論 文 要 旨

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

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Background: The balance between pro-atherogenic and anti-atherogenic factors is very crucial in the development of atherosclerotic lesions. Although the expression of the six-transmembrane epithelial antigen of the prostate 4 (STEAP4) in myeloid cells 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. **Methods**: We induced glycemic spikes twice daily for a one-week duration to rats fed on regular chow and western diet, and analyzed gene expression changes in the peripheral blood mononuclear cells (PBMCs). We also conducted experiments on RAW 264.7 cells to gain insight into some of our in vivo findings. **Results**: Diet-induced obesity and glycemic excursions independently caused a significant increase in STEAP4 mRNA expression in PBMCs. This was also accompanied by an induction of a substantial number of pro-inflammatory cytokines, chemokines, and chemokine receptors. However, the combined effect of western diet and hyperglycemic spikes was subtle and non-additive. In the in vitro setting, 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. This was, however, significantly abrogated with 4-octyl itaconate or attenuated by inhibitors of p38MAPK and NF-kB. **Conclusions**: STEAP4 expression in mononuclear cells is induced by increasing inflammation or oxidative stress. The observed increase in STEAP4 expression in circulating monocytes due to visceral obesity or glycemic excursions is a compensatory response.