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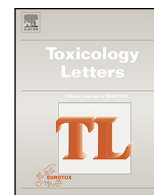

Mitochondria defects are involved in lead-acetate-induced adult hematopoietic stem cell decline

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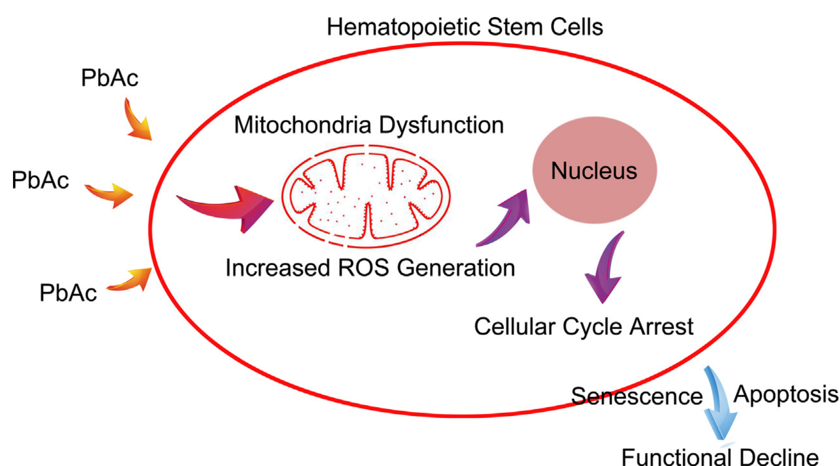
HIGHLIGHTS

- Lead acetate exposure perturbs the hematopoietic stem cells (HSCs) function.
- Exposure lead acetate to HSCs induced premature senescence or apoptosis.
- HSCs senescence or apoptosis is linked with cellular mitochondrial defects.
- Cellular mitochondrial defects led to increased intracellular ROS generation.

GRAPHICAL ABSTRACT



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ABSTRACT

Occupational high-grade lead exposure has been reduced in recent decades as a result of increased regulation. However, environmental lead exposure remains widespread, and is associated with severe toxicity implicated in human diseases. We performed oral intragastric administration of various dose lead acetate to adult Sprague Dawley rats to define the role of lead exposure in hematopoietic stem cells (HSCs) function, and to clarify its underlying mechanism. Lead acetate-exposed rats exhibited developmental abnormalities in myeloid and lymphoid lineages, and a significant decline in immune functions. It also showed HSCs functional decline associated with senescent phenotype with low grade lead acetate exposure or apoptotic phenotype with relative higher grade dose exposure. Mechanistic

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exploration showed a significant increase in reactive oxygen species (ROS) in the lead acetate-exposed $CD90^{+}CD45^{-}$ compartment, which correlated with functional defects in cellular mitochondria. Furthermore, in vivo treatment with the antioxidant vitamin C led to reversion of the $CD90^{+}CD45^{-}$ compartment functional decline. These results indicate that lead acetate perturbs the hematopoietic balance of adult HSCs, associated with cellular mitochondria defects, increased intracellular ROS generation.

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1. Introduction

Lead is a heavy metal that is both poisonous and a ubiquitous environmental toxicant. It is distributed in all parts of the environment in three main forms: metallic lead, lead salts, and organic lead containing carbon (Bellinger, 2004; Ahamed and Siddiqui, 2007a,b). The major sources of occupational lead exposure are traditionally leaded gasoline, lead-based paints, and battery contamination. Lead exposure has been a widely-recognized significant public health problem over recent decades, and high levels of occupational lead exposure are now strictly controlled because of their adverse health effects. However, environmental lead exposure, such as that in domestic tap water, food-borne contamination and household dust, continue to pollute our surroundings in daily life (Spivey, 2007).

Exposure to lead is considered to be detrimental and to be associated with behavioral abnormalities, hearing deficits, neuromuscular weakness, and impaired cognitive functions in humans and experimental animals (Ahamed and Siddiqui, 2007a,b; Flora et al., 2012). Indeed, no blood-lead levels appear to be safe, and sub-clinical effects of lead toxicity have been reported in recent years (Canfield et al., 2003).

