and 53 kDa) arising from alternative start codons in exon 1a (Figure 1) [10]. The PNT domain at its N-terminus is encoded by exons 3 and 4 and the ETS domain at its C-terminus is encoded by exons 6 and 7 flanking a central domain encoded by exon 5 (Figure 1).

The PNT domain is responsible for homo or heterodimerization with a range of proteins, including the closely-related ETV7 protein, the ETS family member FLI1 and the ubiquitin-conjugating enzyme UBC9 [6,7,11,12]. This domain is required for the repression of target genes [13], and also mediates the nuclear export of ETV6, thereby regulating its activity [14]. The positively charged ETS domain is responsible for binding to DNA [15,16]. The less conserved central domain contributes to the repression activity of ETV6 [17-21].

In several studies ETV6 has been identified as a strong transcriptional repressor [17,18]. This has been mapped to the PNT and central domains. PNT domain-mediated repression has been shown to be dependent on interaction with the SPM domain of L3MBTL1 (human homolog of the Drosophila Lethal3 Malignant brain tumor protein), a member of polycomb group of chromatin-associated proteins, which stabilizes the repressive effect of ETV6 on transcription through a HDAC (histone deacetylase) independent mechanism [22]. In contrast, repression by the central domain is mediated through binding of various co-repressors, including SMRT, mSin3A, N-CoR and Tip60, which subsequently recruit HDACs to mediate transcriptional repression [17-21].

While ETV6 would appear to regulate the transcription of genes

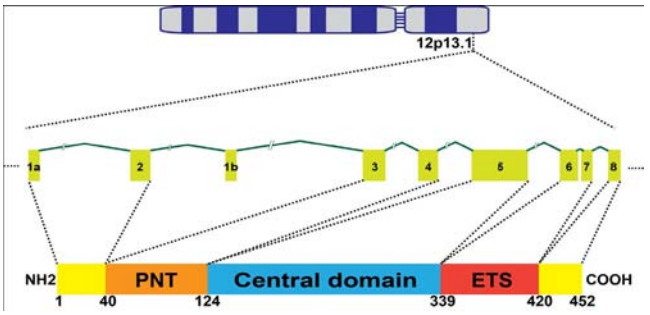

Figure 1: ETV6 chromosomal location, gene and protein structure. Schematic representation of the *ETV6* gene locus on human chromosome 12 (upper panel), the *ETV6* gene transcript with numbered boxes corresponding to exons (middle panel), and the ETV6 protein with domains indicated and relevant amino acids numbered (lower panel).

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with ETS consensus sites in their promoters, only a handful of genes actually targeted by ETV6 are known. These include the *GPIIb* and *GPIbα* genes in myeloid K562 cells induced with TPA [23], the *TCL1* (T-cell lymphoma 1) oncogene in pre-B cell acute lymphoblastic leukemia cells [24], the *BCL-XL* gene in NIH 3T3 cells [13] and *β-globin* in transgenic mice expressing human ETV6 under the control of the *Gata1* promoter [25] as well as acting on the *Stromelysin* (MMP3) promoter in Ras-transformed NIH3T3 cells [26].

Role of ETV6 *in vivo*

ETV6 has been shown to play an important role in normal embryonic development and hematopoietic regulation. Targeted knockout of the *Etv6* gene in mice led to embryonic lethality at day 10.5-11.5 of development due to mesenchymal and neural cell apoptosis accompanied by defective angiogenesis in the yolk sac [27]. Primary erythropoiesis at this time was unaffected. However, further analysis of chimerical mice consisting of $Etv6^{-/-}$ cells and normal ($Etv6^{+/+}$) cells revealed that although $Etv6^{-/-}$ cells contributed to yolk sac and fetal liver hematopoisis, they were totally absent from the bone marrow. These findings revealed that *Etv6* was essential for the establishment of definitive hematopoisis in mice [28]. Knockdown of *etv6* in *Xenopus* also revealed a requirement for this gene in the formation of the first definitive hematopoietic stem cells in the dorsal aorta [29]. Conditional knockouts in adult mice indicated that *Etv6* was essential for survival of adult HSCs within hematopoietic niches [30]. However, ablation of *Etv6* after lineage commitment did not affect adult hematopoietic except for specific maturation defects in the megakaryocytic lineage [30].

In contrast, transgenic mice expressing human *ETV6* under the control of *Gata1* promoter revealed that ETV6 was also involved in both proliferation and differentiation in the erythroid lineage, depending on the stage of erythroid development. During the early stages of erythropoiesis, ETV6 was found to accelerate proliferation, while in the latter stages it increased differentiation including stimulation of hemoglobin synthesis. The latter was achieved through indirect promotion of ALAS-E transcription and direct stimulation of β-globin synthesis [25]. This may explain the observation that enhanced expression of ETV6 in mouse erythroleukemia cells induced their differentiation toward erythrocytes [31]. Recent studies in zebrafish have confirmed a broad role for ETV6 in embryonic hematopoiesis, impacting on progenitor cells, as well as erythroid, myeloid and lymphoid populations [32].

