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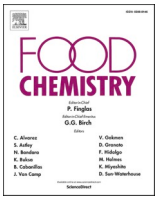

MiR-27a-5p regulates acrylamide-induced mitochondrial dysfunction and intrinsic apoptosis *via* targeting *Btf3* in rats

Lujia Zhang, Li Dong, Liuqing Yang, Yinghua Luo, Fang Chen *

College of Food Science & Nutritional Engineering, National Engineering Research Centre for Fruits and Vegetables Processing, Key Laboratory of Fruits and Vegetables Processing, Ministry of Agriculture, Engineering Research Centre for Fruits and Vegetables Processing, Ministry of Education, China Agricultural University, Beijing 100083, China

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ABSTRACT

Acrylamide (AA), a potential carcinogen, is commonly formed in foods rich in carbohydrates at high heat. It is known that AA-induced mitochondrial dysfunction is responsible for its toxicity. Previously we found AA exposure increased miR-27a-5p expression in livers of SD rats. Here, the regulation mechanism of miR-27a-5p in mitochondrial dysfunction was investigated in rat liver cell lines (IAR20) and SD rats. The results showed that the overexpressed miR-27a-5p contributes to modulating mitochondrial dysfunction and *Btf3* is identified as its target gene. The knockdown of *Btf3* increases the cleaved PARP1 level and the phosphorylation of ATM and p53, which results in mitochondria-dependent apoptosis. Therefore, the miR-27a-5p-*Btf3*-ATM-p53 axis might play a vital role in the promotion of AA-induced cell apoptosis through disrupting mitochondrial structure and function. This would provide a potential target for the assessment and intervention of AA toxicity.

1. Introduction

Acrylamide (AA) is a neurotoxin and potential carcinogen and is usually found in carbohydrate-rich foods such as coffee, bread, and fried potato products owing to the Maillard reaction (Liu et al., 2017). According to the European Food Safety Authority, detectable AA levels in food could reach up to 4700 μg/kg, much higher than the benchmark level (750 μg/kg) published in the European Regulation 2017/2158 (Mesias, Nouali, Delgado-Andrade, & Morales, 2020). Epidemiological experiments have proved that AA can induce neurotoxicity in humans with the following symptoms, such as weight loss, ataxia, and skeletal muscle weakness (Liu et al., 2015). Moreover, AA can also induce genotoxicity, reproductive toxicity, potential carcinogenicity, and hepatotoxicity in animals (Chen, Su, Xu, & Jin, 2017; Zhao, Wang, Hu, Chen, & Chan, 2017). Therefore, the health risk of AA exposure from food has arisen people's attention.

It is well known that mitochondrial dysfunction could contribute to the toxicity induced by AA (Chen, Yang, Wang, Lee, Cheng, & Chou, 2013). In BV2 cell line and mouse liver, AA could result in mitochondrial swelling, collapse of mitochondrial membrane potential (Δψ), and reduced expression of the complex I, III, and IV subunits (Liu et al., 2015). Moreover, the treatment of AA (50 mg/kg bw/day) could also reduce the activities of mitochondrial complexes V, ATPase, and induce the mitochondrial membrane lipid peroxidation in mice (Zhao, Wang, Zhu, Liu, Hu, & Chen, 2015). Recent studies have illustrated that AA could increase the phosphorylated level of mitochondrial apoptosis-related proteins like JNK, ERK, and p38 kinases in HepG2 cells and PC12 cells (Pan, Wu, Yan, Peng, Rao, & Yan, 2018; Tan et al., 2018). Besides, AA could activate apoptosis signaling pathway NF-κB in a time-dependent manner in rat striatum and human neuroblastoma cells SY5Y, which could increase the expression of pro-inflammatory factors such as TNF-α and IL-6 (Yan et al., 2019). As a result, the mitochondrial-dependent apoptosis was triggered by increasing Bax/Bcl-2 ratio and activating caspase-9 and caspase-3 (Zhao et al., 2017). However, more

Abbreviations: ATM, Ataxia telangiectasia mutated; BSA, Bovine serum albumin; Btf3, Basic transcription factor 3; BW, Bodyweight; CYTc, Cytochrome C; DMEM, Dulbecco's modified Eagle's medium; ERK, Extracellular regulated protein kinases; ETC, Electron transport chain; FBS, Fetal bovine serum; HD, High dose group; IL-6, Interleukin-6; JNK, C-Jun *N*-terminal kinase; JUN, Jun proto-oncogene; LD, Low dose group; MtDNA, Mitochondrial DNA; MEM, Minimum Eagle's medium; MitoQ, Mitoquinone; NACA, Co-regulator α; NAD^+, Nicotinamide adenine dinucleotide; NF-κB, Nuclear factor kappa B; p53, Tumor protein p53; PBS, Phosphate buffered saline; PARP1, Poly ADP-ribose polymerase 1; TNF-α, Tumor necrosis factor-α; UTR, Untranslated regions; Δψ, Mitochondrial membrane potential.

* Corresponding author at: College of Food Science and Nutritional Engineering, China Agricultural University, No. 17, Qinghua East Road, Haidian District, Beijing 100083, China.

E-mail address: chenfangch@sina.com (F. Chen).

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