11q23 rearrangements in therapy related leukaemias

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Identity

Note: 11q23 rearrangements are also -and more often- found in de novo leukaemia.

Clinics and pathology

Phenotype / cell stem origin

These treatment related myelodysplasia (t-MDS) or leukaemias (t-AL) exhibit variable phenotypes: CMML or RAEB±T in MDS cases, ANLL most often (M4 or M5a mainly, M1, M2, M5b at times), ALL (and biphenotypic leukaemias), often CD19+; t(4;11) cases are frequently ALL cases.

Etiology

11q23 rearrangements in treatment related leukaemias were thought to be found mainly following a treatment with anti-topoisomerase II (epipodophyllotoxins) or with an intercalating topoisomerase II inhibitor (anthracyclins), as for some 21q22 rearrangements; actually, they may also be found after alkylating agents treatment and/or radiotherapy; the prior cancer is variable: breast cancer, non-Hodgkin lymphoma, Hodgkin disease, leukaemia, lung carcinoma, and other malignancies.

Epidemiology

Up to 30% of t(11;19)(q23;p13.1), 10% or more of t(9;11), 5% of t(4;11) and 5% of t(10;11) are found in secondary leukaemias: altogether 5 to 10% of 11q23 leukaemias are treatment related; these 11q23 second leukaemias are found at any age, from infancy to elder age.

Clinics

Latency for the outcome of the second leukaemia after the first cancer is often short (med 2 yrs), but highly variable, and may not depend on the type of treatment received; it is however most often shorter than in cases of second leukaemias associated with -5/del(5q) or with -7/del(7q).

Prognosis

Is poor, as in other therapy related leukaemias; in a recent excellent study (n=40), only 80% of patients achieved remission, 3/4 relapsed within a year; median remission duration being 5 mths.

Cytogenetics

Cytogenetics, morphological

Various 11q23 rearrangements may be found:
- t(1;11)(p32;q23)
- t(1;11)(q21;q23)
- t(4;11)(q21;q23)
- t(6;11)(q27;q23)
- t(9;11)(p22;q23)
- t(10;11)(p12;q23)
- t(11;16)(q23;p13)
- t(11;17)(q23;q25)
- t(11;19)(q23;p13.3)
- t(11;19)(q23;p13.1)

Additional anomalies

del(6q), -7/del(7q), del(17p).

Genes involved and Proteins

MLL

Location: 11q23

DNA / RNA

21 exons, spanning over 100 kb; 13-15 kb mRNA.
Protein
431 kDa; contains two DNA binding motifs (a AT hook, and Zinc fingers), a DNA methyl transferase motif, a bromodomain; transcriptional regulatory factor; nuclear localisation.

Variable gene, from a variable chromosome partner:
AF1p (1p32), AF1q (1q21), AF4 (4q21), AF6 (6q27), AF9 (9p22), AF10 (10p12), CBP (16p13), ENL (19p13.3), ELL (19p13.1).

DNA / RNA
These genes appear to have, in most cases, no apparent homology to each other; for DNA and protein description of each, refer to their gene entry.

Results of the chromosomal anomaly

Hybrid gene
Description
5’ MLL - 3’ partner.

Fusion protein
Description
N-term AT hook and DNA methyltransferase from MLL fused to (little or most of) the partner C-term part.

References

This article should be referenced as such: