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論 文 名　：Characterization of Selenium-binding protein 1 (Selenbp1) by studying with Selenbp1-knockout mice
（セレン結合タンパク質1（Selenbp1）欠損マウスを用いたSelenbp1の特性評価に関する研究）

区　　分　：甲

論 文 内 容 の 要 旨

Selenium is an essential trace element that is incorporated into selenoproteins as selenocysteine to mediate its functions. However, the precise function of numerous selenoproteins remains unknown. Selenium-binding protein 1 is a highly conserved and unconventional selenoprotein with distinct (perselenide) or undetermined selenium chemistry. The human *SELENBP1* gene, which is homologous to the mouse *Selenbp1* (*SBP56*) gene, which encodes a 56 kDa protein and stably binds with selenium. Previous reports reduced levels of SELENBP1 has been associated with carcinogenesis and poor outcomes in patients. In contrast, patients with schizophrenia have shown elevated brain SELENBP1 levels. A recent study has demonstrated that mutation of human SELENBP1 can result in halitosis. The transfection of human SELENBP1 into the cell serves as a methanethiol oxidase to form hydrogen sulfide from methanethiol. However, the function of purified SELENBP1 has yet to be confirmed experimentally. In mice, Selenbp2 is highly homologous to Selenbp1. The former study in this laboratory demonstrated that dioxin-like coplanar polychlorinated biphenyl, 3,3',4,4',5-pentachlorobiphenyl (PCB126), and 3-methylcholanthrene significantly induce the expression of Selenbp1 protein in the rat liver. Selenbp1 may be involved in TCDD-induced toxicity, but only a few differences were observed between Selenbp1 knockout (KO) and wild-type (WT) mice in apparent phenotypes, possibly due to the compensatory effect of Selenbp2 on the functions of Selenbp1. In contrast, preliminary study in this laboratory suggested that 20 h of fasting did not affect Selenbp1 mRNA expression, but significantly reduced Selenbp2

mRNA expression in the kidney. As the highly homologous isoform, Selenbp2, is expressed at low levels in the kidney, it is worthwhile comparing wild-type C57BL mice and Selenbp1-deficient mice to clarify the role of dioxin-inducible Selenbp1 in the kidney by eliminating other factors altered by dioxin.

In Chapter 1, it was confirmed that the kidney was more suitable for examining the function of Selenbp1 when compared with the liver at the protein level under non-fasting conditions. Given that Selenbp2 kidney levels are low, in Chapter 2, the purpose was aimed in clarifying the role of dioxin-inducible Selenbp1 expression in the kidney by eliminating other factors altered by dioxin. Preliminary study suggested that the 20 h fasting period did not affect Selenbp1 mRNA expression, but significantly reduced Selenbp2 mRNA expression in the kidney. With that in mind, DNA microarray and metabolomic analyses of the kidneys were performed in order to examine the effect of Selenbp1 ablation and increased levels of prostaglandins were detected. Real-time RT-PCR confirmed the decreased expression levels of the peroxisome proliferator-activated receptor-α (Pparα) and retinoid-X-receptor-α (Rxrα), which form a heterodimer with Pparα to promote gene expression, were simultaneously reduced. Furthermore, cytochrome P450 4a (Cyp4a) subfamily, known to be involved in fatty acid ω- and ω-1 hydroxylation. This indicated that reduced Cyp4a expression was mediated via decreased Pparα and Rxrα. Based on the observed results, it can be suggested that Selenbp1 ablation alters lipid metabolism via the downregulation of PPARα. In Chapter 3, to further comprehend the role of Selenbp1 in oxidative stress related to lipid oxidation, examination of the changes in the oxidant status of Selenbp1 deficient mice were performed by measuring indices of lipid peroxidation. Finally, it was suggested that the oxidative stress might be modulated by Selenbp1 deletion, thus inducing changes in lipid metabolism through the PPARα pathway.

Therefore, it inferred that ablation of Selenbp1 elicits oxidative stress caused by increased levels of superoxide anions, which alters lipid metabolism via the Pparα pathway.