Chromosomal translocations involving *ETV6* in hematological malignancy

The human *ETV6* gene is notable for its frequent involvement in chromosomal translocations associated with hematological malignancies. Approximately 50 translocations involving the *ETV6* gene have been described, involving around 30 partner genes [33]. These translocations can be classified according to the type of fusion partners namely: tyrosine kinases, transcription factors and other proteins (Figure 2).

Tyrosine kinases: The ETV6/tyrosine kinase fusions have been detected in a plethora of hematological malignancies. In all cases, including fusions with ABL1, ABL2, JAK2, SYK, FRK, LYN, FGFR3, PDGFRA, PDGFRB, NTRK3 and FLT3, the PNT domain of ETV6

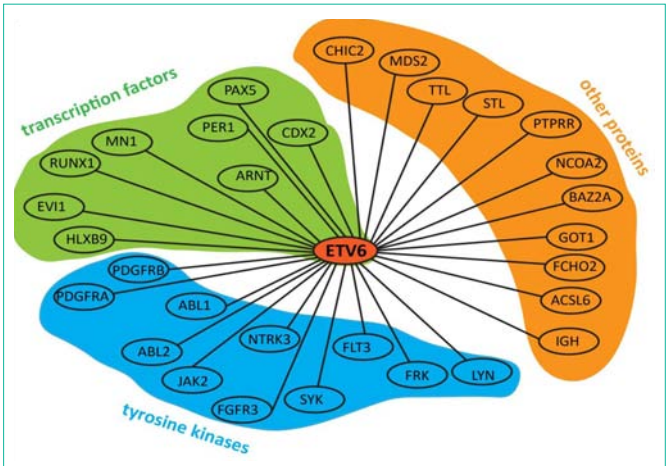

Figure 2: ETV6 fusion partner network.
Graphical representation of the various proteins found fused to ETV6 in malignancy are shown by class: tyrosine kinases (blue), transcription factors (green) and other proteins (orange).

is fused to the tyrosine kinase domain of the fusion partner. In this way the PNT domain mediates dimerization of the tyrosine kinase, resulting in its constitutive activation with subsequent autophosphorylation and phosphorylation of downstream signal transducing proteins, such as STATs (Table 1). The use of animal models has revealed new insights into the function of these fusion oncoproteins, for example ETV6-JAK2 [34,35].

Transcription factors: ETV6/transcription factor fusions have been implicated in variety of leukemias. In these cases, the fusion modifies the transcription activity of ETV6 and/or the fusion partner by converting a transcriptional repressor into an activator or vice versa, which can be achieved in three different ways. Fusions with involvement of the PNT domain of ETV6, such as fusions with RUNX1 and ARNT, result in a dominant-negative effect of the fusion protein over the normal function of the fusion partner. However, in fusions that involve both PNT and ETS domains of ETV6, such as fusions with MN1, PAX5 and HLXB9, the chimeric protein appears to act as an aberrant transcription factor and results in modification of both ETV6 and partner protein transcription activity. Finally, in fusions that involve the promoter – rather than a functional domain – of ETV6, such as with EVI1 and CDX2, ectopic expression of the fusion partner genes in hematopoietic cells has been suggested to mediate leukemogenesis (Table 2).

Other proteins: Other ETV6 translocations not involving tyrosine kinases or transcription factors have been reported in variety of leukemias. In most of these cases, just the first two exons of ETV6 are involved in the translocation. It is believed that in these cases, involving fusions to CHIC2, MDS2, TTL, STL, ACS2 and PER1, the over expression of a neighboring gene is the critical pathogenic mechanism of the translocation (Table 3).

Tumor suppressor function of ETV6

Besides being involved in a vast number of translocations associated with hematological malignancies, there are other studies supporting the notion that ETV6 functions as a tumor suppressor gene. The short arm of chromosome 12 is a hot spot for chromosomal abnormalities in various hematological malignancies, these include interstitial deletions that lead to the loss of genetic material from 12p

Table 1: Tyrosine kinase fusions with ETV6.
Summary of the ETV6 fusions with tyrosine kinases, indicating the disease, translocation, ETV6 breakpoint, ETV6 domain involvement (PNT, ETS), functional mechanisms and references.

