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Leukaemia Section
Review

del(4)(q12q12) FIP1L1/PDGFRA

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Abstract

Review on del(4)(q12q12) FIP1L1/PDGFRA, with data on clinics, and the genes implicated.

Identity

Other names
Interstitial 4q12 deletion
FIP1L1/PDGFRA fusion in eosinophilia-associated hematologic disorders

Clinics and pathology

Disease

An interstitial deletion del(4)(q12q12) generating a FIP1L1-PDGFRA fusion gene is observed in diverse eosinophilia-associated hematologic disorders like hyperseosinophilic syndrome (HES), systemic mastocytosis (SM) and chronic eosinophilic leukemia (CEL).
The updated WHO classification distinguishes these myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1 as chronic eosinophilic leukemia (CEL) not otherwise specified (NOS); lymphocyte-variant hypereosinophilia and idiopathic hypereosinophilic syndrome (HES) (Gleich and Leiferman, 2009; Gotlib, 2014). Occasionally, the FIP1L1-PDGFRA fusion can be identified in patients with acute myeloid leukemia or B-cell or T-cell acute lymphoblastic leukemia or lymphoblastic lymphoma and sporadically in myeloid sarcoma (Metzgeroth et al., 2007; Tang et al., 2012).

Phenotype/cell stem origin

FIP1L1-PDGFRA rearrangement has been found in a variety of cell lineages (neutrophils, monocytes, eosinophils, CD34+ cells, mast cells and even lymphoid) consistent with an origin in an hematopoietic stem cells or early progenitors progenitor (Gotlib and Cools, 2008).

Etiology

The cause of FIP1L1-PDGFRA associated hypereosinophilic syndrome is unknown as well as its association with predominantly male sex.

Epidemiology

FIP1L1-PDGFRA (+) eosinophilias are considered to be rare entities; however the incidence rates for molecularly defined eosinophilic disorders are not known.
Data support a FIP1L1-PDGFRA fusion incidence of approximately 10-20% among patients presenting with idiopathic hypereosinophilia (Gotlib and Cools, 2008).
However, in unselected patients with eosinophilia only 3% of were found to carry the FIP1L1-PDGFRA fusion (Pardanani et al., 2004; Pardanani et al., 2006).

Clinics

Characteristic feature of PDGFRA-associated disorders is eosinophil overproduction in the bone marrow resulting in increased blood eosinophils. Marked and sustained eosinophilia eventually leads to eosinophilic infiltration and functional damage of peripheral organs, most commonly the heart, skin, lungs, or nervous system.
Patients often present with hepatomegaly or splenomegaly hypercellular bone marrows with myelofibrosis, increased number of neutrophils and/or mast cells.
Serum B12 and tryptase levels may be significantly elevated (Vandenberghe et al., 2004; Gleich and Leiferman, 2009).

