Fatty acid synthase and diacylglycerol acyltransferase 1 modulates macrophage and dendritic cell activation during *M. bovis* BCG infection

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Introduction

Tuberculosis (TB) represents a serious question of public health, killing more than 1 million people each year. The actual available treatment is old and faces antibiotic resistance. *Mycobacterium tuberculosis* is transmitted by aerosol and penetrates pulmonary alveolus, where it is phagocyted by alveolar macrophages and dendritic cells, the principal bacterial reservoirs and immune response initiators. This pathogen can change host metabolic pathways as a survival mechanism. Among them, lipidic metabolism is an important target. Lipid accumulation has been shown to be a key-component in host-pathogen interaction, enabling bacteria replication and survival.

Methods

In the present work we aimed to evaluate FAS and DGAT-1 role in bone marrow derived macrophages (BMDM) and dendritic cells (BMDC) activation during *M. bovis* BCG infection. C57BL/6 bone marrow cells were differentiated in BMDM with M-CSF or BMDC with GM-CSF. Cells were infected *Mycobacterium bovis* BCG GFP in MOI 5 and treated with different concentrations of inhibitors of fatty acid synthase (FAS) and diacylglycerol acyltransferase 1 (DGAT-1), C75 and A922500, respectively. Lipid droplet formation and bacterial quantification was performed by fluorescence microscopy and analysed using Image J (NIH, EUA). Activation markers expression was evaluated by flow cytometry. Data we analyze by ANOVA test followed by Student Newman-Keuls or Student’s t-test.

Results

We observed an increase in lipid droplets (LD) formation in BCG-infected BMDMs and BMDCs. The infection also increased the production of IL-1beta, IL-6, IL-12p40, TNFalpha, IL-10 and Prostaglandin (PG)E2. We observed that FAS (C75; 5ug/mL) and DGAT-1 (A922500; 10uM) pharmacological inhibition was able to reduce the LD area and bacterial load in BMDM infected by *M. bovis* BCG. Furthermore, there was a significant reduction in IL-1beta, IL-6 and IL-10 production. In addition, it was observed that C75 also reduced the expression of activation markers (CD80, CD86, MHC I). On the other hand, C75 treatments (1ug/mL) increased LD area in dendritic cells during BCG infection, without affecting bacterial burden. However, the treatment was able to reduce IL-10, TNFalpha and PGE2 production. The treatment with A922500 (20uM) did not affect LD formation, nor bacterial load, yet it reduced the production of IL-10 and PGE2.

Conclusion

Taken together, our results demonstrate that FAS and DGAT-1 inhibition was able to reduce the LD formation, bacterial burden in BMDM, but not in BMDC. Moreover, these treatments modulated cytokines and PGE2 production in both cell types, pointing out the lipid metabolism as a potential therapeutic target against TB and associated *Mycobacterium* sp. diseases.

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Keywords

tuberculosis, metabolism, macrophage and dendritic cell.