氏　　名	加藤　恵美
学位の種類	博士（　人間生物学　）
学位記番号	博甲第　　８７６９　　号
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審査組織	グローバル教育院
学位論文題目	MafB is critical for glucagon production and secretion in pancreatic α-cells *in vivo*. (膵α細胞において、MafBはグルカゴン産生および分泌に重要である)

	（職名）	（学位）	（氏名）
主　　査	筑波大学教授	博士（医学）	大根田 修
副　　査	筑波大学教授（グローバル教育院）	Ph.D.	Tilo Kunath
副　　査	筑波大学教授	博士（医学）	渋谷 彰
副　　査	筑波大学助教	博士（医学）	水野 聖哉

論文の要旨
Abstract of thesis

MafB (v-maf musculoaponeurotic fibrosarcoma oncogene homolog B) transcription factor is expressed in pancreatic α- and β-cells during development but becomes exclusive to α-cells in adult rodents. Previous studies in *Mafb*-null (*Mafb*$^{-/-}$) mice revealed a marked reduction in α- and β-cell numbers throughout embryonic development. However, *Mafb*$^{-/-}$ mice die soon after birth, restricting postnatal analyses of MafB function in the pancreas.

The applicant generated two *Mafb* conditional knockout mouse models: endocrine cell-specific (*Mafb*$^{\Delta Endo}$) and tamoxifen-dependent (*Mafb*$^{\Delta TAM}$) mutant mice, and then analysed. The *Mafb*$^{\Delta Endo}$ mice exhibited a reduced population of insulin^{+} and glucagon^{+} cells on postnatal day 0 but recovered the insulin^{+} cell population by 8 weeks of age. In contrast, the applicant found the transcription factor Aristaless Related Homeobox (Arx)$^{+}$ α-cell population and glucagon expression remained decreased even in adulthood. The *Mafb*$^{\Delta TAM}$ mice, in which *Mafb* was deleted after pancreas maturation, also demonstrated diminished glucagon^{+} cells and glucagon content without an effect on β-cells. The *Mafb*$^{\Delta Endo}$ mice displayed an increased Arx^{+}/pancreatic polypeptide^{+} cell population as compensation for the decreased Arx^{+}/glucagon^{+} cell population. Furthermore, according to the gene expression analyses of both *Mafb*$^{\Delta Endo}$ and *Mafb*$^{\Delta TAM}$

islets, the applicant found MafB is a key regulator of glucagon expression in α-cells. Finally, both mutants failed to respond to arginine, likely due to impaired arginine transporter gene expression and glucagon production ability.

Taken together, the applicant clearly reveals that MafB is critical for the functional maintenance of mouse α-cells *in vivo*, including glucagon production and secretion, as well as in development.

審査の要旨
Abstract of assessment result

【批評 Review】

The applicant showed how MafB acts in the development of α-cell in the pancreas by the conditional knockout mice. Intriguingly, the applicant demonstrated that embryonic *Mafb* deletion reduced the Arx^+ cell population and increased the pancreatic polypeptide producing $(PP)^+$ cell population to compensate for the decreased α-cell differentiation whereas the α-cell fate was unchanged.

We asked the applicant about the relationship between MafA and MafB expressions in the embryonic and neonatal stage in the α-cell and β-cell development. We also asked the applicant how MafB is involved in the process of glucagon secretion in the presence of Arginine. In addition, the phenotype of exogenous expression of MafB in MafB deleted mice was discussed.

The applicant gave us clear answers and explained us the possibility of the regulation of MafB expression during development in association with other key regulator of pancreas.

【最終試験の結果 Result】

The final examination committee conducted a meeting as a final examination on 12th March, 2018. 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】

Therefore, the final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Human Biology.