Tafazzin deficiency impairs mitochondrial metabolism and function of lipopolysaccharide activated B lymphocytes in mice

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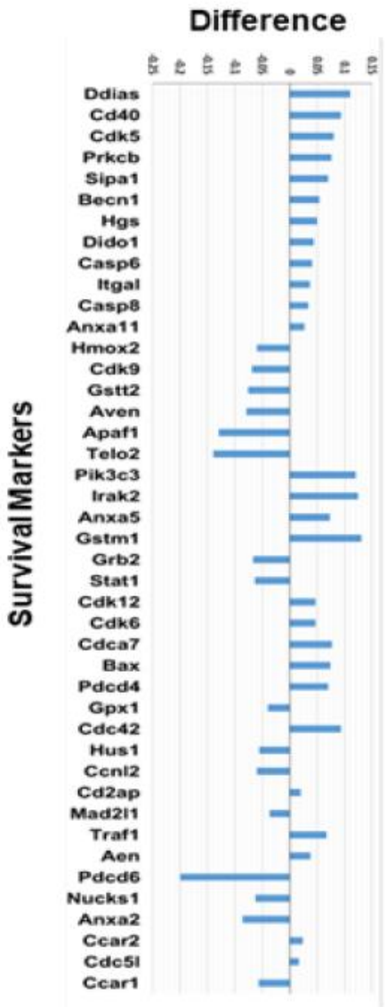
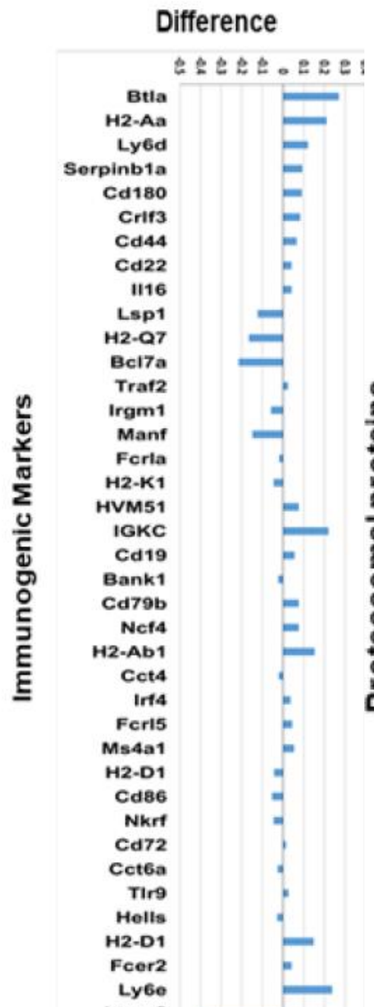
Background: Barth Syndrome (BTHS) is a rare X-linked genetic disease of young boys caused by a mutation in the TAFAZZIN gene which codes for the cardiolipin transacylase enzyme tafazzin (Taz), a cardiolipin remodeling enzyme required for mitochondrial function. BTHS boys are susceptible to severe infections attributed, in part, to neutropenia. However, the effect of Taz deficiency in other cells of the immune system in BTHS is poorly understood. B lymphocytes are responsible for humoral immunity and play a key role in the immune response. Optimal mitochondrial function is required to support B cell activity during activation. We examined how deficiency of Taz alters the metabolic activity of B cells and their response to activation by lipopolysaccharide (LPS) in mice.

