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Insulin-induced IL-10 expression in murine macrophages via ERK-CREB mediated pathway

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Statement of the Problem: Obesity-associated chronic inflammation contributes to the metabolic impairment and risk for development of disease like diabetes mellitus (DM). A potent anti-inflammatory cytokine, Interleukin-10 (IL-10) produced by macrophages, helps in containing inflammatory response and remains at a lower level in circulation in obese subjects. Intensive insulin therapy promotes serum IL-10 level in patients with severe trauma, sepsis or multiple organ dysfunction syndromes (MODS). However, importance of insulin signalling (if any) in macrophage function and polarization is not well characterized and underlying molecular mechanisms of insulin-mediated IL-10 induction in murine macrophages is yet to be determined.

Methodology: Expression of IL-10 was determined at mRNA level through qRT-PCR in insulin stimulated RAW 264.7 cells, in presence or absence of PI3K and MAPK (ERK1/2) inhibitors. Further, expression of TLR-4 and insulin receptor (IR) mRNA was evaluated.

Findings: While expression of IR remains unchanged, insulin alone could attenuate TLR-4 expression in duration-dependent manner, at both mRNA as well as protein level. Additionally, time kinetics data showed a significant up-regulation of IL-10 expression due to insulin in naive as well as in LPS-treated macrophages. While, both ERK1/2 and PI3K was activated by insulin, ERK1/2 inhibitor, U0126 could block the expression of IL-10 but not TLR-4 in RAW 264.7 cells. Conversely, PI3K inhibitor, wortmannin did not show any effect on IL-10 expression but could up regulate TLR-4 level in insulin stimulated cells. Further, insulin could not induce CREB phosphorylation (activation) in ERK1/2 inhibited cells.

Conclusion & Significance: Insulin alone or in endotoxin-treated macrophages could induce IL-10 expression through ERK1/2-CREB mediated pathway. Besides, inhibition of TLR-4 due to insulin might be due to the activation of PI3K pathway. This area of research is beneficial for further understanding of the interplay between insulin signalling and host immune system.

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