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

Integrated Disciplines (Environmental Science)

Title of Project : Molecular Mechanism for Toxic Effect of Methylmercury

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Research Project Number : 15H05714 Researcher Number : 80155952
Research Area : Environmental sciences, Environmental and hygienic pharmacy
Keyword : Methylmercury, Toxicology, Transcriptional regulation, Signal transduction, Autocrine

【Purpose and Background of the Research】

Methylmercury is an environmental pollutant that causes serious central nervous system disorder. However, molecular mechanisms for the selective damage to the central nervous system caused by methylmercury remain poorly understood.

Aiming to understand the molecular mechanisms, we have carried out a study to search proteins affecting the methylmercury toxicity by using a comprehensive gene screening method. We identified the transcription factor-like protein HOXB13 as an intracellular factor that enhances the toxicity of methylmercury. We also found that methylmercury induced synthesis of cytotoxic factors, such as TNFα, through the action of HOXB13, and then released TNFα from the cell, and that these cytotoxic factors induced cell death. By administering methylmercury in mice, we confirmed that the induction of TNFα expression was specific to brain tissue; this finding can be considered a breakthrough for understanding the onset mechanisms for methylmercury toxicity. Thus, in this study, we aim to clarify the overall molecular mechanisms behind this phenomenon.

【Research Methods】

In this study, using cultured nervous system cells derived from humans or mice, we will analyze the mechanisms for activation of HOXB13 by methylmercury, as well as the mechanisms for synthetic derivation of secretory cytotoxic factors including TNFα via HOXB13. We will also examine in detail the mechanisms for inducing cell death or methylmercury toxicity enhancement by secretory cytotoxic factors. In addition, using TNFα- and HOXB13-knockout mice, we will examine the role of TNFα and HOXB13 in the central nervous system toxicity of methylmercury, as well as describing the importance of HOXB13 in TNFα induction by methylmercury in the brain.

【Expected Research Achievements and Scientific Significance】

This study may provide a clear and logical explanation for the brain-specific onset mechanisms for methylmercury toxicity that have remained unknown for more than half a century. The study will make it possible to develop prophylactic measures for methylmercury poisoning, and genetically identify groups that are highly susceptible to methylmercury.

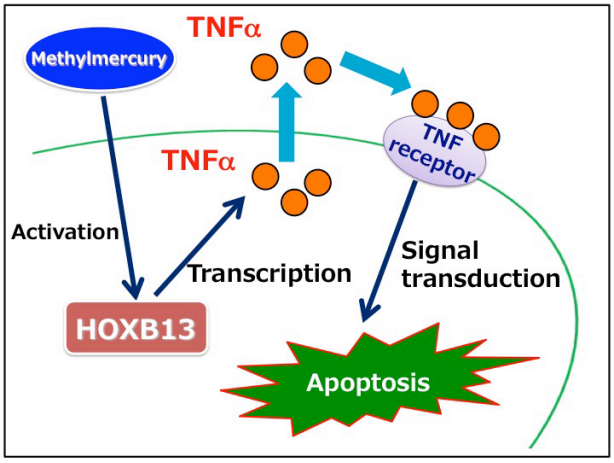

Figure 1 Transcription of TNFα induced by methylmercury through activation of HOXB13, and apoptosis induced by TNFα

【Publications Relevant to the Project】

1. Hwang, G. W., Ryoke, K.,Takahashi, T. and Naganuma, A.: Silencing of the gene for homeobox protein HOXB13 by siRNA confers resistance to methylmercury on HEK293 cells. J. Toxicol. Sci., 35, 941-944 (2010).
2. Hwang, G. W., Murai, Y., Takahashi, T. and Naganuma, A.: The protein transportation pathway from Golgi to vacuoles via endosomes plays a role in enhancement of methylmercury toxicity. Sci. Rep., 4, 5888 (2014).

【Term of Project】 FY2015-2019

【Budget Allocation】 151,400 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.pharm.tohoku.ac.jp/~seitai/seitai-index.html