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Benzene, the exposome and future investigations of leukemia etiology

Martyn T. Smith*, Luoping Zhang, Cliona M. McHale, Christine F. Skibola, Stephen M. Rappaport

Genes and Environment Laboratory, School of Public Health, University of California, Berkeley, CA 94720-7356, United States

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ABSTRACT

Benzene exposure is associated with acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and probably lymphoma and childhood leukemia. Biological plausibility for a causal role of benzene in these diseases comes from its toxicity to hematopoietic stem cells (HSC) or progenitor cells, from which all leukemias and related disorders arise. The effect of this toxicity is manifest as lowered blood counts (hematotoxicity), even in individuals occupationally exposed to low levels of benzene. Benzene can induce AML/MDS via several well-characterized pathways associated with these diseases. Through its metabolites, benzene induces multiple alterations that likely contribute to the leukemogenic process, and appears to operate via multiple modes of action. To improve mechanistic understanding and for risk assessment purposes, it may be possible to measure several of the key events in these modes of action in an *in vitro* model of the bone marrow stem cell niche. Even though benzene is leukemogenic at relatively low occupational levels of exposure, it seems unlikely that it is a major cause of leukemia in the general population exposed to benzene in the ppb range. Other established non-genetic causes of AML, e.g. smoking, ionizing radiation and cancer chemotherapy, also only explain about 20% of AML incidence, leaving ~80% unexplained. The question arises as to how to find the causes of the majority of *de novo* AMLs that remain unexplained. We propose that we should attempt to characterize the 'exposome' of human leukemia by using unbiased laboratory-based methods to find the unknown 'environmental' factors that contribute to leukemia etiology.

1. Introduction

Benzene is a ubiquitous environmental chemical that causes acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and probably other hematological cancers, such as non-Hodgkin lymphoma, which includes chronic lymphocytic leukemia (CLL) [1,2]. Epidemiological studies have also provided evidence for an association with childhood leukemia [3,4]. The mechanism by which benzene produces leukemia has not been fully elucidated, but comprehensive research over many years has revealed that benzene acts through multiple mechanisms. Recently, Meek and Klaunig presented a relatively simple, hypothesized mode of action with proposed key events for benzene-induced leukemia [5]. Below, we describe a more comprehensive "mode of action" based on our current understanding of benzene-induced leukemia that involves multiple key events and modifying factors. We discuss the implications of this mechanism for risk assessment and describe an unbiased approach to finding the causes of leukemia other than benzene.

2. Role of metabolism in benzene-induced leukemia

In order to become carcinogenic and cause leukemia, it is understood that benzene must be metabolized to toxic metabolites [6,7], the general scheme of which is summarized in Fig. 1. The initial metabolic step involves cytochrome P450 (CYP)-dependent oxidation of benzene to benzene oxide, which exists in equilibrium with its tautomer oxepin. Most benzene oxide spontaneously rearranges to phenol (PH), which is either excreted or further metabolized to hydroquinone (HQ), 1,4-benzoquinone (BQ) and 1,2,4-benzetriol (BT). The remaining benzene oxide is either hydrolyzed to produce catechol (CAT) and 1,2-benzoquinone or reacts with glutathione to produce *S*-phenylmercapturic acid (S-PMA). Metabolism of oxepin is thought to open the aromatic ring, yielding the reactive muconaldehydes and *E,E*-muconic acid (MA). Human exposures to benzene at air concentrations between 0.1 and 10 ppm, result in urinary metabolite profiles with 70–85% PH, 5–10% each of HQ, MA and CAT, and less than 1% of S-PMA [8]. Benzene oxide, the benzoquinones, muconaldehydes, and benzene diol epoxides (formed from CYP oxidation of benzene dihydrodiol) are electrophiles that readily react with peptides and proteins [9–12] and can thereby interfere with cellular function [13].

The identification of metabolic susceptibility factors has confirmed the importance of metabolism in benzene toxicity. CYP2E1,

* Corresponding author. Tel.: +1 510 642 8770; fax: +1 510 642 0427.
E-mail address: martynts@berkeley.edu (M.T. Smith).

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which catalyzes the first step in benzene metabolism, represents a key metabolic susceptibility factor [14]. Other cytochrome P450s, such as CYP2F1 and CYP2A13 in the lung may also be involved in benzene metabolism [15–17]. Other metabolic susceptibility factors include epoxide hydrolase, glutathione-S-transferases (GSTT1, GSTM1), myeloperoxidase (MPO) and NAD(P)H:Quinone Oxidoreductase (NQO1) [18,19]. In cellular studies, the levels of MPO and NQO1 have been suggested to modulate the toxicity of phenolic metabolites of benzene particularly in stromal cells where multiple cell types exist with varying enzyme activities [20,21].

It remains unclear what role these different metabolites play in benzene carcinogenicity, but BQ formation from HQ via MPO in the bone marrow has been suggested as being key in benzene carcinogenicity as shown in Fig. 1 [13]. Further, the BQ-detoxifying enzyme NQO1 protects mice against benzene-induced myelodysplasia [22,23] and humans against benzene hematotoxicity [18,19,24]. However, this does not rule out adverse effects from other metabolites, such as the muconaldehydes [25,26].

