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The Role of Epigenetic Changes in Benzene-Induced Acute Myeloid Leukaemia

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Abstract

Acute myeloid leukaemia (AML) is a malignant cancer in blood and bone marrow with overall survival rate about 25% in adult. The main pathological changes of AML involve the dysfunctions of hematopoietic stem and progenitor cells including the abnormal proliferation, blocked differentiation and abolished apoptosis. Benzene is one of the widely used chemicals in petrol and an environmental leukaemogen that can cause AML and haematological malignancies. Although extensive research work has been conducted to investigate the health effects of benzene, the mechanisms behind the benzene-inducedleukaemogenesis remain unclear due to the complex toxicities of benzene. Genotoxic effects of the compound on hematopoietic system have been believed to be the main mechanism underlying benzene-induced leukaemogensis. Emerging evidences suggested that epigenetic modifications play an important role in the occurrence of diseases including AML. This review will summarize the recent studies based on literatures from Pubmed and discusses the role of epigenetics changes in Benzene-induced acute myeloid leukemia.

Keywords: Myeloid leukaemia; Leukaemogen; Malignancies; Epigenetic; Genotoxic

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Introduction

Acute myeloid leukaemia (AML) is a malignant disease of the blood and bone marrow system. Normally, different types of mature blood cells are derived from their progenitor cells and haematopoietic stem cells (HSC). In the haematopoietic system, the fate of the cells such as quiescence, self-renewal or proliferation, and differentiation at the progenitor or precursor level are strictly regulated. This haematopoietic hierarchy is controlled via a variety of growth factors including colony-stimulating factors (CSFs), interleukins (ILs), transcriptional factors, hormones and other regulation factors such as p53 and apoptotic process [1]. It has been established that uncontrolled proliferation, blocked differentiation and dysregulated apoptosis of haematopoietic precursor cells are involved in AML development, but the origin of the etiological changes in AML has not yet been completely elucidated. Some environmental carcinogens including benzene (Bz) can induce AML. Understanding the molecular mechanisms underlying Bz-induced leukaemogenesis will help to elucidate the initiation and progression of AML.

Bz Exposure and AML

It has been suggested that multiple key molecular and cellular events may be involved in myeloid leukaemogenesis. Exposure to environmental factors including chemicals (i.e., the leukaemogenic chemicals and some therapy-related compounds) as well as ionizing radiation is risk factors causing AML and myelodysplastic syndrome (MDS) [2]. Benzene (Bz), a volatile compound, is used in petrol and other manufactured products including rubber, lubricants, dyes, detergents and drugs. Additionally, Bz is an important air contaminant generated from motor vehicles, industrial processes, and cigarette smoking. Therefore, humans may be exposed to Bz through inhalation from a variety of different sources. Notably, Bz has been classified as a human carcinogen by the International Agency for Research on Cancer [3] and exposure to Bz and its association with AML has been well reviewed and documented [2]. After exposure, Bz undergoes metabolism by cytochrome P450 2E1 and 2F1 (CYP2E1 and CYP2F1) mainly in the liver. It has been well established that Bz exerts its toxicity through the reactive metabolites, i.e., catechol, hydroquinone (HQ), benzoquinone (BQ) and others [4]. Bz and its metabolites can redistribute and accumulate in bone marrow tissue where

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they exert their selective toxicity to the haematopoietic stem cells or progenitor cells. The resultant molecular and cellular effects include oxidative stress, changes in gene expression and function, disrupted balance among proliferation, differentiation, apoptosis and cytogenetic abnormalities like chromosomal aberrations [5]. Recently, epigenetic changes induced by Bz and their roles in disease initiation and development have drawn great attentions.

