Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Leukaemia Section

Mini Review

t(4;10)(q12;p11)

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Clinics and pathology

Disease

Myeloproliferative syndrome with hypereosino-philia.

Epidemiology

Only one case to date, a 54-year old male patient.

Evolution

Complete remission could not be obtained with hydroxyurea. Following the identification of the PDGFRA hybrid gene, imatinib was started, and the patient entered complete cytogenetic remission (CR). The patient is still in RT-PCR CR after 18 months

Genes involved and proteins

PDGFRA

Location
4q12
Protein
Composed of an extracellular domain, a trans-membrane domain, a juxtamembrane domain, and an intracellular domain; receptor tyrosine kinase; forms homodimer, and heterodimer with PDGFRB; dimerization induces kinase domain activation, leading to the activation of intracellular signalling pathways (Kawagishi et al., 1995).
Somatic mutations
Hybrid genes between various partners and PDFRGA occur in chronic myeloid leukaemia-like diseases with eosinophilia, mostly chronic eosino-philic leukemia (CEL), a clonal hypereosinophilic syndrome. PDGFRA partners known so far are: STRN (2p24) (Curtis et al., 2007), FIP1L1 (4q12) (Cools et al., 2003; Pardanani et al., 2004), CDK5RAP2 (9q33) (Walz et al., 2006), KIF5B (10p11) (Score et al., 2006), ETV6 (12p13) (Curtis et al., 2007), and BCR (22q11) (Baxter et al., 2002). Mutations of platelet-derived growth factor receptor-alpha (PDGFRA) are observed in a subset of gastrointestinal stromal tumors (GISTs) (Heinrich et al., 2003). Tumours with PDGFRA involvement are responsive to imatinib therapy (Cools et al., 2003; Debiec-Rychter et al., 2004).

KIF5B

Location
10p11
Protein
Composed of a N-terminal globular domain that hydrolyzes ATP and binds microtubule, a central alpha-helical coiled-coil domain (dimerization domain); and a C-terminal domain that interacts with other proteins, vesicles and membranous organelles. Kif5B is involved in microtubule-based polarized vesicular transport to the apical membrane in polarized axonal transport in neurons (Nakata and Hirokawa, 2003; Jacobson et al., 2007; Jaulin and Mostov, 2007). The role of the complex of syntaxin-1-syntabulin-KIF5B in axonal transport has been established (Cai et al., 2007). Kif5B and Kifc1 interact in motility and processing of early endocytic vesicles (Nath et al., 2007). KIF5B has been shown to be essential for axonal transport of mitochondria. KIF5B associates with the kinesin-binding domain (KBD) of RanBP2 to determines mitochondria localization (Cho et al., 2007). JNK forms a complex with KIF5B and ß-tubulin-III in neurites, and TNF disturbs axonal transport of mitochondria via JNK (Stagi et al., 2006).

Result of the chromosomal anomaly

Hybrid gene

Description
In frame fusion of KIF5B exon 23 to PDGFRA exon 12; no reciprocal PDGFRA-KIF5B product.

Fusion protein

Description

156 kDa protein of 1372 amino acids; Composed of the N-terminal globular domain and the central alpha-helical coiled-coil domain (dimerization domain) of KIF5B, fused to the kinase domain of PDGFRA. It is likely that the dimerization domain induces constitutive activation of the kinase domain.

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