ELSEVIER

Cancer Genetics and Cytogenetics 161 (2005) 187–188

CANCER GENETICS AND CYTOGENETICS

Letter to the editor

B-lymphoid or myeloid lineage identity of cell lines derived from chronic myeloid leukemia blast crisis

Chronic myeloid leukemia (CML) develops as a triphasic disease, ultimately leading to fatal blast crisis unless successfully treated [1]. Recent data have identified DOK1/DOK2 [2,3] and β-catenin [4] as important targets in the transition of chronic phase CML into blast crisis, but the molecular mechanism determining blastoid transformation of CML cells is not fully understood. In almost all instances, CML cells carry an oncogenic *BCR-ABL1* gene rearrangement resulting from the t(9;22)(q34;q11) translocation [5]. Studies in murine and human hematopoietic progenitor cells have shown that expression of a *BCR-ABL1* fusion gene is required and sufficient to drive malignant transformation of myeloid progenitor cells [6,7]. Also, B cell precursors can be transformed by oncogenic BCR-ABL1 kinase activity [6]. Indeed, *BCR-ABL1* gene rearrangements represent the most frequent recurrent genetic aberrations in adult B lineage acute lymphoblastic leukemias and are detected in ~25% of the cases [5]. Involvement of the major breakpoint cluster region (MBCR) within the *BCR* gene leading to the expression of a fusion protein of 210 kD (p210 BCR-ABL1) is characteristic for CML (>99%) [5]. In ~70% of *BCR-ABL1*$^+$ B cell lineage acute lymphoblastic leukemia, the leukemia cells carry *BCR-ABL1* fusion genes rearranged within the minor breakpoint cluster region (mBCR) encoding a smaller BCR-ABL1 fusion protein of 190 kD [5]. Recent work has shown that B lymphoid and myeloid cells transformed by p210 BCR-ABL1 markedly differ in their signaling requirements for sustained growth and survival [8]. The reason for different distribution of *BCR-ABL1* breakpoints in CML and B cell lineage acute lymphoblastic leukemia, however, is still currently unclear.

Of note, a significant fraction of cases of CML exhibit a B lymphoid phenotype upon progression into blast crisis. The phenotypic lineage conversion in these cases remains enigmatic. So-called lymphoid blast crisis cells typically express p210 BCR-ABL1 fusion proteins, suggesting that they represent the lymphoid outgrowth of a common initial CML clone. Alternatively, a B lymphoid clone unrelated to chronic phase CML may outcompete CML cells at a later stage of the disease and then emerge as lymphoid blast crisis. To date, it is not resolved whether lymphoid blast crisis cells share a common clonal origin with chronic phase CML or whether they represent the progeny of a B lymphoid tumor clone independent from chronic phase CML. It is also unclear whether B cell lineage leukemia cells expressing p210 BCR-ABL1 can develop as a primary acute lymphoblastic leukemia or only secondary to CML in the context of lymphoid blast crisis.

In either case, however, it is important to distinguish between myeloid and B lymphoid cells in the development of CML blast crisis. For instance, homozygous deletions within the *CDKN2A* locus can be detected in ~50% of the cases of B lymphoid blast crisis, but not in myeloid blast crisis [9]. Moreover, B lymphoid but not myeloid cells transformed by p210 BCR-ABL1 critically depend on SRC-kinase activity [8].

In the meantime, a large panel of CML blast crisis-derived cell lines is available [10], including both myeloid and lymphoid variants of CML blast crisis. Among them two cell lines, BV173 and NALM1, are B lymphoid in origin [11–13] but often referred to as "CML cell lines" [14–29]. The recent study by Pelz and colleagues [30] comprehensively reanalyzed the karyotype of NALM1 cells to establish this cell line as a "CML control." Although we do not question the accuracy of their cytogenetic analysis, we do disagree with their suggestion to use NALM1 cells as a control in studies related to CML cells. Unlike CML cells, NALM1 cells carry an in-frame immunoglobulin heavy chain $V_H3.9–D_H2.21–J_H3$ gene rearrangement on one allele of the *IGH* locus and a $D_H4–J_H$ rearrangement on the second allele [11]. In addition, NALM1 cells can be induced to rearrange *IGK* and *IGL* light chain V- and J-gene segments upon inhibition of BCR-ABL1 kinase activity by STI571 [12]. Finally, NALM1 cells express the pan-B cell marker CD19 [11–13] but myeloid lineage markers (including CD13, CD14, GM-CSFR and IL3Rα) are absent or expressed only at low levels. By genotypic and phenotypic definition, these data collectively identify NALM1 cells as a B lymphoid cell line. Likewise, BV173 cells carry rearranged *IGH* V region genes and express CD19, in apparent contradiction to their widespread designation as "CML cell line" [16–29].

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0165-4608/05/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.cancergencyto.2005.02.016

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