Toxicology Letters 241 (2016) 216–224

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

# Biotin-mediated epigenetic modifications: Potential defense against the carcinogenicity of benzo[a]pyrene

Bo Xia[a,b], Li Pang[c], Zhi-xiong Zhuang[a,*], Jian-jun Liu[a,*]

[a] Key Laboratory of Modern Toxicology of Shenzhen, Medical Key Laboratory of Health Toxicology, Laboratory of Modern Toxicology, Shenzhen Centre for Disease Control and Prevention, Shenzhen 518060, China
[b] College of Food Science and Technology, Hunan Agricultural University, East Renmin Road, Changsha 410128, Hunan, China
[c] College of Horticulture and Gardening, Hunan Agricultural University, East Renmin Road, Changsha 410128, Hunan, China

## HIGHLIGHTS

- Provides an overview of the epigenetic events caused by benzo[a]pyrene.
- Provides an overview of the epigenetic events associated with biotin.
- Discussed the possibility of nutritional treatment against tumorigenesis.
- Biotin supplement may potentially reduce the risk of cancer induced by B[a]P.

## ARTICLE INFO

*Article history:*
Received 30 September 2015
Received in revised form 3 November 2015
Accepted 8 November 2015
Available online 10 November 2015

*Keywords:*
Biotin
Epigenetic modification
Benzo[a]pyrene
Carcinogenicity

## ABSTRACT

Environmental pollution and an unhealthy lifestyle result in direct exposure to dangerous chemicals that can modify endogenous pathways and induce malignant transformation of human cells. Although the molecular mechanisms of tumorigenesis are still not well understood, epigenetic alteration may be associated with exogenous chemical-induced carcinogenicity. Given the association between nutrition and cancer, nutrient supplementation may reduce aberrant epigenetic modifications induced by chemicals, thus decreasing carcinogenesis. This paper provides an overview of the epigenetic events caused by benzo[a]pyrene, a procarcinogenic and environmental pollutant, and biotin, an essential water-soluble vitamin, and investigates potential connections between them. This paper also discusses the potential inhibitory effect of biotin-related epigenetic modifications on the carcinogenicity of benzo [a]pyrene. The effect of nutritional supplementation on tumorigenesis involving epigenetic modifications is also discussed.



## 1. Introduction

Most human cancers are associated with environmental causes (Gilliland, 1997). Our complex environment contains food additives, insecticides, pesticides and industrial chemicals that may cause exogenously induced genetic damage and malignant transformation of normal cells. Thus, humans and other animals, including wildlife are at risk of environmental contamination. Insight into the intricate details of the causes of different cancers, especially those with environmental origins, requires detailed analysis of the mechanisms inherent in different types of cancer. Current challenges include toxicological approaches and integrating recent advances to elucidate the cause and determine ways to prevent human cancer (Carbone et al., 2004). Promising exploratory studies on chemical carcinogens provide useful information about and contribute to the evaluation of human carcinogens. Although the molecular mechanisms of tumorigenesis are not well understood, studies are finding that epigenetic alteration, oxidative stress, DNA lesions, defects in DNA repair and activation of certain transcription factors may be associated with exogenous chemical-induced carcinogenesis (Baccarelli and Bollati, 2009; Klaunig et al., 1998; Lehmann, 1981; Tsapakos et al., 1983).

In this postgenome era, epigenetics are being actively studied. The past several years have witnessed an explosive increase in knowledge of the epigenetic events associated with environmental chemical carcinogens. For example, DNA methylation and DNA

* Corresponding authors. Fax: +86 755 2563 9066.
*E-mail addresses:* zxzhuang2007@sina.com (Z.-x. Zhuang), junii8@126.com (J.-j. Liu).

http://dx.doi.org/10.1016/j.toxlet.2015.11.010
0378-4274/

adducts are important biomarkers in lung cancer induced by long-term exposure to ambient air pollution (AAP) and have the potential to improve AAP exposure assessment (Demetriou and Vineis, 2015). The ubiquitous environmental pollutant 1,3-butadiene (BD) causes tissue-specific condensation of heterochromatin and histone-lysine trimethylation (Thomson et al., 2014). In addition, microRNA (miRNA) and long noncoding RNA (lncRNA) may provide a mechanistic link between chemicals and carcinogenesis. In hepatocarcinogenesis induced by polycyclic aromatic hydrocarbons (PAHs), the miR-181 family is important in targeting MKP-5, which regulates p38 MAPK activation (Song et al., 2013). The novel lncRNA SCAL1 is elevated in numerous lung cancer cell lines and can be induced by cigarette smoke extract both *in vitro*and *in vivo*(Thai et al., 2013).

Much research has focused on carcinogenesis involving benzo [a]pyrene (B[a]P), a procarcinogen and environmental toxin, an especially on the increased incidence and variable prevalence of tumors caused by this molecule. B[a]P is widely distributed in the environment and is classified as carcinogenic to humans by the International Agency for Research on Cancer (Tang et al., 2012). Although the mechanisms of B[a]P-induced carcinogenesis are not clear, anti-7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-benzo[a] pyrene (BPDE), the carcinogenic form of B[a]P, forms DNA adducts. B[a]P modifies DNA and leads to deregulation of gene expression (Sadikovic and Rodenhiser, 2006). A recent study showed that B[a] P may affect gene expression in developing zebrafish by altering DNA methylation (Fang et al., 2015). In addition, B[a]P causes significant changes in histone acetylation (Sadikovic et al., 2008). Thus, the underlying link between epigenetics and the carcinogenicity of B[a]P is worth investigating.