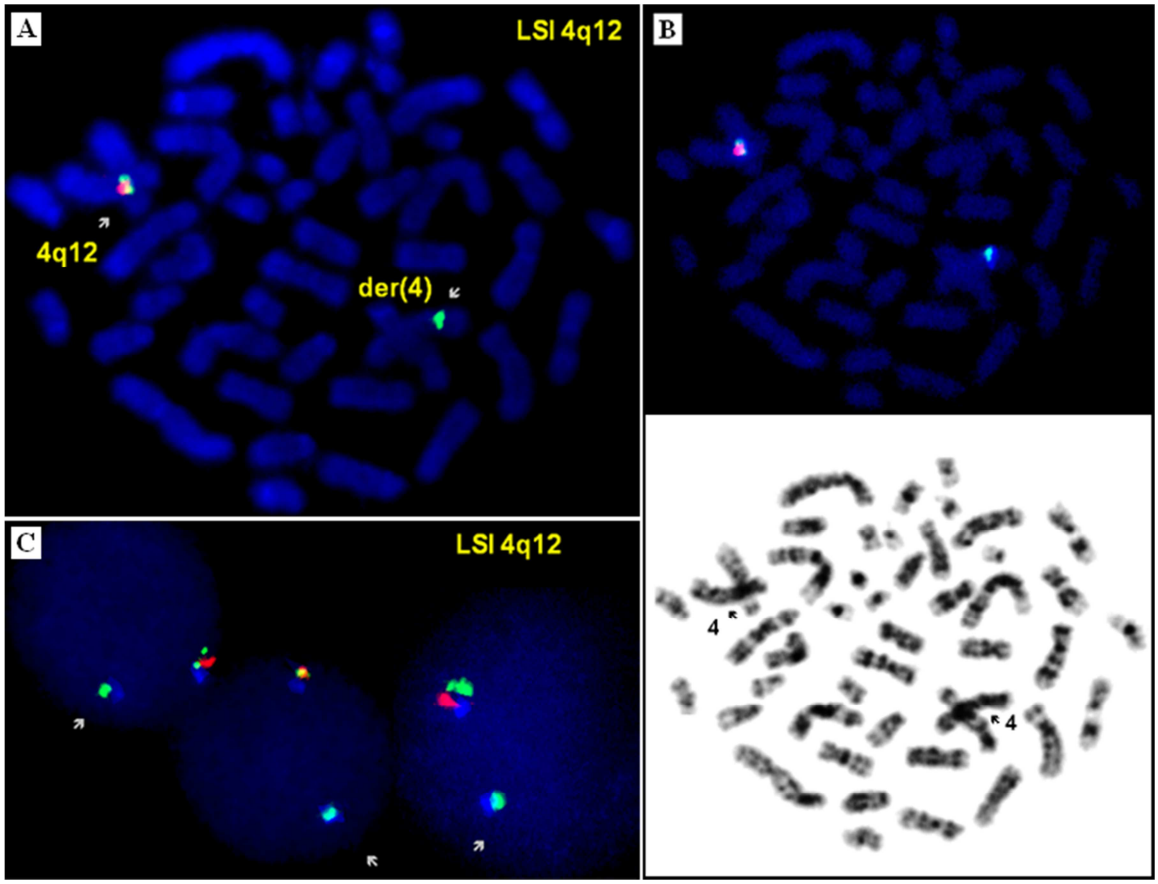

Figure 1. Detection of the del(4)(q12q12) by fluorescence in situ hybridization using the LSI FIP1L1-CHIC2-PDGFRA Triple-Color, split assay (Abott Molecular; Vysis, Denver US) on a metaphase (A) and interphases (B). This probe is designed as a deletion probe when absence of the CHIC2 region is observed as loss of a red signal (arrows) from the co-localized green/blue signal, indicative of the presence of this specific deletion that leads to FIP1L1-PDGFRA fusion on one of the chromosomes 4.

Treatment

FIP1L1-PDGFRA associated hypereosinophilic disorders are sensitive to treatments with tyrosine kinase inhibitors such as imatinib mesylate (imatinib). Imatinib is the first-line therapy for patients with abnormalities of PDGFRA; however chronic eosinophilic leukemia with FIP1L1-PDGFRA is likely to be responsive also to dasatinib, nilotinib, sorafenib and midostaurin (PKC412) (Lierman et al., 2009).

Prognosis

Patients with hypereosinophilic syndrome historically carried a poor prognosis before the successful therapeutic application of tyrosine kinase inhibitors. Targeted therapy has dramatically changed the prognosis of patients carrying the FIP1L1-PDGFRA fusion which show an excellent response to low-dose imatinib. Treatment with low-dose imatinib (100 mg/d) produced complete and durable responses with normalization of eosinophilia. Importantly, these remissions appear to be durable with continued imatinib therapy in a high proportion of patients (Barraco et al., 2014).

