最終試験の結果の要旨

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主査および副査の５名は、令和４年１月５日、学位申請者 SHAYO SIGFRID CASMIR 君に面接し、学位申請論文の内容について説明を求めると共に、関連事項について試問を行った。具体的には、以下のような質疑応答がなされ、いずれについても満足すべき回答を得ることができた。

Q1. What is the prevalence of diabetes and hypertension in your country (Tanzania) in comparison to Japan?

A1. The prevalence of diabetes in Tanzania is lower than that in Japan. According to International Diabetes Federation (2011), 2.8% of adult population in Tanzania had diabetes. On the other hand, a recent national-wide representative surveys shows a higher prevalence of hypertension (26%) among adults aged 25-64.

Q2. Why did you come to study diabetes in Japan?

A2. The prevalence of diabetes in my country is on the rise. I want to be one among the key people who will aid in the fight against Diabetes and helping to improve the quality of life of those living with Diabetes.

Q3. Why did you do experiment on monocytes?

A3. Because the monocytes are key in the process of atherogenesis.

Q4 How do inflammatory cytokines act to induce STEAP4 expression?

A4. We think that they act in a paracrine mechanism. However, to substantiate this, we need to conduct experiments in the future to see if blockage of cytokine receptors will affect the expression of STEAP4.

Q5. Did you measure the cytokine levels in the culture media?

A5. No, I didn't. However, there are reports showing that similar experimental conditions could trigger the secretion of inflammatory cytokines such as TNF and IL6 in the culture media by monocytes.

Q6. How is the accuracy of Freestyle Libre® in measuring blood glucose levels?

A6. According to Abbott Diabetes Care Inc., the Freestyle Libre® system has a proven accuracy of 11.4% MARD (Mean Absolute Relative Difference) compared with blood glucose difference.

Q7. Why glucose spikes did not have metabolic effects in vivo model?

A7. Because the duration of glucose spikes was too short (1week).

Q8. How did you decide the duration of glucose spikes in vivo model?

A8. Based on our preliminary data which showed that 1 week of glucose spikes was sufficient to impair endothelial dysfunction in western diet-induced obese model.

Q9. What's the mechanism for the synergistic effect of palmitic acid and insulin in the induction of inflammatory genes?

A9. Palmitic acid, also, insulin signal increase signaling through MAPK (MEK/ERK)-signaling pathway. Also,

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previous report suggests that increased fatty acid flux through the glycerolipid biosynthesis pathway in the presence of high levels of insulin may be responsible for the observed synergistic effect.

Q10. What's the clinical implication of your basic study?

A10. The use of exogenous insulin to control blood glucose in metabolic syndrome patients may have untoward effect. Judicious clinical decisions are needed to optimize benefits while minimizing the associated risks.

Q11. What type of cell in PBMC express STEAP4?

A11. Monocytes as well as Neutrophils express STEAP4 in a pro-inflammatory state. However, under physiological conditions the expression of STEAP4 in these cells is very low.

Q12. What data support that visceral obesity increases STEAP4 expression?

A12. We have shown that western diet consumption which resulted in a visceral obesity/metabolic syndrome phenotype increased STEAP4 expression in PBMCs (fig.3A of the thesis paper)

Q13. Did you check the effect of adiponectin on STEAP4 expression?

A13. No, I didn't.

Q14. Which tissue is particularly responsible for the observed metabolic derangement in STEAP4 KO mice?

A14. The adipose tissue.

Q15. Does STEAP4 transport iron or copper into the cells?

A15. No, STEAP4 doesn't transport but facilitates the uptake of iron and copper by reducing them into ferrous (Fe2+) and cuprous (Cu +) forms.

Q16. Does infection increase STEAP4 expression?

A16. Yes, there is a study showing that the expression of STEAP4 in the peripheral blood of patients with severe sepsis is higher than that of healthy volunteers.

Q17. Did you check the effect of other fatty acids other than palmitic acid?

A17. No, mainly because palmitic acid is the most common saturated fatty acid in humans. One analysis found it to make up 21–30% (molar) of human depot fat.

Q18. Did you expect that monocytes could sense glucose spikes?

A18. Yes, to some extent, because there exist reports showing that high glucose increases the expression of inflammatory mediators in monocytes.

Q19. What is the receptor of palmitic acid/FFA?

A19. TLR4 receptor, CD36, and so on.

Q20. Can the crosstalk between the NF-κB and insulin signaling through MAPK account for the palmitic acid-high insulin synergistic effect?

A20. Yes, possibly, because FFA (palmitic acid) signaling through the TLR4 receptor activates the downstream NF-κB while at the same time palmitic acid and insulin signal activates MAPK signaling pathway.

Q21. Does STEAP4 promotor have NF-κB binding site?

A21. So far, no study has shown that STEAP4 promoter region has NF-κB binding site.

以上の結果から、５名の審査委員は申請者が大学院博士課程修了者としての学力・識見を有しているものと認め、博士（医学）の学位を与えるに足る資格を有するものと認定した。