Fusion gene	Disease	Translocation	Breakpoint in ETV6	PNT	ETS	Functional mechanisms	References
ETV6-ABL1	AML, B-cell ALL, T-cell ALL, MPN, CML (Ph negative) in CP and BP	t(9;12)	int 4 or 5	+	-	• Constitutive activation of PTK domain of ABL1	[45-49]
ETV6-ABL2	AML-M4, M3, T-cell ALL	t(1;12)	int 5	+	-	• Constitutive activation of PTK domain of ABL2	[50-52]
ETV6-JAK2	Pre-B cell ALL, aCML, T-cell ALL	t(9;12)	int 4 or 5	+	-	• Constitutive activation of PTK domain of JAK2	[53,54]
ETV6-FGFR3	Peripheral T-cell lymphoma	t(4;12)	int 5	+	-	• Constitutive activation of PTK domain of FGFR3	[55]
ETV6-SYK	MDS	t(9;12)	int 5	+	-	• Constitutive activation of PTK domain of SYK	[56]
ETV6-FRK	AML-M4	t(6;12)	int 4	+	-	• Constitutive activation of PTK domain of FRK	[57]
ETV6-LYN	Primary myelofibrosis	Ins(12;8)	int 5	+	-	• Constitutive activation of PTK domain of LYN	[58]
ETV6-PDGFRA	MPN	t(4;12)	int 6	+	-	• Constitutive activation of PTK domain of PDGFRA	[59]
ETV6-PDGFRB	CMML, AML-M0 on CIM, AML-M2, aCML in Bc	t(5;12)	int 4 or 7	+	-	• Constitutive activation of PTK domain of PDGFRB	[59-62]
ETV6-NTRK3	AML-M2, M0, CEL	t(12;15)	int 4 or 5	+	-	• Constitutive activation of PTK domain of NTRK3	[63-65]
ETV6-FLT3	MPN with hypereosinophilia, T-lymphoblastic lymphoma	t(12;13)	int 4 or 5	+	-	• Constitutive activation of PTK domain of FLT3	[66,67]

AML: Acute Myelogenous Leukemia; ALL: Acute Lymphocytic Leukemia; MPN: Myeloproliferative Neoplasm; CML: Chronic Myelogenous Leukemia; Ph: Philadelphia chromosome; CP: Chronic Phase; BP: Blastic Phase; aCML: atypical CML; MDS: Myelodysplastic Syndrome; CMML: Chronic Myelomonocytic Leukemia; CIM: Chronic Idiopathic Myelofibrosis; Bc: Blastic crisis; CEL: Chronic Eosinophilic Leukemia

Table 2: Transcription factor fusion partners of ETV6.
Summary of the ETV6 fusions with other transcription factors, as detailed in Table 1.

Fusion gene	Disease	Translocation	Breakpoint in ETV6	PNT	ETS	Functional mechanisms	References
ETV6-RUNX1	B-cell ALL	t(12;21)	int 4 or 5	+	-	• Dominant negative effect of the fusion protein over wild type ETV6 allele • Repression of RUNX1 target genes	[37,68,69]
MN1-ETV6	AML-M0, M2, M4, CML, RAEB, AML on MDS	t(12;22)	int 2 or 3	+	+	• Activation of ETV6 target genes • Repression of retinoic acid mediated transcription • Dominant negative effect of the fusion protein over wild type MN1 allele	[70-76]
ETV6-ARNT	AML-M2, T-cell ALL	t(1;12)	int 4	+	-	• Dominant negative effect of the fusion protein over wild type ETV6 allele • Modification of ARNT into a transcriptional repressor	[77,78]
ETV6-EVI1	aCML, Bc-CML, RAEB, AML-M0	t(3;12)	int 2	-	-	• Ectopic expression of EVI1	[53,79,80]
ETV6-CDX2	AML-M1	t(12;13)	int 2	-	-	• Ectopic expression of CDX2	[50,81]
PAX5-ETV6	B-cell ALL	t(9;12)	int 2	+	+	• Modification of ETV6 and/or PAX5 transcription activity	[82,83]
HLXB9-ETV6	AML-M0, M1, M2, M3, M7	t(7;12)	int 2	+	+	• Modification of ETV6 and/or HLXB9 transcription activity?	[84-87]

ALL: Acute Lymphocytic Leukemia; AML: Acute Myelogenous Leukemia; RAEB: Refractory Anemia with Excess of Blasts; MDS: Myelodysplastic Syndrome; aCML: atypical Chronic Myelogenous Leukemia; Bc-CML: Blastic Crisis of CML

which has been mapped to a small locus containing the *ETV6* and *KIP1* genes [36]. In many cases of childhood ALL carrying t(12;21) the wild-type *ETV6* allele is deleted [9,37,38]. Interestingly, in cells harboring these translocations, consistent loss of *ETV6* expression was observed even in the absence of detectable *ETV6* deletion, suggesting that secondary structural abnormalities and epigenetic modifications may lead to the silencing of *ETV6* alleles [38]. Frequent point mutations of *ETV6* have been reported in T-ALL and AML leading to truncated forms of ETV6 which exerted a dominant-negative effect to abolish wild type ETV6 function [39-41]. Furthermore, in several cases of leukemia including *ETV6* translocations, neither functional fusion protein was identified nor was ectopic expression of a neighboring proto-oncogene reported. In these cases, haploinsufficiency of ETV6 has been raised as a contributing factor in the etiology of leukemia [42,43].

