DPP-4 inhibition by linagliptin attenuates obesity-related inflammation and insulin resistance by regulating M1/M2 macrophage polarization

【総説】

第15回　高安賞優秀論文賞受賞

論文　「DPP-4 inhibition by linagliptin attenuates obesity-related inflammation and insulin resistance by regulating M1/M2 macrophage polarization」
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「リナグリプチンによるDPP-4阻害は、マクロファージのM1/M2極性を調節し、肥満による炎症とインスリン抵抗性を減弱する」

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Background

Obesity is a state of low-grade sustained inflammation. Macrophage-mediated inflammation plays a role in the pathogenesis of obesity and its comorbidities, including insulin resistance and type 2 diabetes. In particular, macrophage recruitment and polarization are pivotal in obesity-induced inflammation and insulin resistance[1, 2]. Tissue macrophages are phenotypically heterogeneous and are characterized according to their activation/polarization state as M1 (or "classically activated" proinflammatory macrophages) or M2 (or "alternatively activated" noninflammatory macrophages)[1].

Dipeptidyl peptidase-4 (DPP-4) inhibitors are effective in the treatment of type 2 diabetes, as they maintain blood glucose levels by inhibiting the degradation of incretin peptides. DPP-4, also known as CD26, cleaves a large number of chemokine and peptide hormones involved in the regulation of the immune system. In the present study, we hypothesized that DPP-4 plays a role in regulating macrophage activation in response to obesity and that DPP-4 inhibition may attenuate obesity-induced inflammation. We demonstrated that DPP-4 is predominantly expressed in M1-polarized macrophages in white adipose tissue (WAT) of high-fat diet (HFD) -induced obese (DIO) mice[3]. Furthermore, we present evidence suggesting that DPP-4 inhibition attenuates obesity-related insulin resistance and inflammation by regulating both macrophage recruitment and M1/M2 status in DIO mice[3].

Results

To examine DPP-4 activity and quantify adipose tissue macrophages in obesity, mice were fed with normal chow (NC) or HFD for 8 weeks. The results showed that DPP-4 activity in plasma, WAT, and liver were significantly increased in HFD-fed mice. Immunofluorescence analysis showed that DPP-4 was expressed in F4/80$^+$ macrophages in crown-like structures. However, it was poorly expressed by perilipin$^+$ adipocytes. Furthermore, most of CD11c$^+$ M1 macrophages expressed DPP-4, but fewer CD206$^+$ M2 macrophages expressed DPP-4 (Fig. 1).

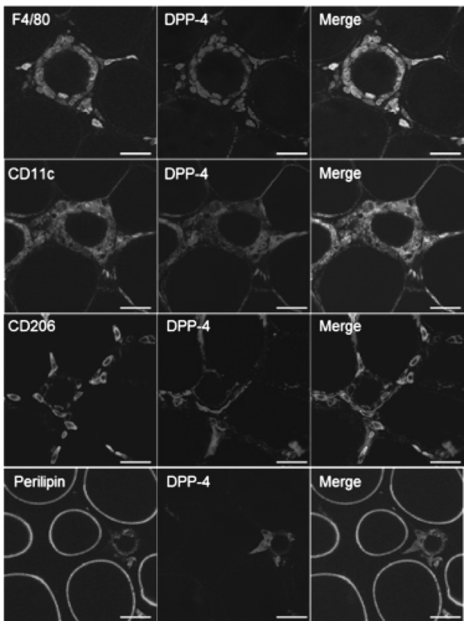

Fig. 1 Immunofluorescence staining for F4/80, CD11c, CD206, perilipin (green) and DPP-4 (red) in epididymal white adipose tissue from DIO mice.

FACS analysis also revealed that the percentage of DPP-4^{+} adipose tissue macrophages (ATMs), particularly DPP4^{+} M1 ATMs increased in DIO mice. These results suggested that DPP-4^{+} M1 macrophages accumulated in the WAT of obese mice[3].

To investigate the effect of DPP-4 inhibition by linagliptin on adipose tissue inflammation and insulin resistance in DIO mice, mice were fed with NC or HFD with or without linagliptin for 8 weeks. Linagliptin ameliorated hepatic steatosis and insulin resistance in obese mice. Moreover, linagliptin decreased accumulation of macrophages, and attenuated inflammation in adipose tissue and liver[3].

An important question is that anti-inflammatory effect of linagliptin is due to class effect of DPP-4 inhibitor or other functions induced by its specific structure. To answer this question, we compared the effect of linagliptin with other DPP-4 inhibitor, sitagliptin. 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[3].

Much like incretin peptides, chemokines act as DPP-4 substrates. After its cleavage by DPP-4, macrophage inflammatory protein (MIP)-1α or CCL3 is the most efficient monocyte chemoattractant among the chemokines. We next investigated whether the linagliptin-mediated amelioration of macrophage polarization and insulin resistance depended on MIP-1α. MIP-1$\alpha^{-/-}$ mice were fed a HF diet either with or without linagliptin for 8 weeks. The results showed that in MIP-1$\alpha^{-/-}$ mice, linagliptin significantly reduced DPP-4 activities, but it had almost no effect on glucose homeostasis and M1/M2 status. Therefore, linagliptin improved obesity-related inflammation and insulin resistance at least partly through its actions on MIP-1α[3].

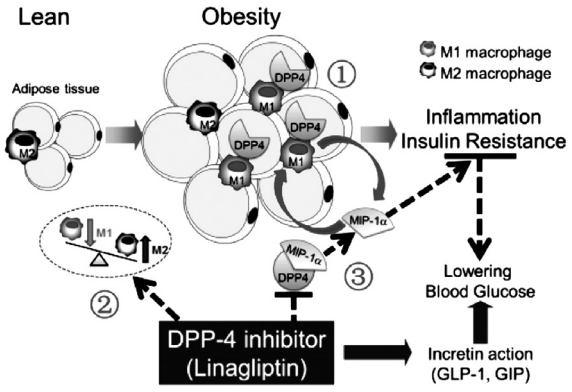

Fig. 2 Schematic summary: DPP-4 and macrophage-mediated inflammation

Conclusion

Our study revealed that DPP-4 was predominantly expressed by macrophages, particularly M1 macrophages. Inhibition of DPP-4 with linagliptin resulted in macrophage polarization toward an anti-inflammatory phenotype in adipose tissue and liver, thereby attenuating obesity-induced inflammation and insulin resistance. These effects were partly regulated by chemokine MIP-1α (Fig. 2). Therefore, DPP-4 plays a critical role in macrophage-mediated inflammation in obesity induced insulin resistance.

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Profile

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