【Grant-in-Aid for Scientific Research (S)】

Broad Section K

Title of Project : Environmental electrophiles exposome and reactive sulfur species as its regulator molecule

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Keyword : Electrophiles, Exposome, Redox signaling, Reactive sulfur species, Sulfur adduct

【Purpose and Background of the Research】

We are exposed to a variety of environmental electrophiles (EEs) through food life, life style and life environment on a daily basis. While it has been reported that such reactive species covalently bind to protein nucleophiles, we found that EEs activate redox signaling pathways at lower doses and disrupt these pathways and substantial cytotoxicity at higher doses. It was also found that reactive sulfur species (RSS) negatively regulate modulation of redox signaling and toxicity caused by exposure to EEs, presumably through formation of their sulfur adducts.

Exposome has been defined as the cumulative environmental exposures, including diet, lifestyle, pollutants, and others across the life span; however, the full characterization of the exposome throughout the whole lifespan remains an outstanding challenge. In the current study, we attempt modeling an exposome specialized for EEs with cultured cells and mice in the absence and presence of RSS. We also explore how sulfur adduct derived from methylmercury (MeHg), a model of EEs, undergoes biotransformation by RSS, and then is excreted into out of the body.

【Research Methods】

We perform combined exposure to naphthoquinones, MeHg, cadmium, crotonaldehyde, 1,4-bennzoquinone, acrylamide and/or (*E*)-2-alkenals, and then assess covalent modifications to cellular protein, modulation of 4 different types of redox signaling and toxicity under treatments with and without RSS. We identify unknown metabolites of bismethylmercury sulfide produced from MeHg during interaction with RSS from biological samples of cultured cells and mice given MeHg.

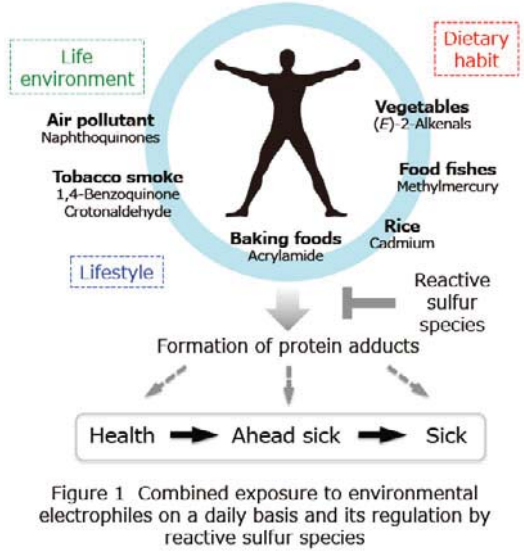

Figure 1 Combined exposure to environmental electrophiles on a daily basis and its regulation by reactive sulfur species

【Expected Research Achievements and Scientific Significance】

We postulate that combined exposure to EEs would lower the threshold for modulation of redox signaling and toxicity negatively regulated by RSS. It was also speculated that RSS plays a role in discharging MeHg into out of body. Therefore, the current study is associated with not only advance in the exposome study for EEs but also a proposal for relief of the health risk caused by EEs.

【Publications Relevant to the Project】

1. Kumagai Y, Abiko Y. Environmental electrophiles: protein adducts, modulation of redox signaling and interaction with persulfides/polysulfides. *Chem Res Toxicol* **30**: 203-219, 2017.
2. Akaike T, Ida T, Fan-Yan Wei FY, Nishida M, Kumagai Y *et al.* Cysteinyl-tRNA synthetase governs cysteine polysulfidation and mitochondrial bioenergetics. *Nature Commun* 8: 1177, 2017.

【Term of Project】 FY2018-2022

【Budget Allocation】 150,200 Thousand Yen

【Homepage Address and Other Contact Information】

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