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

Integrated Disciplines (Environmental Science)

Title of Project : Multiple Omics Analysis to Understand the Species Difference in Chemical-intracellular Receptor Signaling Disruption

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Research Area : Environmental Science
Keyword : Toxicology, Endocrine Disrupting Substances

【Purpose and Background of the Research】

There are large interspecies differences in the sensitivity and response to chemicals. However, when extrapolating the differences in response and sensitivity of the experimental model animals to individual non-model species, we unwillingly apply the uncertainty factor with no scientific basis. Thus, to assess the risk of a variety of non-model species, it is necessary to directly measure the reactions in the species of interest. As intracellular receptors are mediators for converting chemical signals to biological signals in animal bodies, the species difference in the signaling pathway may be useful as one of the factors to account for the differential sensitivity and the diversity of responses to chemicals.

On the other hand, because of the difficulty of administration experiments and sample collection, measuring the reaction in non-model animals is not easy. As a result, the need for ecotoxicological testing has dramatically increased, but the evaluation of a majority of chemicals has remained untested. Translational science that bridges toxicology targeting model animals and environmental toxicology for wild and companion animals is lacking. Knowledge of the multiple functions of intracellular receptors is mostly gained from experiments on mice, but such findings cannot be generalized to diverse species such as birds and fish. In addition, as there is currently no tool to envisage an overview of the receptor signaling in environmental animals, this becomes a barrier to verify the diversity of effects of chemicals through the receptors.

This study intends to exhaustively explore the disruption of the system *via* the intracellular receptor signaling caused by chemical substances by constructing a platform to monitor the system in wild and companion animals. The aims are to assess the effect of chemicals on receptor-mediated signaling, and to determine the factors underlying the susceptibility that cause species differences in the receptor-mediated disruption.

【Research Methods】

We will focus on the disruption of intracellular receptor signaling by chemical exposure in environmental and experimental model animals including fish, birds, and mammals. Changes at multi-ome levels through intracellular receptors caused by chemical exposure will be measured. To identify factors underlying species differences in susceptibility at genome, gene and protein levels, we will address the following sub-themes (A-E).

A) Exposome analysis of chemical substances accumulated in wild and companion animals
B) Comprehensive analysis of the interaction of exposome and intracellular receptors
C) Multiple omics and pathway analyses of experimental model animals
D) Multiple omics and pathway analyses of environmental animals
E) Searching the factors underlying the susceptibility of intracellular receptor signaling

【Expected Research Achievements and Scientific Significance】

Putting multiple omics analysis in practice will lead to a systematic understanding of the effects of chemical exposure, and identification of biomarkers in a variety of species. In addition, advantages and limitations of the usefulness of model and environmental animals will become clear and the achievements will serve as a model for developing standardized and sophisticated ecotoxicological testing.

【Publications Relevant to the Project】

Thuruthippallil, L. M., Kubota, A., Kim, E. Y., Iwata, H. (2013): Alternative *in vitro* approach for assessing AHR-mediated CYP1A induction by dioxins in wild cormorant (*Phalacrocorax carbo*) population. *Environmental Science and Technology*, 47(12), 6656-6663.

Hirakawa, S., Imaeda, D., Nakayama, K., Udaka, M., Kim, E. Y., Kunisue, T., Ogawa, M., Matsuda, T., Matsui, S., Petrov, E. A., Batoev, V. B., Tanabe, S., Iwata, H. (2011): Integrative assessment of potential effects of dioxins and related compounds in wild Baikal seals (*Pusa sibirica*): Application of microarray and biochemical analyses. *Aquatic Toxicology*, 105(1-2), 89-99.

【Term of Project】

FY2014-2018

【Budget Allocation】

150, 000 Thousand Yen

【Homepage Address and Other Contact Information】

http://ecotoxiwata.jp/en/index.html