Lead has toxic effects in a wide variety of organs, causing impairments in the nervous, hematopoietic, renal, cardiovascular and reproductive systems following ingestion, inhalation or skin absorption (Baranowska-Bosiacka et al., 2012; Guidotti et al., 2008; Rastogi, 2008). Oxidative stress has been reported to be a major mechanism of lead toxicity. One of the main effects of lead toxicity in the hematopoietic system involves impairment of the hemoglobin synthesis pathway through disrupted expression of genes encoding δ-aminolevulinic acid dehydratase, ferrochelatase and aminolevulinic acid synthetase (Piomelli, 2002). This is attributed to the induction of oxidative stress by elevation of reactive oxygen species (ROS) such as superoxide radicals, hydrogen peroxide and hydroxyl radicals and lipid peroxides (Ahamed and Siddiqui, 2007a,b,b; Flora, 2011). In mammals, ROS are generated either by the mitochondrial electron transport chain or NADPH (Nicotinamide Adenine Dinucleotide Phosphate) oxidase in virtually all cell types, and are involved in regulating cell proliferation and differentiation, and genomic stability (Kamata, 2009; Katsuyama et al., 2012). However, increased ROS production occurs in numerous pathologic situations, including hematopoietic stem cell (HSC) apoptosis and premature senescence. The role of oxidative stress in lead-exposure-induced HSC function remains unclear (Taniguchi Ishikawa et al., 2012; Ito et al., 2006).

In this study, we examined the effects of lead acetate exposure on the balance of hematopoiesis and HSC function. We also investigated the involvement of ROS in the mitochondria on the mechanisms of lead toxicity.

2. Materials and methods

2.1. Reagents and animals

Lead-acetate [$(CH_3COO)_2Pb \cdot 3H_2O$] was obtained from Sigma–Aldrich (St. Louis, MO, USA). Eight-week-old Sprague Dawley rats (200–230 g) of either sex were purchased from the Laboratory Animal Center of Chongqing Medical University (China). All animal experiments were performed in accordance with the Chinese legislation on the use and care of laboratory animals and were approved by Chongqing Medical University committees for animal experiments.

2.2. Drug preparation and administration

Lead acetate (PbAc) was dissolved in 0.9% normal saline and orally administered to rats at a dose of 200, 400 or 600 mg/kg body weight per day by gavage throughout the whole experimental period (4 weeks), designated as relative lower (L-PbAc), moderate (M-PbAc) or higher dose group (H-PbAc). Each rat was weighed prior to each gavage to allow the dose to be adjusted accordingly. Vitamin C was dissolved in clinical normal saline and administered to moderate dose (M-PbAc) exposed rats at a dose of 100 mg/kg body weight for 2 weeks. The same amount of normal saline was given to littermates as a control. The dose of lead acetate was determined based on previous studies that identified 45–180 mg/kg given to rats by intragastric gavage as small doses and 1000 mg/kg as the highest non-lethal dosage (Kishi et al., 1983; Toews et al., 1978). The rats were kept in pathogen-free conditions at 22–25 °C and had free access to sterile water and food.

2.3. Determination of lead content in peripheral blood

Lead concentration in peripheral blood (PB) was calculated by graphite furnace atomic absorption spectrometry (GFAAS). The blood samples were collected into a heparinized tube and added by 0.5% Triton X 100 for mixture. The lead concentration in the PB was measured by Spectr AA800 (Varian, USA).

2.4. Analysis of peripheral blood cells and bone marrow mononuclear cell counts

For analysis of peripheral blood counts, PB from the postorbital vein was collected into a heparinized tube and analyzed using a Sysmex XE-5000 automated hematology analyzer (Sysmex, Japan). Bone marrow mononuclear cells (BMMNCs) counts were performed using BMMNCs isolated by Ficoll-Paque (Amersham Biosciences, Sweden) density-gradient centrifugation and analyzed on a hemocytometer. All counts were performed at least three times.

2.5. Flow cytometry

For detection of $CD4^{+}$ lymphocytes, $CD8^{+}$ lymphocytes, $CD4^{+}CD8^{+}$ lymphocytes, blood cells were collected and lysed with Lysing Buffer (BD Biosciences, San Diego, CA, USA), the remaining cells in blood were washed twice with phosphate-buffered saline (PBS) and staining with fluorescein isothiocyanate (FITC)-conjugated mouse-anti-rat CD4 (eBioscience Inc., San Diego, CA, USA) and phycoerythrin (PE)-conjugated mouse anti- rat CD8a (eBioscience Inc., San Diego, CA, USA) antibodies for 15 min at room temperature in the dark. The

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