Leukaemia Section
Short Communication

del(5)(q32q33) EBF1/PDGFRB

Gauthier Decool, Benoît Ducourneau, Nicolas Duployez, Catherine Roche-Lestienne

CHU Lille, Laboratoire d'Hématologie, Centre de Biologie-Pathologie (GD, BD, ND), INSERM UMR-S 1172, Institut de Recherche sur le Cancer de Lille (ND, CRL), CHU Lille, Institut de Génétique Médicale, Hôpital Jeanne de Flandre (CRL), F-59000, France; gauthier.decool@gmail.com; btducourneau@gmail.com; nicolas.duployez@chru-lille.fr; catherine.roche@chru-lille.fr

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Abstract
Review on del(5)(q32q33) EBF1/PDGFRB fusion with clinical data and genes involved.

Keywords
EBF1, PDGFRB; fusion transcript, tyrosine kinase, BCR/ABL1-like; chromosome 5

Identity
According to the recent revision to the WHO classification of myeloid neoplasm and acute leukemia (Arber et al, Blood, 2016), BCP-ALL with EBF1/PDGFRB fusion should be referred as 'BCR/ABL1-like B-lymphoblastic leukemia/lymphoma' (provisional entity). BCR/ABL1-like ALL (or Ph-like ALL) lack the BCR/ABL1 fusion but demonstrate a gene expression profile and a poor outcome similar to BCR/ABL1-positive ALL (den Boer et al, Lancet Oncol, 2009). Kinase activating alterations (including the EBF1/PDGFRB fusion) are a hallmark of the disease and could be found in virtually all patients with BCR/ABL1-like ALL (Roberts et al, Cancer Cell 2012; Roberts et al, N Engl J Med 2014).

Clinics and pathology

Disease
B-cell precursor acute lymphoblastic leukemia (BCP-ALL)

Phenotype/cell stem origin
B-cell precursor

Epidemiology

The EBF1/PDGFRB fusion accounts for about 0.5% of BCP-ALL, 3% of B-other ALL and 8% of BCR-ABL1-like ALL (Schwab et al, Blood, 2016). The prevalence of EBF1/PDGFRB-positive ALL is expected to increase with age in parallel with the prevalence of BCR-ABL1-like ALL which ranges from 10% in children to 20% in adolescent and near 30% in young adults.

Clinics

About 25 cases have been reported so far (Schwab et al, Blood, 2016; Lengline et al, Haematologica 2013; Weston et al, J Clin Oncol, 2013, Robert et al, Cancer Cell 2012; Roberts et al, N Engl J Med 2014). Patients were aged from 4 to 20y (median: 12y) and often displayed high leukocyte counts at presentation, especially in IKZF1-deleted cases.

Treatment

The detection of the EBF1/PDGFRB fusion is critical since the fusion protein could be targeted by tyrosine kinase inhibitors (TKIs) such as imatinib or dasatinib. Importantly, recent reports have shown successful TKI therapy even in patients refractory to conventional therapy.

Evolution

Patients with EBF1/PDGFRB-positive ALL are characterized by high levels of minimal residual
disease and a higher tendency of relapse compared with other ALL subtypes. However, there is evidence of durable remission especially after intensive chemotherapy. Finally, considering several reports, the use of TKIs should be assessed in EBF1/PDGFRB-positive patients and could decrease relapse rate and avoid the need of intensive chemotherapy.

**Cytogenetics**

Note
The EBF1/PDGFRB is usually not seen by conventional karyotype.

*Cytogenetics morphological*

Karyotype is normal by conventional cytogenetics in half of the cases. The EBF1/PDGFRB fusion usually results from a cryptic 5q33 deletion requiring the use of fluorescent in situ hybridization (FISH), comparative genomic hybridization (CGH) or single nucleotide polymorphism (SNP)-array. Rarely, it could result from a t(5;5)(q32q33.3) translocation or a complex 5q rearrangement. Additional cytogenetic events could include trisomy 5 (containing the EBF1 and PDGFRB genes) or abnormal chromosome 5, deletion of the short arm of chromosome 5 as well as atypical aberrations.

*Cytogenetics molecular*

The EBF1/PDGFRB fusion results most often from a del(5)(q32q33.3) of about 8.6 Mb with breakpoints located within EBF1 and PDGFRB. Interestingly, multiplex ligation dependent probe amplification (MLPA) (SALSA MLPA kit P335 IKZF1, MRC Holland) shows deletion of EBF1 exon 16 in more than 70% of EBF1/PDGFRB-positive ALL (Schwab et al, Blood, 2016). Among the genes tested by MLPA, PAX5, IKZF1 and/or CDKN2A/CDKN2B are often deleted.

**Genes involved and proteins**

Note
The 5q33 deletion (more rarely t(5;5) translocation) leads to the fusion of EBF1 and PDGFRB.

*PDGFRB (platelet-derived growth factor receptor, beta polypeptide)*

**Location** 5q32

**DNA/RNA**
The PDGFRB gene contains 22 exons.

**Protein**
PDGFRB is a cell surface tyrosine kinase (TK) receptor for the platelet-derived growth factor family. PDGFRB belongs to the type III group of TKs (which also include KIT, FLT3 and CSF1 (the M-CSF receptor)) and consists of five extracellular immunoglobulin-like domains, a single-spanning transmembrane domain and an intracellular kinase domain, split in two domains by a kinase insert. The TK domain is normally activated in response to ligand binding and receptor dimerization. PDGFRB is involved in embryonic development and modulation of hematopoietic cell functions.
**EBF1 (early B-cell factor 1)**

**Location** 5q33.3

**DNA/RNA**

The EBF1 gene contains 16 exons.

**Protein**

EBF1 is a transcription factor critical for B cell differentiation, signal transduction and function. EBF family proteins consist of an N-terminal DNA-binding domain including a zinc binding motif, designated as "zinc-knuckle", a transcription factor immunoglobulin (TIG) domain and a helix-loop-helix domain, followed by a C-terminal transactivation domain.

**Result of the chromosomal anomaly**

**Hybrid gene**

**Description**

The hybrid gene The fusion usually involved PDGFRB exon 11 fused to EBF1 exon15 (rarely alternative breakpoints involving EBF1 exon 14).

**Detection**

FISH detection with PDGFRB and EBF1 breakapart probes or identification of the EBF1/PDGFRB transcript fusion by ligation-dependent reverse transcriptase-polymerase chain reaction (LD-RTPCR).

**Fusion protein**

**Description**

The fusion consists of the in-frame fusion of the N-terminal part of the transcription factor EBF1, including the DNA-binding domain, with the tyrosine kinase domain of PDGFRB.

**Oncogenesis**

The tyrosine kinase domain of the fusion protein is constitutively activated, triggering downstream signalling.

**References**


This article should be referenced as such: