Letter to the editor

Array-based comparative genomic hybridization characterization of cytogenetically polyclonal myeloid malignancies

The paradigmatic view in cancer biology today is that neoplasia has a monoclonal origin [1]. Occasionally, however, clones with different aberrations are found within individual tumors [2]. Whether such a cytogenetic polyclonality represents a true polyclonal origin of the different clones or whether they share a submicroscopic primary change, indicating a monoclonal origin, is unknown. Recently, we reported that multicolor fluorescence in situ hybridization did not reveal any primary cryptic changes in fourteen investigated polyclonal hematologic malignancies [3]. We concluded that other methods to screen for common cryptic changes, such as genome-wide array-based comparative genomic hybridization (aCGH), perhaps could be fruitful.

We have performed aCGH on 6 polyclonal myeloid malignancies, comprising four acute myeloid leukemias and two myelodysplastic syndromes (Table 1), using a 32K array set, consisting of 32,433 BAC clones covering 98% of the human genome, produced at the SWEGENE DNA microarray resource center (Lund University, Sweden). In all hybridizations, male reference genomic DNA was used (Promega, Madison, WI). Analyses of the microarray images were performed with GenePix Pro 4.0 software (Axon Instruments, Foster City, CA). To identify imbalances, the MATLAB toolbox CGH plotter was used, applying moving mean average of 3 clones and amplification/deletion limits of log2>0.2. Mapping of gains or losses was based on identification as such by the CGH plotter and by visual inspection of the log2 ratios. All these analyses were performed in the BioArray Software Environment database [4].

Apart from 15 copy number polymorphisms [5], not expected to be involved in the leukemogenic process, no cryptic changes, linking the different clones together, were found in the aCGH analyses. However, it should be stressed that this does not necessary exclude the presence of such abnormalities. First, a large admixture of normal, nonneoplastic cells could hamper detection of common cryptic changes. Second, aCGH does not identify balanced abnormalities; thus, if the cryptic change is a translocation or inversion it would remain undetected. A final possibility could, of course, be that the cytogenetic polyclonality really indicates a true polyclonal origin of the tumor cells.

Acknowledgments

This study was supported by grants from the Swedish Cancer Society, the Ingabritt and Arne Lundberg Foundation, and the Knut and Alice Wallenberg Foundation via the SWEGENE program.

Josef Davidsson[a]

Markus Heidenblad[a]

Åke Borg[b,c]

Bertil Johansson[a]

Departments of [a]Clinical Genetics and [b]Oncology and the [c]Lund Strategic Research Center for Stem Cell Biology and Cell Therapy, Lund University Hospital

SE – 221 85 Lund, Sweden

E-mail address: josef.davidsson@med.lu.se (J Davidsson)

References

[1] Nowell PC. The clonal evolution of tumor cell populations. Science 1976;194:23-8.

[2] Johansson B, Billström R, Broberg K, Fioretos T, Nilsson P-G, Ahlgren T, Malm C, Samuelsson BO, Mitelman F. Cytogenetic polyclonality in hematologic malignancies. Genes Chromosomes Cancer 1999;24:222-9.

[3] Davidsson J, Paulsson K, Johansson B. Multicolor fluorescence in situ hybridization characterization of cytogenetically polyclonal hematologic malignancies. Cancer Genet Cytogenet 2005;163:180-3.

[4] Saal L.H., Troein C, Vallon-Christersson J, Gruvberger S, Borg Å, Peterson C. Bioarray software environment: A platform for comprehensive management and analysis of microarray data. Genome Biol. 2002;3:software0003.1-0003.6

[5] The Database of Genomic Variants [Internet]. Updated December 2005. Available at http://projects.tcag.ca/variation/.

Table 1

Clinical and cytogenetic features of the 6 analyzed myeloid malignancies

Case No.	Sex/ age (yrs)	Diagnosis	Karyotype
1[a]	M/66	AML	47,X,der(Y)t(Y;3)(q12;q21),+8[7]/46,XY,+1,der(1;3)(q10;q10)[3]/ 46,XY[15]
2	F/36	AML (rel)	46,XX,t(1;6)(q21;p21)[11]/46,XX,t(6;15)(p25;q22)[8]/46,XX[6][b]
3[a]	M/49	AML	46,XY,der(18)t(11;18)(q13;p11)[15]/47,XY,+11[6]/46,XY[4]
4	M/77	AML	46,XY,+13,der(13;13)(q10;q10)[8]/47,XY,+13[5]/46,XY[11]
5	F/66	t-MDS	46,XX,del(20)(q11)[5]/46,XX,t(1;8)(q24;p12)[3]/46,XX[14]
6	M/51	t-MDS	46,XY,del(12)(q21q24)[10]/46,XY,+1,der(1;7)(q10;p10)[4]/46,XY[14]

Abbreviations: M, male; F, female; AML, acute myeloid leukemia; rel, relapse; t-MDS, treatment-related myelodysplastic syndrome.

[a]The original karyotypes of cases 1 and 3 have previously been published in [3].

[b]Normal karyotype at diagnosis.