Additional evidence of a potential tumor suppressor role for ETV6 comes from its functional studies. A transient increase in endogenous ETV6 expression was also reported during the first 3 days of differentiation of Mouse Erythroleukemia (MEL) cells [31]. Over-expression of ETV6 in these cells enhanced erythroid differentiation while introduction of a dominant-negative mutant of ETV6 completely blocked this process with cells continuing to proliferate. Enforced expression of ETV6 inhibited cell growth in Ras-transformed cells [26] and retarded proliferation of both primary wild type and immortalized cells possibly through inducing G1 arrest [44] or decreasing survival via direct repression of the Bcl-X_L promoter

Table 3: Other protein fusion partners of ETV6.
Summary of ETV6 fusions with other proteins as detailed in Table 1.

Fusion gene	Disease	Translocation	Breakpoint in ETV6	PNT	ETS	Functional mechanisms	References
CHIC2-ETV6	AML-M0,M1,M2, M/NK cell leukemia, RAEB	t(4;12)	int 1 or 2	-	-	• Overexpression of adjacent gene (GSX2)	[88-92]
ETV6-MDS2	RAEB	t(1;12)	int 2	-	-	• Overexpression of adjacent gene (PRL11)	[89]
ETV6-TTL or TTL-ETV6	Pre B-cell ALL	t(12;13)	int 1	- +	- +	• Loss of function of ETV6 or/and TTL • Overexpression of adjacent genes (p27 and FOXO1A)?	[93]
ETV6-STL or STL-ETV6-S or STL-ETV6-L, M	Pre-B ALL	t(6;12)	int 2	- + -	- + -	• Deregulation of adjacent gene (OSTL*) • Loss of ETV6 function	[94]
ETV6-PER1	AML on CMML	t(12;17)	int 1	-	-	• Overexpression of adjacent gene (HES7 or STK12)	[95]
ETV6-ACS2	RAEB, MDS, AML, AEL, PV, CML	t(5;12)	int 1 or 2	-	-	• Overexpression of adjacent gene (IL-3)	[89,96-99]
ETV6-PTPRR	AML-M2	inv(12)	int 4	+	-	• Dominant negative effect of the fusion protein over wild type ETV6 allele	[100]
ETV6-NCOA2	AML-M2, ALL	t(8;12)	int 4 or 5	+	-	• Constitutive activation of ETV6 target genes • Modification of transcriptional activity of CBP-dependent activators	[101]
ETV6-BAZ2A	Pre B-cell ALL	t(12;12)	int 2	-	-	• Haploinsufficiency of ETV6 and/or BAZ2A? • Deregulation of BAZ2A or a gene in vicinity of BAZ2A?	[43]
ETV6-GOT1	RA, RAEB	t(10;12)	int 2 or 3	-	-	• Dominant negative effect of fusion protein over both GOT and ETV6	[102,103]
ETV6-FCHO2	AML-M1	t(5;12;22)	int 2	-	-	• Haploinsufficiency of ETV6 and/or FCHO2	[42]
ETV6-IGH	Pre B-cell ALL	t(12;14)	?	?	?	?	[104]

AML: Acute Myelogenous Leukemia, RAEB: Refractory Anemia with Excess of Blasts, ALL: Acute Lymphocytic Leukemia, CMML: Chronic Myelomonocytic Leukemia, MDS: Myelodysplastic Syndrome, AEL: Acute Eosinophilic Leukemia, PV: Polycythemia Vera, CML: Chronic Myelogenous Leukemia, RA: Refractory Anemia, RAEB: Refractory Anemia with Excess of Blasts.
*OSTL (or opposite STL) shares the first exon with STL but is transcribed in the opposite direction.

[13]. It has also been demonstrated that ETV6 over expression slowed the Ras-induced tumor formation in nude mice [44].

Conclusion

ETV6 remains best known for its role as a hot spot for translocation, yielding a large number of chromosomal fusions important in the etiology of hematological malignancy. However, more recent studies have indicated that the encoded protein is both a tumor suppressor and an important regulator of hematopoiesis, which provides new insights into how its disruption contributes to malignancy. Key questions remaining for future research are, firstly, which genes are targeted by ETV6 in both its tumor suppressor and oncogenic roles and, secondly, whether pharmacologic agents can be developed to either enhance the former or hinder the latter.

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