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学位の種類	博士（ 医学 ）
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審査研究科	人間総合科学研究科
学位論文題目	Studies on transcriptional control of metabolic changes in the liver induced by a high protein diet (高タンパク食のもたらす肝臓の代謝変化の転写調節機構に関する研究)

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論文の内容の要旨
Abstract of thesis

In this doctoral dissertation, Ms. MEHRAZAD SABER describes the mechanisms underlying gene expression regulation in response to high protein diet. The summary is as follows:

（目的　Purpose）

The author tried to elucidate the mechanisms underlying gene expression regulation in response to high protein diet. Regarding to vast application of high protein diet based on growing body of evidence that suggests high protein diet is even an affordable and positive accede in management and prevention of chronic diseases such as obesity and related comorbidities, it is crucial to find out about mechanisms that lead to such profits.

（対象と方法　Materials and Methods）

To gain more insight into molecular mechanisms by which high protein diet controls expressions of genes involved in amino acid metabolism in the liver, the author performed RNA-seq analysis of mice fed high protein diet containing 60 percent protein, in comparison to mice fed low protein diet containing 5 percent protein for 3 days. The author used *Klf15* knockout mice to determine which of the genes involved in amino acid metabolism have altered regulation in response to lack of *Klf15* gene while receiving high protein diet. The genes that their regulation pattern have not been changed were considered *Klf15* independent and those with decreased expression were considered *Klf15* dependent. Then the author used in vivo Ad-luc analytical system in order to confirm the target genes of *Klf15* transcription in *Klf15* knock out mice under high protein diet condition. Hormonal responses to high protein diet were also measured.

（結果　Results）

Compared to a low protein diet, high protein diet feeding significantly increased hepatic expressions of enzymes involved in the breakdown of all the 20 amino acids. Based on the Q-RT PCR results in *Klf15* knockout mice, *Cth* was chosen as a possible *Klf15*-dependent candidate gene alongside with genes such as *Hpd, Otc, Prodh, Tdo2, Gpt, Acmsd, Gls2, Aass* and *Ivd*. On the contrary, *Ast* was assumed to be *Klf15*-independent. Also, it was suggested that *Oat, Tat, Ast, Ass1, Cps1, Ahcy, Afmid* and *Asl* were most likely transcriptionally regulated via *Klf15*-independent pathways too. Moreover, *Klf15* knockout mice exhibited significantly lower activities of *Cth* promoter at high protein diet fed state in comparison to wild type mice as assessed by in vivo Ad-luc analytical system. However, high protein diet fed state *Ast* promoter activities in *Klf15* knock out mice was significantly higher than wild type mice. From these results, the author identified *Cth* as a new target gene of *Klf15* transcription as well as *Ast* as an example of *Klf15*-independent gene despite its remarkable responsiveness to high protein diet. In this study, blood glucose was not meaningfully changed after diet consumption in any of the groups, thus plasma concentrations of insulin, glucagon and corticosterone hormones did not differ between low protein diet and high protein diet fed mice.

（考察　Discussion）

The author think that these findings provide a clue to elucidate the entire transcriptional regulatory mechanisms of amino acid metabolic pathways. *Klf15* plays a major role in this path. *Cth* catalyzes the last step in the trans-sulfidation pathway and it is one of the three major sources of H_2S production in body. The *Cth*-H_2S pathway has recently become one of the hot topics of cardiovascular disease pathology research. It is assumed that *Cth* can exhibit an anti-atherosclerotic effect since the H_2S deficiency is shown to affect progress of vascular complications of diabetes, coronary vascular disease, atherosclerosis and cardiac ischemic damage as some examples. Therefore, the author think that elucidating the mechanisms underlying the regulation of *Cth* gives a chance to evaluate the perspectives of pharmacological enhancement or inhibition of *Cth* activity as a strategy for new drug design.

審査の結果の要旨
Abstract of assessment result

（批評　General Comments）

In this thesis, the author was able to identify the cis-elements in the genome which relay the high protein diet-induced signals using in vivo Ad-luc analytical system. This approach can provide more detailed insight into the mechanisms regulating the high protein diet-induced metabolic changes in the future investigation.

（最終試験の結果　Assessment）

The final examination committee conducted a meeting as a final examination on Jan. 5, 2022. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

（結論　Conclusion）

The final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Medical Sciences.