Study: BHPF represses YTHDF2 to induce tissue-specific cell deaths and consequent developmental abnormalities

September 6 2023

Behind the positive image of "BPA-FREE" being synonymous with "safe," a BPA substitute called BHPF is "destroying" a vital cellular protein, YTHDF2. Credit: Wanning Wei.

Bisphenol A (BPA) is widely used in a range of plastic products. In recent years, many studies have found that BPA has adverse effects on both ecosystems and human health, and has been banned by many countries for use in the maternal and child products, such as baby bottles and children's water cups. As a result, a variety of bisphenol analogs (BPs) have been introduced as alternatives to BPA in these products.

However, the potential developmental toxicity of these alternatives, particularly the health risks during early development, remains largely unknown. m^6A modification is the most abundant modification found in eukaryotic mRNAs and, like histone/DNA modifications, it quickly responds to environmental stimuli, subsequently affecting gene expression and cellular homeostasis.

"We found that a common BPA substitute, BHPF, induced tissue-specific ferroptosis and apoptosis in an m^6A dependent manner, leading to cardiac and vascular developmental defects, respectively. These findings not only reveal novel mechanisms of m^6A/YTHDF2-mediated regulation of tissue-specific PCDs, but also provide a previously unappreciated mechanistic insight into BHPF-induced cardiovascular defects," Hsu says.

Published in the journal *National Science Review*, the study was led by Dr. Chih-Hung Hsu (Institute of Genetics, Zhejiang University), Dr. Fudi Wang (Zhejiang University School of Medicine, and Hengyang Medical School, University of South China), and Dr. Peng-Fei Xu (Institute of Genetics, Zhejiang University).

Firstly, the researchers comprehensively examined the concentration levels of eight common BPA substitutes in the serum of 100 pregnant participants. The results showed that three BPA substitutes have been detected in the blood samples of pregnant participants. Among them, BHPF (with high detection rate, 14%) has been associated with

cardiovascular developmental defects in zebrafish embryos and the offspring from BHPF-gavage mice.

In addition, in the pregnant subjects with detectable BHPF levels, the participant with the highest BHPF-detected concentrations was found to have fetus with ventricular septal defect (VSD). Together, these findings suggest that the widely used BHPF poses potential health threats to the environment, animals, and humans, representing an urgent environmental health issue that requires attention.

Through in-depth exploration of the underlying mechanisms, researchers found that BHPF induced cardiovascular developmental defects through m^6A/YTHDF2-mediated regulation of tissue-specific cell death.

Mechanistically, BHPF-mediated downregulation of YTHDF2 reduced YTHDF2-facilitated translation of m^6A-gch1 for cardiomyocyte ferroptosis, and decreased YTHDF2-mediated m^6A-sting1 decay for caudal vein plexus (CVP) apoptosis. In other words, under BHPF stimulation, the same responsive protein YTHDF2 in different tissues regulates two entirely independent cell death pathways through its multiple m^6A regulatory functions, leading to distinct phenotypes.

"Therefore, m^6A/YTHDF2 can be considered as a 'bifurcation' for BHPF-induced tissue-specific ferroptosis and apoptosis, which deepens our understanding of m^6A functions at the organismal level," Hsu says.

Consequently, the discovery of these new mechanisms suggests possible ways to counteract the damage caused by BHPF. Researchers demonstrated that blocking ferroptosis and apoptosis pathways induced by BHPF-m^6A-YTHDF2 axis could substantially rescue the defective phenotypes of heart failure and CVP damage.

Notably, the preclinical trials show that sapropterin dihydrochloride (an

orally active synthetic form of BH4, the major component of the clinically used drug, KUVAN) can rescue heart failure in cardiomyocyte-specific Ythdf2 conditional knockout mice, suggesting a feasible therapeutic strategy for dealing with BHPF-induced cardiac defects.

In conclusion, "BPA-free" plastic products are generally considered by the public as a "high-quality" and "safety" indicator. However, this study shows that "BPA-free" does not necessarily equal "absolutely safe" and serves as a good warning for the public on how to properly understand and view "BPA-free" maternal and infant products.

More information: Jiebo Lin et al, YTHDF2-mediated regulations bifurcate BHPF-induced programmed cell deaths, *National Science Review* (2023). DOI: 10.1093/nsr/nwad227

Provided by Science China Press