A4.2 ADIPOCYTES MODULATE T CELL FUNCTION THROUGH RELEASE OF LIPIDS

doi:10.1136/annrheumdis-2013-203217.2

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Background and Objectives Obesity is characterised by the presence of inflammation in adipose tissue. Accumulation of several immune cell-types, including CD4+ T cells, has been previously reported in the increasing adipose tissue. This accumulation is also paralleled by changes in cytokine profiles and phenotype of the infiltrating cells. One of the possible mechanisms involved in these changes is the modulation of T cell function by tissue-resident adipocytes. Therefore, we investigated whether adipocytes derived from various adipose tissues can modulate CD4+ T cell cytokine production and proliferation and studied the mechanisms involved in this process.
Materials and Methods CD4+ T cells were purified from peripheral blood mononuclear cells using magnetic beads coated with anti-human CD4. Plate-bound anti-CD3 and soluble anti-CD28 antibodies were used to activate T cells. Adipocytes were isolated from IFP of OA patients by collagenase digestion and were either cultured with purified CD4+ T cells or were cultured in vitro for 24 hours in DMEM/F12 medium supplemented with 0.5% bovine serum albumin to generate adipocyte-conditioned medium (ACM). Cytokine/adipokine production was measured by intracellular cytokine staining (ICS), ELISA or cytokine multiplex. Lipids were isolated using hapten and lipid profiling was performed by liquid chromatography combined with mass spectrometry.
Results CD4+ T cells produced increased levels of IFNγ when activated in the presence of adipocytes. This effect is mediated by soluble mediators, as shown in transwell and adipocyte-conditioned medium (ACM) transfer experiments. Additionally, ACM induced increased proliferation of CD4+ T cells upon activation. Furthermore, adipose tissue contained more IFNγ-producing CD4+ T cells than peripheral blood of the same individuals, in 3 out of 3 cases tested, which indicates a possible in vivo relevance of our results. To investigate the possible molecular mechanisms involved in this effect, we separated the protein and lipid fraction of ACM. Surprisingly, despite previous data indicating that several adipocyte-derived proteins can modulate T cell function, we have found that the increased proliferation of T cells is mainly due to the lipids isolated from ACM. Further separation of these lipids based on polarity revealed that the modulatory effect is mainly confined to fractions containing free fatty acids. All identified fatty acids were able to individually enhance T cell proliferation.
Conclusions These data indicate that adipocytes can modulate CD4+ T cell function through release of soluble mediators. Remarkably, within the soluble mediators identified, lipids and especially free fatty acids are the most prominent modulators of T cell proliferation.

A4.3 ADIPOCYTES MODULATE THE PHENOTYPE OF MACROPHAGES THROUGH SECRETED LIPIDS

doi:10.1136/annrheumdis-2013-203217.3

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Background Adipose tissue secretes a wide range of soluble factors that can influence whole body metabolism. Previous studies have shown an accumulation of macrophages and an enhanced pro-inflammatory profile of these cells in adipose tissue of obese mice. Modulation of macrophages by soluble mediators released by adipocytes has been proposed as a possible mechanism underlying these changes. In humans, an increased number of macrophages in adipose tissue of obese individuals have been observed, although no clear change in macrophages phenotype could be established. Moreover, no information exists about the interaction between macrophages and adipocytes in humans.
Objective In the present study, we explored the possibility that adipocytes modulate the phenotype of macrophages and studied the possible molecular pathways involved in this modulation.
Results Treatment of macrophages with adipocyte-conditioned medium (ACM) resulted in a strong reduction in IL-12p40 secretion upon LPS stimulation, whereas TNFα and other cytokines remained largely unaffected. This effect was independent of the source of ACM. Interestingly, the inhibition increased with increase in Body Mass Index (BMI) of the adipocyte donor. Therefore, it was hypothesised that the effect is mediated by a soluble factor whose release is correlated to the BMI of the adipocyte donor. To this end, we measured several cytokines, adipokines and lipids present in ACM. Among these, the release of several free fatty acids (FA) and PGE_2 correlated with the BMI of the adipocyte donor. Further tests indicated that oleic and linoleic acid, as well as PGE_2 were able to inhibit IL12p40 secretion, whereas palmitic acid could not. Upon separation of ACM protein and lipid fractions, we confirmed that inhibition of IL12p40 resides mainly in the ACM lipid fraction.
Conclusions These results provide first evidence that obesity-related changes in macrophage phenotype could be mediated by adipocytes in humans. These effects are mainly mediated through lipids released by adipocytes. Intriguingly, modulation appears different than in murine obesity, indicating that the immunomodulatory effects of obesity could be different in humans and mice.

A4.4 CIRCULATING METASTASIS PROMOTING PROTEIN S100A4 IN IDIOPATHIC INFLAMMATORY MYOPATHIES

doi:10.1136/annrheumdis-2013-203217.4

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Background and Objectives Metastasis promoting protein S100A4 is involved in the pathogenesis of tumours and chronic autoimmune diseases such as rheumatoid arthritis (RA) and psoriasis. We recently described increased expression of S100A4 in inflamed muscle tissue in patients with idiopathic inflammatory myopathies (IIM). Since circulating levels of S100A4 correlate with disease severity in RA patients, we therefore evaluated the association between S100A4 protein and disease activity in patients with IIM and compared S100A4 serum levels in myositis patients and healthy controls in this study.
Methods Serum levels of S100A4 protein were determined in 43 dermatomyositis (DM), 39 polymyositis (PM) and 22 cancer associated myositis (CAM) patients and in 89 healthy controls. In 11 patients (4 DM, 3 PM, 4 CAM), S100A4 serum levels were measured before and after the start of treatment. The associations between S100A4 levels, inflammation, disease activity and muscle strength were examined. Disease activity was assessed using Disease Activity Core Set Measures developed by International Myositis Assessment & Clinical Studies Group (IMACS). Serum levels of