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Advantages of the CBA Mouse in Leukemogenesis Research

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ABSTRACT: The objectives of this review are to: (a) demonstrate that the male CBA/Ca mouse has several characteristics that make it an excellent animal for the study of leukemogenesis, (b) show that several of the genetic abnormalities observed in the male CBA/Ca mouse during the development of radiation induced acute myeloid leukemia (AML) are syntenic with those frequently detected in patients with myeloid disorders such as myelodysplastic syndrome and AML, (c) illustrate that leukemia-related chromosomal lesions are the indicators for high risk individuals.
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INTRODUCTION

Several inbred mouse strains, i.e. CBA (CBA/Ca, CBA/Cne, and CBA/H), C3H/He, RF, and SJL/J, have been used for many years as animal models involving leukemogenesis following exposure to ionizing radiation (1-7) and benzene (8,9). CBA mice are the preferable animal model used because they: (a) have a low spontaneous leukemia incidence (0.1 to 1%), (b) develop acute myeloid leukemia after exposure to radiation or benzene, (c) have cytogenetic, molecular, and histopathological characteristics that are comparable to those seen in human acute leukemia.

The CBA mouse was developed in 1920 by L.C. Strong at Cold Spring Harbor, NY, by crossing the Bagg albino with the DBA mouse (see Ref. #10 for a review). When brought to Edinburgh, UK, by Carter, it was renamed CBA/Ca. Subsequently sublines of the original mouse have been derived, e.g. CBA/H (MRC Harwell AE Laboratory, UK), CBA/CaJ (Jackson Laboratory, USA), CBA/CaBNL (Brookhaven National Laboratory, USA), and CBA/Cne (ENEA Casaccia Laboratory, Italy).

A wide spectrum of histopathological changes has been seen in radiation-induced acute myeloid leukemia (AML) (11). Diseased mice vary substantially with respect to

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the degree of differentiation along the granulocytic pathway. However, all show infiltration into the liver, kidneys and sometimes lymph nodes. Numerous megakaryocytes are found in the spleen and bone marrow. Splenomegaly is found consistently. Some cases showed extensive invasion of adjoining muscle through canaliculae in cortical bone. In benzene induced acute leukemias, histological changes are compatible with acute lymphoblastic leukemia, lymphoma, or mixed-lineage leukemias (9,12). Acute mixed myeloid and lymphoid leukemia has been observed in patients with some subsets of human AML (13-21). It is possible that the phenotypic myeloblastic leukemia in benzene-induced acute leukemias is uncommon because lymphoblastic leukemias and lymphomas may kill mice before the myeloblastic leukemia develops.

Using G-banding analysis, we (11) and others (22-25) demonstrated that a specific deletion involving one copy of mouse chr2 was frequently found in acute myeloid leukemic cells isolated from mice that had developed the disease following exposure to radiation. Although the deleted segment varied in size, all deletions remove regions D-E from one copy of chr2 [del(2)(D-E)]. In our studies, this genetic change was present in acute myeloid leukemia induced by exposure to either low- or high-LET radiation. However, Bouffler et al (26) reported no apparent indications of persistent chromosome changes in neutron induced acute myeloid leukemia in CBA/H mice. Translocations or inversions involving one copy of mouse chr2, in addition to del2(D-E) were also detected in some cells of radiation-induced acute myeloid leukemia with minimal tissue infiltration of leukemic cells (11) suggesting that these lesions produced a less malignant disease.

Information on cellular and molecular mechanisms underlying the induction of leukemia by benzene is limited. In our laboratory, cells from five benzene-exposed mice with histologically confirmed acute leukemia were examined using G-band analysis (27). Clones of cells with deletions and translocations involving chr2 were found suggesting that lesions on this chromosome are important genetic events for benzene induced leukemia. In contrast to radiation induced ML, other aberrant clones, e.g., trisomy of chr3, trisomy of chr15, trisomy of chr16, and a loss or gain of the Y chromosome were frequently detected in benzene-induced leukemic cells with or without lesions on chr2. The presence of aneuploidy in workers exposed to benzene has also been reported (28). These cytogenetic findings support the previous observation of spindle-fiber disruption or abnormal cytokinesis caused by metabolites of benzene, i.e., hydroquinone (29,30), and 1,2,4-benzenetriol (31). Aneuploidy has been previously detected in human acute myeloid or lymphoblastic leukemia, e.g., trisomy 4 (32-34), trisomy or tetrasomy 8 (35-38), trisomy 21 (39-41). This type of numerical abnormality has also been observed in murine T-cell leukemia, i.e., trisomy 15 (42-44). It should be noted that mouse chromosomes 3, 15, and 16 have syntenic regions with human chromosomes 4, 8, and 21 respectively (45,46).