Acquired resistance is exceedingly rare; the T674I mutation in the ATP-binding region of PDGFRA (mutation of the threonine at position 674) is the most common. Interestingly, the T674I mutation that is analogous to the T315I mutation of BCR-ABL1 in chronic myeloid leukemia also confers imatinib resistance (Cools et al., 2003; Jain et al., 2013). For refractory disease, interferon-a may be a therapeutic option.

Cytogenetics

Note

The cryptic interstitial deletion on chromosome band 4q12 leading to FIP1L1-PDGFRA fusion is quite unique as it is generated by a cryptic chromosomal deletion, rather than a translocation (Gotlib and Cools, 2008).

Cytogenetics morphological

Because FIP1L1-PDGFRA is generated by a cryptic deletion at 4q12 that is only 800 kb in size, it remains undetected with standard cytogenetics. Therefore; most of the patients with the fusion have an apparently normal karyotype.

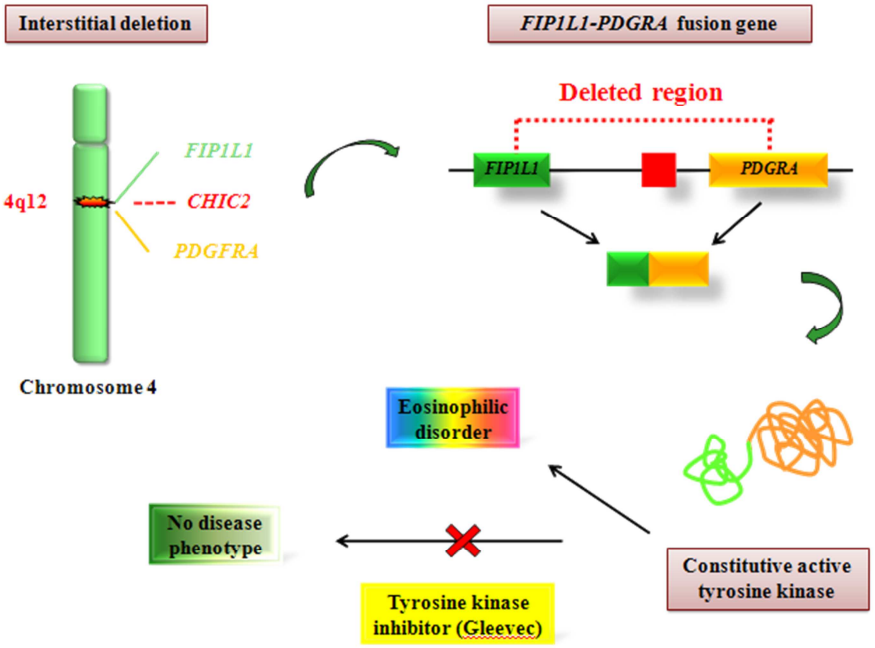

Figure 2. Model of the involvement of PDGFRA-FIP1L1 fusion gene in the pathogenesis of hypereosinophilic disorders. A cryptic deletion on chromosome 4 brings the normally distant PDGFRA and FIP1L1 genes into close proximity, generating a fused gene. Fusion of FIP1L1 to the PDGFRA protein results in a constitutive kinase activation of PDGFRA with transforming potential that may lead to eosinophilic disorders. Administration of the kinase inhibitor such as imatinib is highly effective molecularly targeted therapy for this group of patients.

Occasional patients have had a chromosomal rearrangement with a 4q12 breakpoint, such as t(1;4)(q44;q12), which ultimately led to the identification of the fusion gene or t(4;10)(q12;p11) (Cools et al., 2003; Gotlib et al., 2004).

Cytogenetics molecular

One of the best techniques to detect the presence of the FIP1L1-PDGFRA fusion gene is using triple-color FISH probes hybridizing to the region between the FIP1L1 and PDGFRA genes incorporating the CHIC2 (cysteine-rich hydrophobic domain 2) gene.
A more sensitive technique is the use of reverse-transcription polymerase chain reaction (RT-PCR) (La Starza et al., 2005) or quantitative RT-PCR methods, used for monitoring therapy response to tyrosine kinase inhibitors.

