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Leukaemia Section

Mini Review

t(4;14)(p16;q32)

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Clinics and pathology

Disease

Found in plasma cell leukaemia, multiple myeloma, plasmacytoma and monoclonal gammopathy of unknown significance (MGUS).

Phenotype/cell stem origin

Malignant plasma cells have the phenotype of mature terminally differenciated B-cells; there origin may be a pluripotent stem cell.

Epidemiology

Poorly described before FISH, quite karyotypically undetectable: found initially in cell lines, it represents the second more frequent IgH associated rearrangement, after t(11;14); detected by interphase FISH or RT-PCR in 25% MM cell lines, 15-20% primary MM and 0-10% MGUS lines; might be frequent but karyotypically undetected.

Clinics

Found in MM cases with unfavorable prognosis, even in patients treated with high dose chemotherapy.

Cytogenetics

Cytogenetics morphological

May be undetectable (telomere-telomere translocation).

Cytogenetics molecular

Therefore molecular probes are indicated, and FISH is relevant.

Additional anomalies

Hypodiploid karyotype and -13 / 13q- in major part of cases.

Genes involved and proteins

FGFR3

Location
4p16.3

c-FGFR3 (4p16.3) in normal cells: PAC 884J17 - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

Protein
Member of the tyrosine-kinase FGF receptor family, contains an extracellular domain with Ig-like loops, a transmembrane domain, and intracellular tyrosine kinase domains; localisation: plasma membrane; tyrosine kinase receptor; role in signal transduction, activates multiple signaling pathways regulating cell proliferation and differentiation; constitutional point mutations resulting in ligand-independent activation, are responsible of familial dominant achondroplasia / thanatophoric dwarfism.

IgH

Location
14q32

MMSET (multiple myeloma SET domain), also kown as WHSC1 (Wolf-Hirschorn syndrome candidate 1)

Location
4p16.3

DNA/RNA
90 kb, 25 exons, 5' - 3' centromeric orientation - complex alternative splicing.

Protein
136 KDa, 4 domains: PWWP domain (proline-tryptophan-tryptophan-prolin motif), HMG box (high mobility group), PHD-type (plant-homeodomain) zinc finger domain and SET (suppressor of variegation enhancer of zeste and Trithorax) domain. One full length 1365 aa isoenzyme and 4 possible truncated variants. Transcription factor, ubiquitously expressed but preferentially in growing embryonic tissues. Chromatin remodelling agent, regulates histones methylation.
Constitutional deletion of one copy is responsible for Wolf-Hirschhorn syndrom by haplo-insufficiency.

Result of the chromosomal anomaly

Hybrid gene

Description
4p16.3 breakpoint in a 110 kb region between MMSET (centromeric) within the 5' introns, and FGFR3 (telomeric). 14q32 breakpoint in the IgH switch region involving JH + constant region.
Two fusions generated, FGFR3 brought under the influence of the Ig gene enhancer Ea on der(14); MMSET under the influence of enhancer Eμ on der(4). Both FGFR3 and MMSET genes are deregulated by the translocation and a IgH-MMSET fusion transcript, detectable by RT-PCR, is generated.

Fusion protein

Description
No IgH-FGFR3 fusion protein, but promoter exchange between both partner genes; however, somatic mutations similar to what has been found in thanatophoric dwarfism have been identified in some cases; they may also contribute to abnormal FGFR3 activation. According to the variable breakpoint inside MMSET gene, the translocation may generate either a full length MMSET protein or a NH2-terminal truncated one.

Oncogenesis
Overexpression and activation of FGFR3 provides an oncogenic signal enhancing cell proliferation and survival. The functional consequences of MMSET deregulation are not completely investigated. All t(4;14) positive cases express MMSET whereas 30% lack FGFR3 expression, sometimes correlated with loss of der(14), which tends to demonstrate that MMSET dysregulation should be the crucial oncogenic event.

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