

# Dipeptidyl Peptidase-4 Inhibition by Linagliptin Attenuates Obesity-Related Inflammation and Insulin Resistance by Regulating M1/M2 Macrophage Polarization

メタデータ	言語: English 出版者: 公開日: 2017-10-05 キーワード (Ja): キーワード (En): 作成者: 諸葛, 芬, Zhuge, Fen メールアドレス: 所属: 金沢大学, 金沢大学, 金沢大学
URL	<a href="http://hdl.handle.net/2297/47006">http://hdl.handle.net/2297/47006</a>

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## Paper Outline (論文要約)

The title of the main paper(主論文題名)

Dipeptidyl Peptidase-4 Inhibition by Linagliptin Attenuates Obesity-Related Inflammation and Insulin Resistance by Regulating M1/M2 Macrophage Polarization

Diabetes 2016年10月掲載予定

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**Background & Aims:** Obesity activates the innate immune system with subsequent recruitment of immune cells such as macrophages and T cells into metabolic tissues, leading to the development of insulin resistance. In particular, macrophage recruitment and polarization are pivotal in obesity-induced inflammation and insulin resistance. Dipeptidyl peptidase-4 (DPP-4), also known as CD26, is widely expressed, including in immune cells. It cleaves a large number of chemokine and peptide hormones involved in the regulation of the immune system. Additionally, DPP-4 may also be involved in macrophage-mediated inflammation and insulin resistance. We investigated the effect of linagliptin, an inhibitor of DPP-4, on macrophage migration and polarization in white adipose tissue (WAT) and liver of high-fat diet-induced obese (DIO) mice. **Methods:** C57BL/6 mice were fed a NC or HF diet for 8 weeks, DPP-4 activity and expression in DIO mice were examined. Then mice were fed with HF or HF with 0.0003% linagliptin for 8 weeks, DPP-4 inhibition on adipose tissue inflammation and insulin resistance was examined. Finally, MIP-1 $\alpha$ <sup>-/-</sup> mice were fed with HF or HF with 0.0003% linagliptin for 8 weeks, to investigate the mechanism of DPP-4 inhibition on macrophage mediated inflammation. **Results:** DPP-4<sup>+</sup> macrophages in lean and obese mice were quantified by fluorescence-activated cell sorting (FACS) analysis. DPP-4 mRNA expression was significantly higher in the stromal vascular fraction than in the adipocyte fraction from the WAT of DIO mice. Immunofluorescence study revealed that DPP-4 was predominantly expressed in F4/80<sup>+</sup> macrophages in crown-like structures compared with adipocytes in WAT of DIO mice. FACS analysis also revealed that, compared with chow-fed mice, DIO mice had a significant increase in DPP-4<sup>+</sup> expression in cells within adipose tissue macrophages (ATMs), particularly M1 ATMs. After 8 weeks of feeding, linagliptin administration ameliorated hepatic steatosis, improved glucose intolerance and insulin resistance, attenuated adipose tissue and liver inflammation in DIO mice. Moreover, linagliptin showed a greater DPP-4 inhibition and anti-oxidative capacity than sitagliptin, and reduced M1-polarized macrophage migration while inducing an M2 dominant shift of macrophages within WAT and liver, thereby attenuating obesity-induced inflammation and insulin resistance. Loss of macrophage inflammatory protein-1 $\alpha$ , a chemokine and DPP-4 substrate, in DIO mice abrogated M2 macrophage-polarizing and insulin-sensitizing effects of linagliptin. **Conclusions:** The

inhibition of DPP-4 by linagliptin reduces obesity-related insulin resistance and inflammation by regulating both macrophage recruitment and M1/M2 status.