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Leukaemia Section
Mini Review

t(2;4)(p22;q12)

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Clinics and pathology

Disease

Myeloproliferative disease with eosinophilia

Epidemiology

Only one case to date, a 64 year old male patient.

Prognosis

The patient remained in complete remission for 24 months of treatment with imatinib, but refused any more treatment, althoughthere was no side effect. Elevated eosinophil counts were again detected 14 months after end of treatment.

Genes involved and proteins

STRN

Location
2p22.2

Protein
Composed of a caveolin-binding domain, a coiled-coil domain, a calmodulin-binding domain, and at least 6 WD-repeats. Striatin (STRN) binds many proteins, and forms multi-protein complexes. It is a scaffolding protein; striatin contains a caveolin-binding consensus motif, and binds caveolin-1, the major protein involved in caveolae and lipid rafts. Striatin is also involved in signaling and trafficking in a Ca^{2+} dependant manner, exhibiting a dual role in endocytic process and signaling.

PDGFRA

Location
4q12

Protein
Composed of an extracellular domain (the immunoglobulin-like motifs), a transmembrane domain, with an inhibitory juxtamembrane WW-like domain (Irusta et al., 2002), and an intracellular domain (kinase 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 eosinophilic leukemia (CEL), a clonal hypereosinophilic syndrome. PDGFRA partners known so far are: STRN (2p24), herein described (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).

Result of the chromosomal anomaly

Hybrid gene

Transcript
5' STRN-3' PDGFRA; Fusion between STRN intron 6

and a truncated PDGFRA exon 12; reciprocal product not found -> in frame fusion between STRN exon 6 and PDGFRA exon 12.

Fusion protein

Description

The N-term STRN - C-term PDGFRA fusion protein retains the caveolin-binding domain, the coiled-coil domain, and the calmodulin-binding domain, but not the WD-repeats of STRN, fused to a truncated WW-like domain and the kinase domain of PDGFRA; the coiled-coil domain from STRN may act as a dimerization motif that could constitutively activate PDGFRA tyrosine kinase.

References

Kawagishi J, Kumabe T, Yoshimoto T, Yamamoto T. Structure, organization, and transcription units of the human alpha-platelet-derived growth factor receptor gene, PDGFRA. Genomics. 1995 Nov 20;30(2):224-32

Couet J, Li S, Okamoto T, Ikezu T, Lisanti MP. Identification of peptide and protein ligands for the caveolin-scaffolding domain. Implications for the interaction of caveolin with caveolae-associated proteins. J Biol Chem. 1997 Mar 7;272(10):6525-33

Gaillard S, Bartoli M, Castets F, Monneron A. Striatin, a calmodulin-dependent scaffolding protein, directly binds caveolin-1. FEBS Lett. 2001 Nov 9;508(1):49-52

Baxter EJ, Hochhaus A, Bolufer P, Reiter A, Fernandez JM, Senent L, Cervera J, Moscardo F, Sanz MA, Cross NC. The t(4;22)(q12;q11) in atypical chronic myeloid leukaemia fuses BCR to PDGFRA. Hum Mol Genet. 2002 Jun 1;11(12):1391-7

Irusta PM, Luo Y, Bakht O, Lai CC, Smith SO, DiMaio D. Definition of an inhibitory juxtamembrane WW-like domain in the platelet-derived growth factor beta receptor. J Biol Chem. 2002 Oct 11;277(41):38627-34

Cools J, DeAngelo DJ, Gotlib J, Stover EH, Legare RD, Cortes J, Kutok J, Clark J, Galinsky I, Griffin JD, Cross NC, Tefferi A, Malone J, Alam R, Schrier SL, Schmid J, Rose M, Vandenberghe P, Verhoef G, Boogaerts M, Wlodarska I, Kantarjian H, Marynen P, Coutre SE, Stone R, Gilliland DG. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med. 2003 Mar 27;348(13):1201-14

Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, Singer S, Griffith DJ, Haley A, Town A, Demetri GD, Fletcher CD, Fletcher JA. PDGFRA activating mutations in gastrointestinal stromal tumors. Science. 2003 Jan 31;299(5607):708-10

Debiec-Rychter M, Dumez H, Judson I, Wasag B, Verweij J, Brown M, Dimitrijevic S, Sciot R, Stul M, Vranck H, Scurr M, Hagemeijer A, van Glabbeke M, van Oosterom AT. Use of c-KIT/PDGFRA mutational analysis to predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 2004 Mar;40(5):689-95

Pardanani A, Brockman SR, Paternoster SF, Flynn HC, Ketterling RP, Lasho TL, Ho CL, Li CY, Dewald GW, Tefferi A. FIP1L1-PDGFRA fusion: prevalence and clinicopathologic correlates in 89 consecutive patients with moderate to severe eosinophilia. Blood. 2004 Nov 15;104(10):3038-45

Benoist M, Gaillard S, Castets F. The striatin family: a new signaling platform in dendritic spines. J Physiol Paris. 2006 Mar-May;99(2-3):146-53

Score J, Curtis C, Waghorn K, Stalder M, Jotterand M, Grand FH, Cross NC. Identification of a novel imatinib responsive KIF5B-PDGFRA fusion gene following screening for PDGFRA overexpression in patients with hypereosinophilia. Leukemia. 2006 May;20(5):827-32

Walz C, Curtis C, Schnittger S, Schultheis B, Metzgeroth G, Schoch C, Lengfelder E, Erben P, Müller MC, Haferlach T, Hochhaus A, Hehlmann R, Cross NC, Reiter A. Transient response to imatinib in a chronic eosinophilic leukemia associated with ins(9;4)(q33;q12q25) and a CDK5RAP2-PDGFRA fusion gene. Genes Chromosomes Cancer. 2006 Oct;45(10):950-6

Curtis CE, Grand FH, Musto P, Clark A, Murphy J, Perla G, Minervini MM, Stewart J, Reiter A, Cross NC. Two novel imatinib-responsive PDGFRA fusion genes in chronic eosinophilic leukaemia. Br J Haematol. 2007 Jul;138(1):77-81

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