論文審査の要旨

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Dietary obesity and glycemic excursions cause a parallel increase in STEAP4 and pro- inflammatory gene expression in murine PBMCs

〔肥満及び血糖変動はともにマウス末梢単核球での STEAP4 と炎症関連遺伝子の発現を増加させる。〕

The balance between pro-atherogenic and anti-atherogenic factors is very crucial in the development of atherosclerotic lesions. Although the role of pro-atherogenic factors such as visceral obesity and/or glycemic excursions in the development atherosclerosis have been studied in detail, the studies on the role of anti-atherogenic factors are relatively few. Especially the expression of the six-transmembrane epithelial antigen of the prostate 4 (STEAP4) in myeloid cells which is known to be atheroprotective. There is not a single study reporting on the status of STEAP4 expression in circulating monocytes in the early stages of diet-induced obesity or in events of glycemic excursions. Therefore, in this study, the author investigated whether there are any glucose spikes or dietary obesity-induced changes in STEAP4 expression in mononuclear cells, the correlation of such changes with obesity-related factors, and mechanisms responsible for such expressional alterations and found following the observations.

1) Diet-induced obesity and glycemic excursions independently caused a significant increase in STEAP4 mRNA expression in rat PBMCs.

2) This was also accompanied by an induction of a substantial number of pro-inflammatory cytokines, chemokines, and chemokine receptors such as IL1β, TNFα, and CCL2 (MCP-1). However, the combined effect of western diet and hyperglycemic spikes was subtle and non-additive.

3) In the in vitro setting using cultured RAW cells, either glucose spikes, persistent hyperglycemia, or a combination of palmitic acid and insulin resulted in a parallel increase in expression of STEAP4 and pro-inflammatory genes.

4) This was, however, significantly abrogated with 4-octyl itaconate or attenuated by inhibitors of p38MAPK and NF-kB.

From these observations, the author concluded that STEAP4 expression in mononuclear cells is induced by increasing inflammation or oxidative stress. Moreover, it was suggested the observed increase in STEAP4 expression in circulating monocytes due to visceral obesity or glycemic excursions is a compensatory response. Since this study has shown for the first time that hyperglycemic spikes and early stages of diet-induced obesity are associated with a concurrent increase in STEAP4 and pro-inflammatory gene expression in mononuclear cells, we concluded that this report is worth for the doctoral thesis.

よって本研究は学位論文として十分な価値を有するものと判定した。