TNF-alpha modulates macrophage polarization to M1 phenotype via lipid metabolism

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Introduction

Over the past decade the prevalence of obesity in Kuwait, and worldwide, has increased at an epidemic proportion. It is estimated that 42% of the Kuwaiti population is obese, while 52.5% are considered overweight (1, 2). It is well documented that obesity occurs due to the excessive consumption of a diet high in saturated fat, and that it is correlated with both chronic inflammation and deranged cellular metabolism. All of which are believed to be risk factors of insulin resistance syndrome (3, 4).

Tumour necrosis factor (TNF)-alpha is a key protein that is secreted by adipose tissue, which is found in excess levels in both obese humans and animals, its expression leads to the activation of pro-inflammatory pathways known to influence insulin sensitivity(5). At gene level, TNF- α acts as a local signal regulator that induces fatty acid lipolysis in an organ specific manner. This in turn leads to increased accumulation of intercellular fatty acids (FA) and ultimately lipotoxicity (6). This effect was further documented in obese patient sera, where excess TNF- α expression in sera was found to influences the behavior of monocytes leading to lipid laden monocytic cells. The higher FA content within the monocyte the more it aggravates their inflammatory phenotype favoring pro-inflammatory macrophages (M1) that secrete high levels of pro-inflammatory cytokines such as IL-1 β , IL-6 IL-8 and TNF- α (7). This process of up-regulation of TNF- α creates a vicious cycle of inflammation and insulin resistance that correlates with the pathology of Type 2 Diabetes (T2D) (3, 8).

It is still unclear how functional changes within the monocytic lipid metabolites are essential to the monocyte/macrophage inflammatory response, and how it influences the phenotypic switch over the course of obesity-related inflammation. Therefore, in this current study, we aim to investigate the potential link between the inhibition of different lipid metabolites and inflammatory responses in TNF- α stimulated monocyte/macrophage cultures.

Materials and methods

THP-1 cell cultures were induced to different lipid metabolite inhibitors; Myriocin, a serine palmitoyltransferase inhibitor (SPT-1), an inhibitor involved in Sphingolipids biosynthesis as well as Fumonisin B1 (FB1), a mycotoxin that inhibits ceramide synthases (CerS) and Triacsin C, a Long chain acyl-CoA synthetase (ACSL-1) inhibitor. All cultures were stimulated with 10ng/ml TNF- α overnight. Cells were then harvested and analysis through FACS analysis for pro-inflammatory markers. Intercellular lipid content were investigated through cell sorting (FACS).

Monocytic THP-1 cells were transformed to macrophages with phorbol 12-myristate 13-acetate for three days followed by a day rest in serum starved media. Oil red O staining was used to visualizes lipid content in macrophage cultures. Culture supernatant was investigated for the secretion of IL-1 β and MCP-1 through Enzyme-linked immunosorbent assay (ELISA)

Conclusion

Our observations show that the acyl-CoA pathway is centrally and selectively important in mediating the inflammatory phenotype of macrophages associated with obesity-related inflammation.

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Further information

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Results

TNF- α mediated lipid accumulation and induce M1 pro-inflammatory production.

The effect of different lipid enzymes inhibition in cellular lipid accumulation and M1 pro-inflammation production

ACSL inhibitor attenuates TNF- α induced foam cell and pro-inflammatory production in THP-1 transformed macrophages