Environmental Factor-Induced Epigenetic Changes

Epigenetic refers to inheritable changes in phenotype and function without alteration of DNA sequences [6]. In other words, epigenetic modulation regulates or modulates in some degree gene expression and consequent functions. This means that normal physiological functions of cells are controlled by not only genetic mechanisms but also balanced epigenetic pattern which plays an important role in the control of many cellular functions of the body. In addition, environmental factors can cause epigenetic modifications through various mechanisms. In addition, many genetic changes induced by environmental factors such as environmental chemicals are virtually through epigenetic modifications. One of the mechanisms of the environmental chemical-induced epigenetic alterations is due to the generation of reactive oxygen species (ROS) [7, 8]. The environmental factor-induced epigenetic changes and consequent health effects have drawn great attentions in recent years in clinical and health research areas. The epigenetic modifications include DNA methylation, histone modifications and non-coding RNAs (ncRNA) expression. Methylation of DNA, a process involving the addition of methyl groups to DNA typically at CpG dinucleotide context, can cause the conformational change of DNA structure and consequent alteration in gene expression [9, 10]. DNA methylation is import regulation mechanism for mammalian development [11]. However, abnormal DNA methylation patterns, hypermethylation or hypomethylation can lead to various pathogenesis or oncogenesis. Hypermethylations are generally associated with gene silencing or down regulation, whereas hypomethylation or unmethylated promoters are mostly linked to gene activation [12]. Epigenetic regulation of gene expression can also be through modification of histone through post-translational modifications such as acetylation, phosphorylation, methylation and ubiquitination [13]. Histone modifications are important in genetic process including transcriptional regulation, DNA repair, DNA replication, alternative splicing and chromosome condensation [13-15]. Another important epigenetic modifier is ncRNA including microRNAs (miRs) and long non-coding RNAs (LncRNAs) [16]. Many environmental chemicals including benzene can modify normal epigenetic pattern.

Bz-Induced Epigenetics Alterations and Association with AML

Although Bz has been well studied for its genotoxic and carcinogenetic effects in animal and human studies, the exact mechanisms underlying are still remained to be understood. Bz has been known to have genotoxic effects, but emerging evidence has suggested that this compound can also induce epigenetic changes. The reason of Bz-induced epigenetic modifications is unclear but ROS may be one of the pathways involved since Bz and its metabolites have been shown to generate ROS during metabolic transformation [17-19] and ROS can cause epigenetic changes as mentioned above. Further work is required to investigate the cause of Bz-induced epigenetic alterations, which will provide more mechanistic clues.

The epigenetic role in Bz-induced carcinogenesis has emerged only in recent years with some studies published. Although the epigenetic effect of Bz in progression, development and survival of the leukemic clone was proposed as early as in 1996 [20], recent studies suggested an earlier and broader involvement of epigenetic modification in Bz-induced hematotoxicity. Bollati V and his colleagues conducted the earlier human study of Bz exposure and associated epigenetic changes [21]. They found that exposure to Bz at low level can cause to significant reduction in long interspersed nuclear element-1 (line 1) and AluI repetitive elements methylation and hypomethylation in MAGE-1 and p15. The epigenetic alterations in these genes were also found in AML cells [22-25]. Hypomethylation of Melanoma-associated antigen 1 (MAGE-1) was further confirmed together with finding of another gene associated with AML, runt-related transcription factor 1 (RUNX1T1) in an *in vitro* study in which TK6 cells were treated with hydroquinone, one of Bz's metabolites [26]. In addition, Bz induce methylation of PTEN (Phosphatase and tensin homolog deleted on chromosome 10), a tumor suppresser gene, leading to altered expression and function of this gene [27].

Furthermore, Bz was found to cause aberrant promoter methylation of genes for DNA repair such as ERCC1 [28] and PARP-1 [29]. It has been believed Bz elicits its carcinogenesis through its metabolites which can directly or indirectly induce ROS leading to DNA damage. In this context, DNA repair plays important role in Bz-induced carcinogenesis and reduced DNA repair capacity may lead to increased susceptibility to Bz toxicity.