Variants

A few other variant PDGFRA fusion genes have been described: t(4;22)(q12;q11)/BCR-PDGFRA, t(2;4)(p24;q12)/STRN-PDGFRA, ins(9;4)(q33;q12q25)/CDK5RAP2-PDGFRA, complex karyotype/KIF5B-PDGFRA and t(4;12)(q12;p13)/ETV6-PDGFRA (Gleich and Leiferman, 2009). The involvement of FIP1L1 was described in a t(4;17)(q12;q21) with FIP1L1/RARA fusion in a patient with juvenile myelomonocytic leukemia (Shah et al., 2014).

Genes involved and proteins

PDGFRA

Location
4q12

Note
platelet-derived growth factor receptor, alpha polypeptide

DNA/RNA
PDGFRA contains 23 exons spanning about 65 kb. The gene encodes a cell surface tyrosine kinase receptor. An important paralog of PDGFRA is FLT4.

Protein
1089 amino acids; PDGFA belongs to a family of receptor tyrosine kinases that include PDGFRA and PDGFRB that have intracellular tyrosine kinase activity that binds members of the platelet-derived growth factor family.
It plays an essential role in the regulation of embryonic development, organ development, wound healing, angiogenesis and chemotaxis; role in the differentiation of bone marrow-derived mesenchymal stem cells, cell proliferation and survival (Hsieh et al., 1991; Kawagishi et al., 1995).

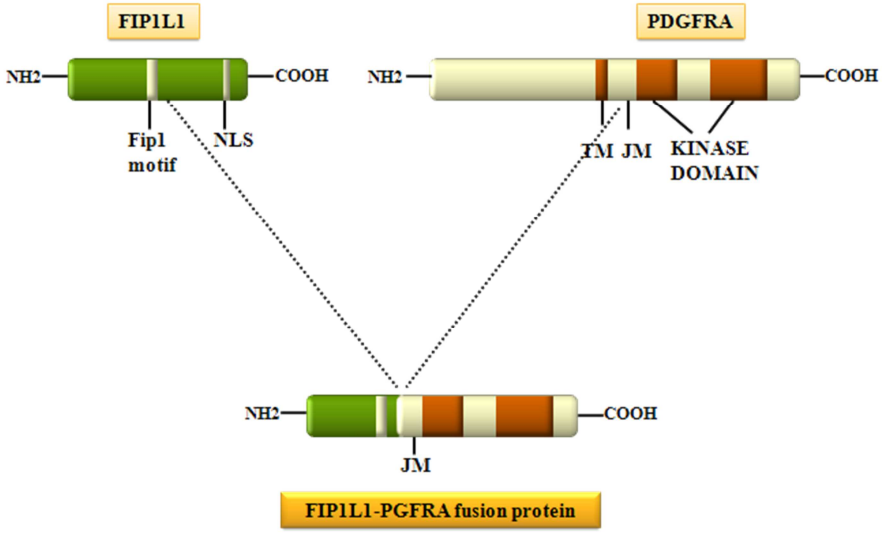

Figure 3. Generation of the FIP1L1-PDGFRA fusion protein. Splicing of FIP1L1 exons to the truncated exon 12 of PDGFRA results in disruption of the autoinhibitory juxtamembrane domain of PDGFRA. FIP1L1-PDGFRA expression became under control of the ubiquitous FIP1L1 promoter leading to dysregulated tyrosine kinase activity. NLS indicates nuclear localization signal; TM, transmembrane region; JM, juxtamembrane region. Adapted from Cools et al., 2003; Vandenberghe et al., 2004; Gotlib and Cools, 2008; Gleich and Leiferman, 2009.

PDGFRA is involved in the pathogenesis of various disorders, including cancer.