The observation of a cytogenetic and histopathologic difference between radiation and benzene induced murine acute leukemias may reflect a difference in the initial interactions of DNA molecules with these disparate leukemogens. Benzene, like most chemical

carcinogens, is enzymatically metabolized to reactive electrophilic species by cytochrome P450 (CYP) mono-oxygenases, which are structurally specific, prior to covalently binding to specific sites of DNA molecules (DNA adduct formation) (47). The CYP2E1 isoform is primarily responsible for the activation of benzene to toxic metabolites (48).

Cytogenetic findings in radiation induced acute myeloid leukemia (11,22-25), together with those derived from studies of benzene induced acute murine leukemia (9) indicate that translocations and deletions involving chr2 are associated with the development of acute murine leukemia. It is possible that these cytogenetic changes lead to a loss of tumor suppressor gene(s) localized to this region, cause malfunction of the genes mapped adjacent to the 2(D-E) region, or even create a fusion of genes leading to the production of a leukemogenic protein.

The identification of genes mapped within or close to mouse 2(D-E) remains a challenge. To date, only a few genes associated with differentiation, development, and growth regulation of hematopoiesis have been cloned and mapped to mouse chr2. For example, homeobox 4.1 (Hox4.1), Wilms tumor (WT), and interleukin-1β (IL1β) genes are mapped to mouse 2D (49), 2E3 (50), and 2F (51), respectively. A deletion of one copy of the Hox4.1 gene has been detected in radiation-induced ML cells from CBA mice (52), suggesting that loss of function of this gene may contribute to the development of the disease. However, it is difficult to draw a conclusion on the role of the Hox gene in leukemogenesis because neither its expression in hematopoietic cells nor the abnormality of the knockout mice with heterozygous Hox gene has been reported (ref.#53 for a review). With respect to the IL-1β gene, an alteration in the methylation pattern of the IL-1β gene has been detected in myeloid leukemic cells from CBA mice containing chr2 translocations (54). However, the role of the IL-1β gene in leukemogenesis remains obscure. Although there is increasing evidence suggesting the involvement of the Wilms' tumor gene in human acute ML (55), the role of this gene in murine leukemogenesis remains unknown.

Our studies on the evolution of x-ray induced genetic lesions during the development of radiation induced acute myeloid leukemia (56) provide evidence that x-irradiation induces persistent genomic instability in up to 25% of the male CBA/Ca mice between 300 to 800 days post-irradiation when leukemia is diagnosed. At early times after irradiation with 2.0 Gy X rays, the predominant types of chromosomal lesions detected in metaphase cells obtained from the bone marrow of exposed mice are translocations, inversions, and deletions involving the distal portion of chr2, i.e., 2F-2H. The fraction of bone marrow cells with chr2 lesions progressively increased with time, suggesting the expansion of a clone of cells with one abnormal chr2. Subsequently clones of cells with del2(D-E) become apparent as the disease progresses towards a clinically diagnosable myeloid leukemia. The breakpoints on chr2 were clustered in the distal region of the mouse chr 2 (i.e. 2F to 2H) during the progression of x-ray induced acute myeloid leukemia.

The highlights of our past studies were, first, clonal expansion of cells with translocations involving chr2 in x-irradiated mice

without detectable leukemic phenotype as a function of time after exposure. Next, the observation of clones of cells that contained translocations, as well as deletions on chr2, in myeloid leukemic cells. This was seen only in mice that were in an early stage of this disease (as evidenced by a minimum infiltration of leukemic cells). Thus, the results lead to the conclusion that genomic lesions within or close to chr2(D-E) are associated with radiation leukemogenesis. Finally, our past results also suggest that mice with x-ray induced abnormal chr2 are at increased risk of developing leukemia later in life.