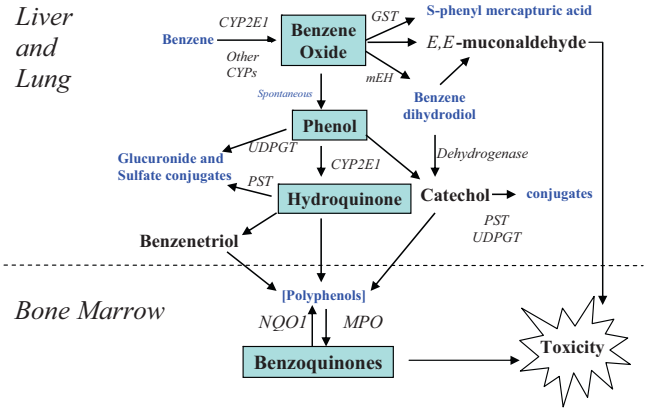

Fig. 1. Metabolism of benzene to toxic metabolites.

3. Mechanisms of benzene-induced leukemia

In order to produce leukemia, the reactive metabolites of benzene probably mutate a critical gene or set of genes related to proliferation and differentiation in human stem cells (HSC) by causing chromosome aberrations (aneuploidy, translocations, inversions, and deletions), aberrant mitotic recombination, gene mutations, and/or epigenetic alterations [4]. Ensuing genomic instability, or continued exposure to benzene, may result in the acquisition of additional alterations (Fig. 2). Initiated HSC express these mutations as they enter the cycling state from quiescence, a process triggered by benzene exposure through the aryl hydrocarbon receptor (AhR) [27], generating leukemic stem cells (LSC in Fig. 2). Concomitantly, adverse effects of benzene on the marrow stromal cells that regulate hematopoiesis can promote inappropriate survival/proliferation of the initiated HSC (Fig. 2). Further, benzene metabolites and NQO1 deficiency can potentially disrupt the vascular stem cell niche by interfering with endothelial cell adhesion molecules [28,29]. Oxidative stress resulting from benzene metabolism can cause both DNA damage and altered hematopoietic cell signaling. Reduced immunosurveillance could allow pre-leukemic clones to escape detection and elimination (Fig. 2). Hence, there are multiple key events and modifying factors involved in benzene-induced leukemia suggesting that it has multiple modes of action.

4. Implications for the risk assessment of benzene

Quantification of the key events and modifying factors described above will be challenging and the generation of a biologically based risk model for risk assessment purposes will require additional mechanistic research. Key events in benzene-induced leukemia include the induction of genetic and epigenetic changes in HSC,

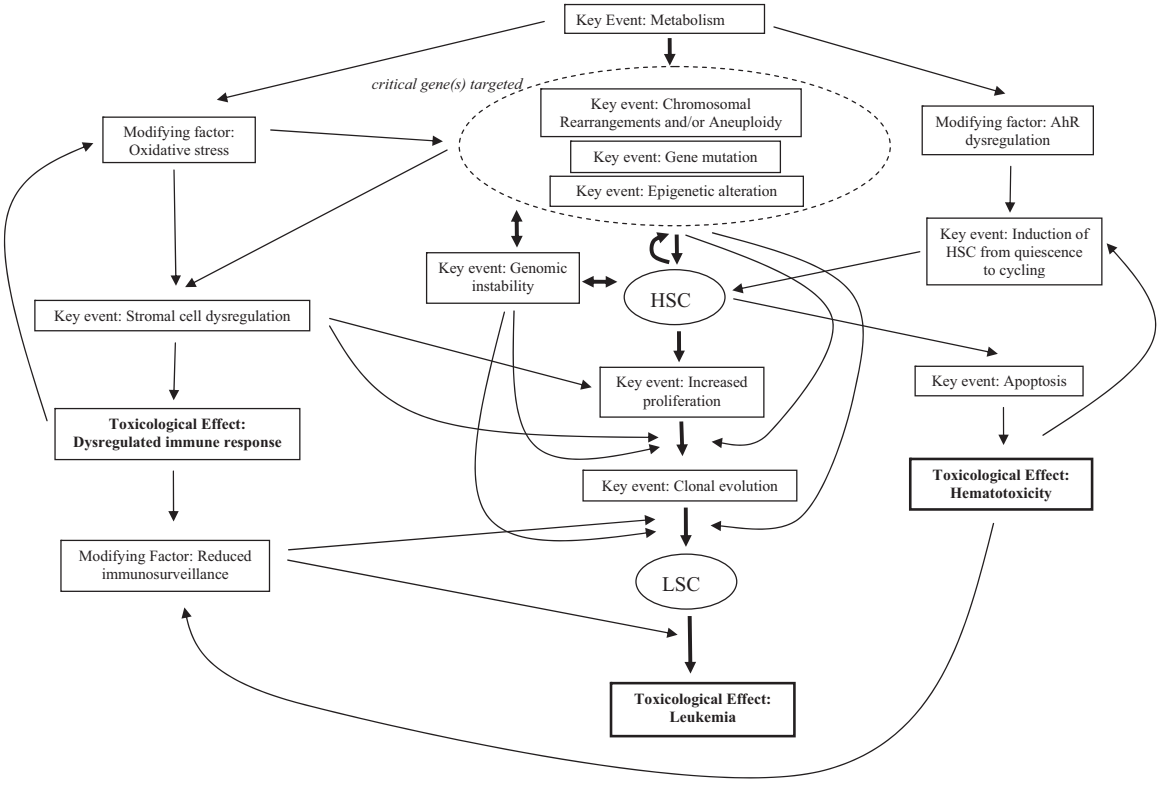

Fig. 2. Probable mechanism of benzene-induced leukemia.