Bz may also elicit its hematotoxicity through increase the histone deacetylases (HDAC) [30]. Bz metabolites have been found to Methyl-CpG-binding domain protein 2 (MBD2) and DNA methyltransferases (DNMTs) were found to be hypomethylated by benzene exposure [31]. Among the epigenetic modifiers, HDAC and DNMTs (DNMT3A) have been showed to associate with the early stage of AML [32-34]. Therefore, the dysfunction of these epigenetic modifiers by Bz and its metabolites may further contribute to its carcinogenesis at initiation and development stage.

In conclusion, recent epigenetic studies on Bz although not many suggested that Bz can induce a variety of epigenetic alterations on genes involving in tumor suppresser (p15 and PTEN), cancer antigen (MAGE-1), transcription (RUNX1T1), DNA repair (PARP-1, ERCC-1), and even epigenetic modification (HDAC and DNMTs) as summarized in **Figure 1**. Importantly, some of these genes are found to be modified epigenetically in AML cells which may indicate the role of these epigenetics alterations in Bz-induced leukaemogensis of which further research work will provide more mechanistic information.

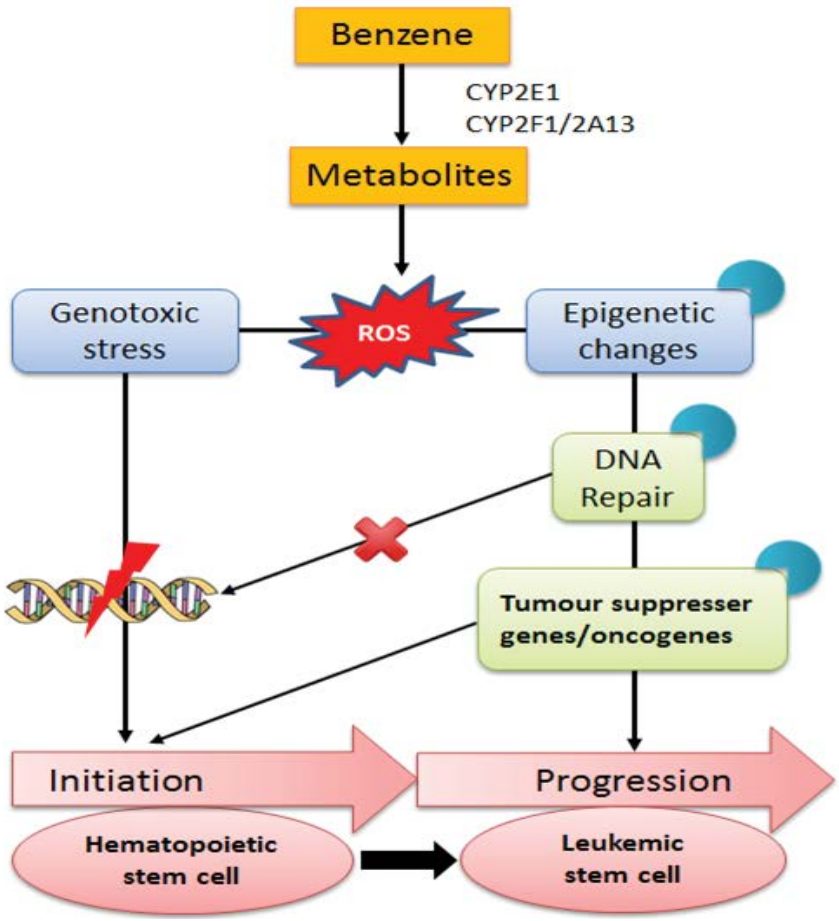

Figure 1 Illustration of the role of epigenetic changes in benzene-induced leukaemogenesis. In cells Benzene is biotransformed by cytochrome P450 mainly (mainly CYP2E1) to reactive metabolites during which ROS can be generated. ROS may not only induce genotoxic effects but also epigenetic alterations. Epigenetic changes may cause impaired DNA repair abilities and dysfunctional oncogenes and tumour suppressor genes which acts together with genotoxic effects to induce leukaemogenesis.

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