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

Paper　Outline（論文要約）

The title of the main paper(主論文題名)
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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$\alpha^{-/-}$ 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^{+} 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^{+} 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^{+} 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-1α, 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.