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

Integrated Disciplines (Environmental science)

Title of Project : Comprehensive study on environmental electrophiles-mediated signal transduction pathways regulated by active sulfur species

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Research Area : Environmental and hygienic pharmacy
Keyword : environmental response, electrophile, chemical modification, signal transduction, active sulfur species

【Purpose and Background of the Research】

Environmental electrophiles (EEs) covalently bind to thiol groups in proteins, such as sensor proteins, to form protein adducts, and this can lead to the development of cancer as well as injury to the surrounding tissue. However, very little is currently known about the mechanistic details of these phenomena and the role of EEs in these processes. A variety of different cellular signal transduction pathways are known to be associated with homeostasis and the failure of cellular signaling can result in a number of physiological problems.

In the current study, we examine concentration-specific changes in the redox signal transduction pathways that are promoted by the activation of effecter molecules coupled to the chemical modification of a sensor protein following the reaction of its thiol groups with EEs. We also explore the possibility that active sulfur species (ASS) such as hydrogen sulfide, persulfide and polysulfide would negatively regulate EEs-mediated redox signaling processes.

【Research Methods】

As models for EEs, we use with 1,4-benzoquinone, 1,4-naphthoquinone, methylmercury, cadmium, lead, acetaldehyde and formaldehyde. We examine (1) the development of a convenient assay for the detection of covalent modifications to the cellular proteins caused by their exposure to EEs; (2) the concentration-specificity during the activation and disruption of the signal transduction pathways following the exposure of cultured cells or experimental animals to EEs; (3) the impact of the negative regulation of the ASS on the EEs-dependent modulation of the redox signal transduction pathways; and (4) the beneficial effect of phytochemical extracts containing the ASS on the toxicities of EEs in wild-type and CSE (an enzyme responsible for production of such ASS) knockout mice.

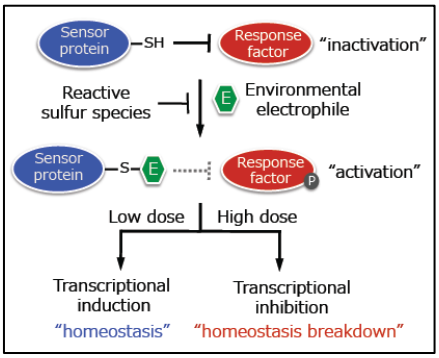

Fig.1 Modulation of environmental electrophiles-mediated the signal transduction pathways regulated by the active sulfur species

【Expected Research Achievements and Scientific Significance】

Our rationale for this project is focused on our belief that EEs are capable of modifying sensor proteins by reacting with their thiol groups, and that this could result in structural changes, thereby activating (under lower exposure) and disrupting (under higher exposure) the redox signal transduction pathways. It is noteworthy that ASS react readily with EEs, leading to the loss of their reactivity.

【Publications Relevant to the Project】

1. Kumagai Y, Shinkai Y *et al.* The chemical biology of naphthoquinones and its environmental implications. ***Annu Rev Pharmacol Toxicol*** **52**: 221-247, 2012
2. Nishida M, Sawa T, Kumagai Y, Akaike T *et al.* Hydrogen sulfide anion regulates redox signaling via electrophile sulfhydration. ***Nature Chem Biol*** 8: 714-724, 2012.

【Term of Project】 FY2013-2017

【Budget Allocation】 165, 900 Thousand Yen

【Homepage Address and Other Contact Information】

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