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学位授与の要件	環境生命科学研究科　農生命科学　専攻 （学位規則第４条第１項該当）
学位論文の題目	The biological significance of decreased secretory immunoglobulin A reactivity against gut microbiota in mice fed with high-fat diet （高脂肪食摂取マウスにおける分泌型免疫グロブリンAの腸内細菌に対する反応性の減少の生体的意義）
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学位論文内容の要旨

Secretory immunoglobulin A (SIgA) is the predominant intestinal antibody and specifically coats gut microbiota. SIgA coating of gut microbiota is thought to maintain a stable gut microbial composition in healthy individual. High-fat diet (HFD)-induced obesity (DIO) altered gut microbial composition (gut dysbiosis), which lead to a variety of disorders including impairment of intestinal barrier function, peripheral inflammation and insulin resistance. In this thesis, SIgA coating of gut microbiota is focused as an immune response against gut microbiota relating to induce gut dysbiosis and DIO-related disorders. Three experiments were carried out to study the role of SIgA coating of gut microbiota in the onset of gut dysbiosis and DIO-related disorders.

In the first experiment, the amount of SIgA coating gut microbiota (SIgA coating level) and microbiota composition in the feces were evaluated in normal fat diet (NFD)-fed and HFD-fed mice. HFD consumption significantly decreased SIgA coating level. Significant correlations were observed between SIgA coating level and relative abundance of some bacterial family including *Clostridiaceae* and *Lactobacillaceae.*

In the second experiment, the SIgA coating level and the state of colonic barrier function, inflammation in the adipose tissue and insulin sensitivity were evaluated in NFD-fed and HFD-fed mice. Significant positive correlations were observed between SIgA coating level and gene expression of tight junction proteins. Furthermore, *Mcp1* expression and the IAUC value for Oral glucose tolerance test was significantly negatively correlated with the SIgA coating level.

In the third experiment, same analysis with second experiment was done using wild-type mice (WT) and SIgA deficient mice (KO) fed HFD. HOMA-IR was significantly higher in KO than WT while there were no significant difference in the gene expression of tight junction proteins in the colon and pro-inflammatory cytokines in the adipose tissue between WT and KO. This result shows that the state of insulin sensitivity is exacerbated by deficiency of SIgA coating of gut microbiota implying that HFD-induced decrease in the SIgA coating level might directly affect the onset of insulin resistance.

It is concluded that prolonged HFD consumption reduces SIgA reactivity against commensal gut microbiota. The reduction of SIgA reactivity against gut microbiota might relate to induce gut dysbiosis and DIO-related disorders, particularly with regard to insulin resistance. This study suggests that SIgA reactivity against gut microbiota is one of the important factor to be evaluated for future advance in prevention and treatment of gut dysbiosis and a series of disorders in DIO.

論文審査結果の要旨

学位論文提出者は腸管免疫の主要分子である分泌型免疫グロブリンA（SIgA）の腸内細菌への反応性が高脂肪食の摂取によって大幅に低下することを明らかにし、この内容を学術論文として発表した。また、高脂肪食の摂取にともなうSIgAの腸内細菌に対する反応性の低下は高脂肪食の摂取後の菌叢の変動と関係しており、*Clostridiaceae*や*Turicibacteraceae*の占有率はSIgAの腸内細菌への結合活性と負の相関を、*Desulfovibrionaceae*の占有率は正の相関をそれぞれ示した。この結果は、SIgAの腸内細菌への結合が高脂肪食摂食時の腸内細菌叢の大幅な変化に影響を及ぼしていることを示唆しており、大変興味深い知見である。さらに、高脂肪食誘導性肥満によっておこる腸管バリア機能の低下、末梢組織炎症、インスリン抵抗性といった生体異常と相関していることも明らかにした。これらの結果は、高脂肪食誘導性肥満にともなう生体異常の発症において腸管内に分泌されるSIgAが深くかかわっていることを示唆している。学位論文提出者は本研究によって世界に先駆けてSIgAと肥満の関係性に関する新たな知見を示しており、学位を授与するに値すると考えられる。