Acta Pharmaceutica Sinica B 2016;6(5):426–429

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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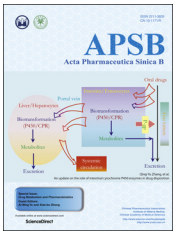

REVIEW

Exposure to inorganic arsenic can lead to gut microbe perturbations and hepatocellular carcinoma

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Received 28 March 2016; revised 29 April 2016; accepted 10 May 2016

KEY WORDS

Arsenic;
Microbiome;
Epigenetics;
Liver cancer;
Hepatocellular carcinoma;
Gut microbiota;
Lipopolysaccharide

Abstract Arsenic is a carcinogenic environmental factor found in food and drinking water around the world. The mechanisms in which arsenic alters homeostasis are not fully understood. Over the past few decades, light has been shed on varying mechanisms in which arsenic induces cancer. Such mechanisms include gut microbe perturbations, genotoxic effects, and epigenetic modification. Gut microbe perturbations have been shown to increase the level of pathogen-associated molecular patterns such as lipopolysaccharide (LPS) leading to uncontained inflammation. Increase in inflammation is the major factor in cirrhosis leading to hepatocellular carcinoma. Alterations in gut permeability and metabolites have also been observed as a fallout of arsenic induced gut microbe modification. The guts proximity and interaction through portal flow make the liver susceptible to gut perturbations and ensuing inflammatory responses. Genotoxic and epigenetic dysregulation induced by arsenic and its toxic metabolites present a more direct mechanism that works synergistically with gut microbe perturbations to induce the incidence of cancers. These pathways combined could be some of the main causes of arsenic-induced carcinogenesis.

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Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

http://dx.doi.org/10.1016/j.apsb.2016.07.011

1. Introduction

Arsenic is the 20th most common element in the earth's crust and is considered a group 1 carcinogen[1]. Arsenics abundance and known cariogenic properties make it a global health concern. Arsenic is an environmental factor that is known to contaminate drinking water and food supply if not adequately regulated. Over 100 million people worldwide rely on arsenic-contaminated drinking water on 5 of the earth's continents[2]. There are multiple forms of arsenic, but naturally occurring trivalent inorganic arsenic possess the highest toxicity. Trivalent arsenic can be directly methylated leading to volatile products while pentavalent arsenic is not readily taken up by cells and is often reduced to trivalent arsenic[3]. Once ingested arsenic is metabolized in the liver where hepatocytes uptake trivalent arsenic, within the hepatocytes, subsequent conjugations and methylations occur leading to volatile products[4].

Arsenic has been found to increase the incidence of cancers including skin, lung, kidney, urinary bladder, prostate, and liver[1]. Hepatocellular carcinoma (HCC) is the leading form of liver cancer and will serve as the focus for this review. The mechanisms in which arsenic induces such cancers are continually investigated.

The carcinogenic effects of arsenic cannot be pinpointed to one simple mechanism, since arsenic perturbs physiological functions through multiple interworking pathways. Such proposed mechanisms leading to cancers include shifts in gut microbiota, genotoxic effects, and epigenetic dysregulation[5–7]. These mechanisms work synergistically to induce cancers, such as HCC.

The human body is host to many trillions of gut microbes and this microbial community works in symbiosis to aid in normal physiological functions, such as digestion and metabolism[8]. Perturbations in the gut microbiota have been associated with many diseases from obesity to various forms of cancer[9]. It has been shown that arsenic can alter the microbiome and metabolic profile in mice. It is proposed that alterations in the gut microbiota by arsenic can lead to many physiological imbalances aiding in HCC development.

As mentioned previously, arsenic has the potential to induce genotoxic fallout and abnormal epigenetic modifications[5]. Arsenic is considered a genotoxic metalloid with the ability to cause DNA strand breaks, sister chromatid exchanges, and micronuclei[10]. Aberrant epigenetic modifications have also been related to arsenic exposure[11]. Arsenic has the potential to induce HCC through multiple mechanisms, therefore proving an elusive environmental carcinogen (Fig. 1).

2. Arsenic perturbs gut microbiota

When inorganic arsenic is ingested into the body through contaminated food and water, it is metabolized by the liver, where hepatocytes uptake trivalent arsenic *via* aquaglyceroporins and hexose permeases. Within the hepatocyte, arsenic is conjugated with glutathione, generating arsenic triglutathione. Methylation may also take place leading to dimethylarsenic glutathione which has been found to be excreted in bile and into the blood stream. Dimethylarsenic glutathione is unstable and has the potential to form volatile compounds, such as dimethylarsine. Red blood cells are also able to efficiently take up arsenic and store the arsenic as protein-bound trivalent dimethylarsenicals throughout the body[4].

Whether arsenic is stored in the cells of the human body or within the gut microbe population, negative effects ensue. A metagenomics and metabolomics analysis conducted by Lu et al.[7], in which mice were treated with arsenic through drinking water at a concentration of 10 ppm for four weeks, revealed that the control and treated animals were well separated with 19.95% and 10.66% variation explained by principal component analysis. In a second study, mice were treated with arsenic for 2, 5, and 10 weeks at low to moderate levels of arsenic (10–250 ppb) and microbial biofilms that lined the intestine of control mice were degraded in the

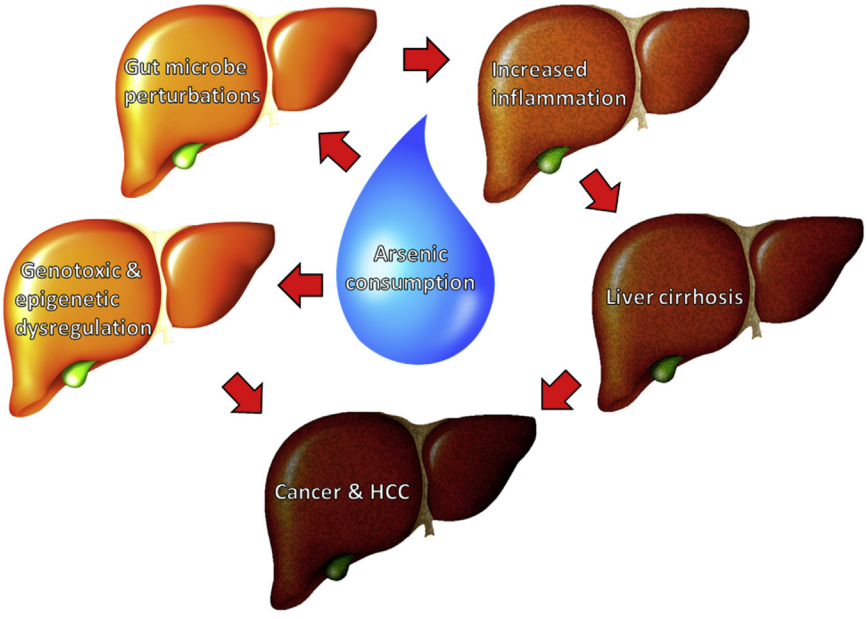

Figure 1 Schematic summary of arsenic-induced disease progression demonstrating synergistic mechanisms leading to liver cirrhosis and hepatocellular carcinoma (HCC). Arsenic consumption leads to both genotoxic/epigenetic dysregulation and gut perturbations. Gut perturbation increases the incidence of inflammation leading to cirrhosis and potentially HCC. Genotoxic and epigenetic dysregulation disrupts intracellular mechanisms, increasing the potential for HCC development.