Oxidative stress and mercury-induced pancreatic β-cell injury

Ya-Wen CHEN¹, Chun-Fa HUANG², Shing-Hwa LIU³
¹Department of Physiology and Graduate Institute of Basic Medical Science, College of Medicine, China Medical University, Taiwan, ²Graduate Institute of Chinese Medical Science, School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taiwan, ³Institute of Toxicology, College of Medicine, National Taiwan University, Taiwan

A recent study suggested that simultaneous exposure of non-diabetics to high levels of dioxins and mercury increases their risk of insulin resistance. An increased incidence of diabetes existed in patients with documented Minamata disease (methylmercury poisoning) in Japan. Previous in vitro studies have shown that HgCl₂ altered intracellular Ca²⁺ homeostasis in pancreatic β-cells isolated from mouse islets, and decreased insulin secretion from secretion granules isolated from toadfish islets. Mercury is a well-known toxic metal, which induces oxidative stress. The toxicity of mercury in islets is highly related to oxidative stress. It has been shown that 8-hydroxy-2'-deoxyguanosine, a biomarker of oxidative DNA damage, is significantly elevated in urine samples of people from mercury-contaminated areas. Our studies have also shown that submicromolar-concentration HgCl₂ or methylmercury is capable of affecting the islet β-cell function and survival through an oxidative stress pathway in vivo and in vitro. Low-dose mercury induced mouse pancreatic islet β-cell dysfunction through a phosphoinositide 3-kinase (PI3K)–activated or oxidative stress-triggered Akt pathway in cell culture and animal models. Antioxidant N-acetyl-L-cysteine prevented mercury-induced insulin secretion inhibition and Akt phosphorylation. Moreover, methylmercury could induce oxidative stress–triggered β-cell apoptosis and death. HgCl₂ could also be capable of inducing the oxidative stress-related insulin secretion suppression and cell death in pancreatic β-cells. The further evidences indicate that HgCl₂ enters β-cells and triggers oxidative stress to induce cell death through both apoptotic and necrotic pathways. Taken together, these observations provide evidences to confirm the possibility that mercury is an environmental risk factor for diabetes.

Peroxiredoxin and redox signaling

Shusuke KUGE, Hayato IROKAWA, Kenta IWAI, Ayako OGASAWARA, Takumi OHDATE, Toshihiko WATANABE
Department of Microbiology, Tohoku Pharmaceutical University, Japan

Oxygen serves as an electron acceptor, enabling efficient production of ATP. However, oxygen can also be converted into toxic reactive oxygen species (ROS), such as superoxide and hydrogen peroxide (H₂O₂); ROS can damage a variety of cellular components, including proteins and unsaturated lipids. Detection of ROS (peroxides) is an important step in the oxidative stress response.

Peroxiredoxin (Prx) is a family of ubiquitous peroxidases found in species ranging from Escherichia coli to humans. In many cases, Prx can reduce H₂O₂ and/or alkylhydroperoxides at the expense of electrons from NADPH through the Trx-dependent redox system (Tpx activity). The catalytic cysteine (Cys) residue of Prx is directly oxidized by hydroperoxides. This oxidation event is followed by the formation of a disulfide bond linkage with a resolving Cys of the same molecule of Prx or with a resolving Cys of another Prx molecule (dimer formation). The disulfide bond can be reduced by Trx. We have suggested that, in addition to their function as peroxidases, Prx family proteins may serve as intrinsic receptors of H₂O₂ and possible other hydroperoxide. Additionally, Prx proteins may relay information about the presence of hydroperoxides to the independent target proteins of each Prx.

In this symposium, I will introduce our recent progress in both yeast and mammalian systems that underscores the role of Prx on hydroperoxide and the redox-dependent modulation of the Prx’s target proteins.