FIP1L1

Location

4q12

Note

factor interacting with PAPOLA and CPSF1

DNA/RNA

4 distinct isoforms; alternative splicing results in multiple transcript variants.

Protein

pre-mRNA 3'-end-processing factor; 520 amino acids. FIP1 belongs to the FIP1 family. It has RNA binding protein kinase activity as a component of cleavage and polyadenylation specificity factor (CPSF) complex. Plays a key role in polyadenylation of the 3' end of mRNA precursors and in the transcriptional process. FIP1L1 is predicted to be under the control of a ubiquitous promoter. Many additional functions of the protein are largely unknown (Gotlib et al., 2004).

Result of the chromosomal anomaly

Hybrid gene

Description

In-frame fusion of the 5' part of FIP1L1 to the 3' part of PDGFRA.

The generation of the fusion between the 5' part of the FIP1L1 gene and the 3' part of the PDGFRA gene is the consequence of a deletion of the 800 kb genomic region between the two genes on 4q12. Several genes between FIP1L1 and PDGFRA have been identified: LNX1 (the ligand of numb-protein X 1), the hypothetical protein LOC402176 (LOC402176), CHIC2 (cysteine-rich hydrophobic domain 2) and the homeobox protein GSH-2 (GSH2). While breakpoints in FIP1L1 are scattered over a region of 40 kb (introns 7-10), breakpoints within the PDGFRA gene are tightly clustered and are always within exon 12, encoding the juxtamembrane region (JM). Truncations of the JM region invariably results in the removal of part of the juxtamembrane domain and generation of in-frame fusion transcripts (Cools et al., 2003; Vandenberghe et al., 2004). Rarely, FIP1L1 breakpoint is located outside of the common FIP1L1 breakpoint regions (Lambert et al., 2007).

Transcript

5'FIP1L1-3'PDGFRA; no reciprocal PDGFRA-FIP1L1 fusion gene can be detected as the fusion is the consequence of an interstitial deletion and not a reciprocal translocation.

As the normal splice site at 5' part of exon 12 of PDGFRA is deleted, cryptic splice sites in FIP1L1 introns or within exon 12 of PDGFRA are used to generate in-frame FIP1L1-PDGFRA fusions (Gotlib and Cools, 2008).

Fusion protein

Description

The FIP1L1-PDGFRA protein is made by the first twelve exons of FIP1L1 and from truncated exon 12 (containing the last 17 amino acids) to exon 23 of PDGFRA. The FIP1L1-PDGFRA fusion protein is a constitutively activated tyrosine kinase that joins the first 233 amino acids of FIP1L1 to the last

523 amino acids of PDGFRA (Gotlib and Cools, 2008).

Oncogenesis

An interstitial deletion on chromosome 4q12 site brings the normally distant PDGFRA and FIP1L1 genes into proximity generating a hybrid FIP1L1-PDGFRA gene. In the translated protein, the juxtamembrane domain of PDGFRA that is known to serve an autoinhibitory function is truncated and became under control of the ubiquitous FIP1L1 promoter resulting in its constitutive kinase activation. Dysregulated tyrosine kinase activity leads to proliferation of multiple myeloid lineages via activation of several pathways. The STAT1/3 and STAT5 (signal transducers and activators of transcription) transcriptional factors appear to be activated either directly or via interaction with JAK (Janus activated kinase) pathways. However, the exact mechanism, by which FIP1L1-PDGFR affects the development of HES/CEL and why preferentially affects eosinophils remains unclear. Mouse models of FIP1L1-PDGFRA induced disease revealed that FIP1L1-PDGFRA expression induce a myeloproliferative phenotype without eosinophilia. Therefore, it is likely that FIP1L1-PDGFRA expression alone is not sufficient to cause eosinophilia and additional processes such as cooperation with nuclear factor-kB and IL-5 signaling are required in differentiation towards the eosinophil lineage (Yamada et al., 2006; Montano-Almendras et al., 2012).

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