In a study by Bouffler et al (57) using CBA/H mice, carried out over 15 months, hyper-mutability and the clonal development of abnormalities in chr2 were also reported. The authors concluded that neither the induction of chr2 aberrations nor the presence of a chr2 aberrant clone specifically predicts the development of acute myeloid leukemia. Although these results appear to differ from ours, the lack of cytogenetic, histological, and hematological data for an early stage of the disease makes an adequate comparison difficult. Nevertheless, results from both studies suggested that certain regions of chr2 are particularly prone to expression of genomic instability after exposure to radiation and may play an important role in leukemogenesis. Sensitive or fragile sites have been also observed in chr2 of mice following treatment with methotrexate (58), or aphidicolin (59).

The mouse 2(D-E) region is homologous with regions on several human chromosomes (see ref.#60 for a review). These include 2q24-32, 11p11-13, 15q11-14, and 15q21-22. A del(2)(q31q32), a del(112)(p11p12p13), and a del(15)(q11) have been detected in some cases of human acute myeloid leukemia (46). A del(15)q21 has been found in a few cases of myelodysplastic syndrome (46). Chromosome translocations involving 2q31 and 11p13 have been found in a patient with myelodysplastic syndrome (61). The breakpoint clustered region, i.e. 2F- 2H, is syntenic to human chr 20q11-13 in which several candidate tumor suppressor genes associated with growth regulation and apoptosis have been mapped, e.g., a hematopoietic cell kinase gene (62) and a CD40 gene (63). A deletion within human chr 20q11-13 has been detected in disorders such as polycythemia vera, myelodysplastic syndrome, and acute myeloid leukemia (64,65). Deletions of specific segments of human chromosomes 5, and 7, i.e., $5q^-$, $7q^-$, have frequently been found in patients with acute myeloid leukemia or myelodysplastic syndrome occurring spontaneously or following chemotherapy (66,67). In these myeloid disorders, no evidence of homozygous deletion in any of the human chromosomes frequently involved has been reported. Therefore, the finding of a hemizygous deletion of chr2 in murine acute myeloid leukemic cells indicates the similarity of genetic mechanisms involving the induction of acute myeloid leukemia in the mouse and in some cases of human acute myeloid leukemia. The current available gene mapping data do not indicate homology between mouse 2(D-E) and human 5q or 7q. However, it is likely that information on the entire molecular characterization of the mouse 2(D-E), its flanking regions and those on human 5q and 7q will be obtained. The finding of translocations involving chr2 in acute murine myeloid leukemic cells also demonstrates the similarity of genetic

mechanisms involving the induction of acute myeloid leukemia in the mouse and in humans. The preponderance of evidence showing homology between mouse chr2 and human chromosomes, together with the closely similar histopathological characteristics of murine and human acute leukemic cells, indicate that the identification of induced lesions on mouse chr2 will provide a valuable tool for a better understanding of human leukemogenesis, not only in the context of pathogenesis but also for risk assessment.

This review of the advantages of the CBA mouse model for leukemogenesis suggests that cancer related chromosomal aberrations are of great value in identifying individuals who, in the interval between exposure and the clinical manifestation of cancer, are at greater risk of developing the disease. A similar conclusion has been reached in human lung carcinogenesis (68,69). In these studies, individuals at high risk for lung cancer, i.e., smokers and ex-uranium miners, had specific chromosomal aberrations similar to those frequently found in lung tumor cells (e.g., trisomy 7) in their airway epithelial cells. Such aberrations were not observed in non-exposed control subjects. These human subjects were chronically exposed to cigarette smoke and radon. In contrast, mice in our study were given whole body exposures to a single dose of X rays. Although the modes of exposure are thus different in these two studies, the cytogenetic findings suggest that chromosomal abnormalities observed in subjects with cancer are the indicators of an increased probability of malignancies in those exposed to these agents.

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