Increasing evidence supports the relationship between nutrition and epigenetic modifications. Dietary behavior is an important determinant of cancer because some nutrients markedly affect key intracellular nodes that are related to cancer (Davis et al., 2010). By interacting with epigenetics, nutrients may affect the expression of genes associated with the developmental programming of disease (Junien, 2006). Although the effect is controversial, certain nutrients are beneficial for cancer risk reduction. Therefore, identifying and developing nutritional agents that are effective for particular types of cancer is a focus of cancer prevention research. Biotin, an essential water-soluble vitamin that serves as the carrier for biotin-dependent carboxylases, binds covalently to histones (Stanley et al., 2001). Biotinylated histones participate in important biological functions such as gene silencing, mitotic condensation of chromatin, cell proliferation, and the cellular response to DNA damage (Camporeale et al., 2007a,b; Hassan and Zempleni, 2006; Kothapalli et al., 2005). This paper provides an overview of the epigenetic events induced by B[a]P and biotin. We also discuss the possibility of nutritional treatment for tumorigenesis that involves epigenetic regulation.

## 2. Carcinogenicity of benzo[a]pyrene

B[a]P is a polycyclic aromatic hydrocarbon (PAH) and is an environmental toxin associated with car exhaust, incomplete fossil fuel combustion, municipal waste incineration, tobacco smoke,

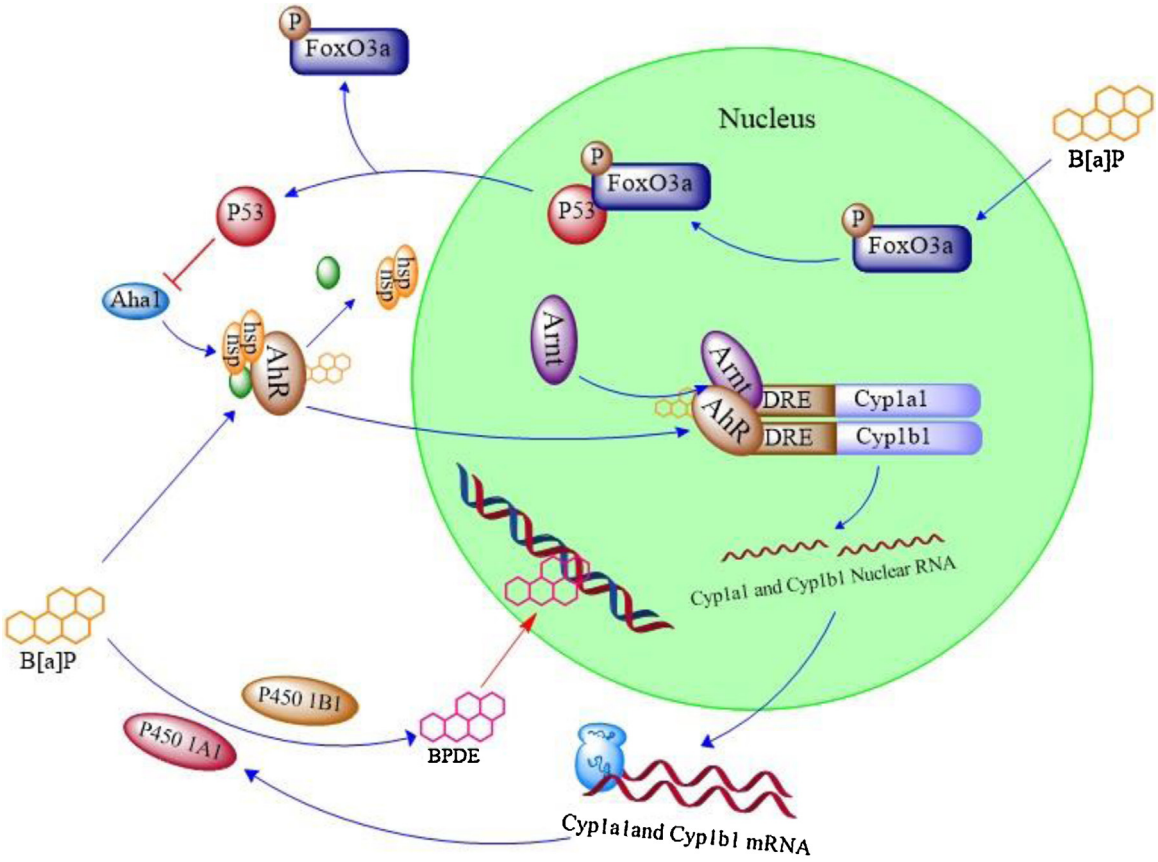


**Fig. 1.** The interaction of B[a]P and P450 enzymes.
The metabolism of B[a]P to its carcinogenic form BPDE requires P450 enzymes, in particular Cyp1A1 and Cyp1B1. Concomitantly, B[a]P affects the transcription of P450 enzymes by promoting translocation of p53, which regulates AhR signaling by modulating Hsp90 ATPase (Aha1) activity, by moving from the nucleus to the cytoplasm. AhR, aryl hydrocarbon receptor; AIP, AhR-interacting protein (green oval); Arnt, aryl hydrocarbon receptor nuclear translocator; hsp, heat shock protein 90 (yellow ovals); DRE, dioxin responsive element. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)