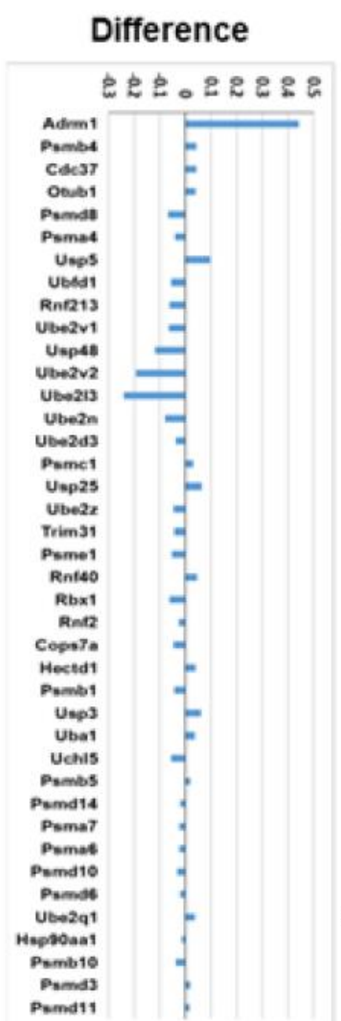
Methods: B cells were isolated from 3-month-old wild type (WT) or Taz knockdown (TazKD) mice and incubated for up to 72 h with LPS and proteomic analysis was performed to identify proteins involved in survival, immunogenic, proteasomal and mitochondrial processes.

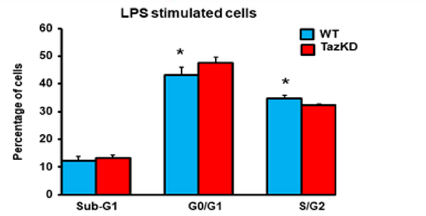
Results: Compared to WT B cells, TazKD B cells exhibited significant alterations in key protein targets that regulate cell survival, immunogenicity, proteasomal processing and mitochondrial function. These included reduced expression of Aven, PSMA4, NDUFV1, and elevated expression of BTLA – all representative markers of survival, proteasomal, mitochondrial and immunogenic processes, respectively. In addition, reduced surface maker expression (CD86+), cytokine (KC) and immunoglobulin (IgM) secretion and proteosomal activity were accompanied by reduced phosphatidylinositol-3-kinase (PI3K), phosphorylated protein kinase B (pAKt) and glycolysis indicative of reduced proliferation and confirmed by reduced number of cells in S/G2 of the cell cycle. Reduced mitochondrial Complex IV expression was accompanied by lowered mitochondrial respiration (OCR).

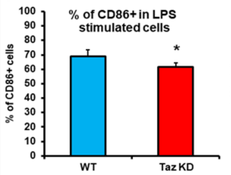
Conclusions: Taz plays a key role in regulating mouse B cell metabolic activity and immune function during activation through modulation of mitochondrial function. The results of this study may contribute to the development of new therapies to treat infections in BTHS.

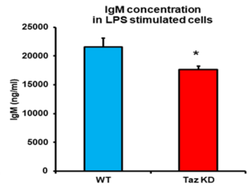


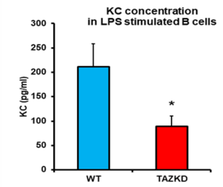


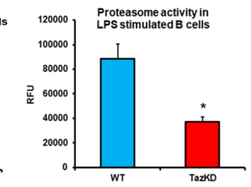


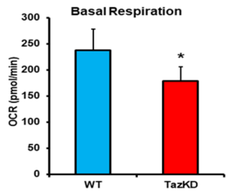


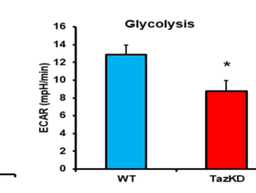


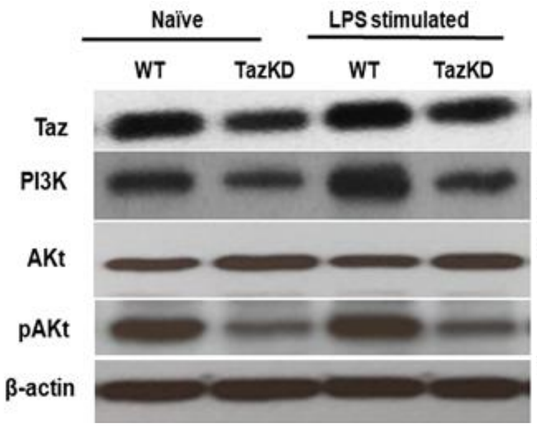


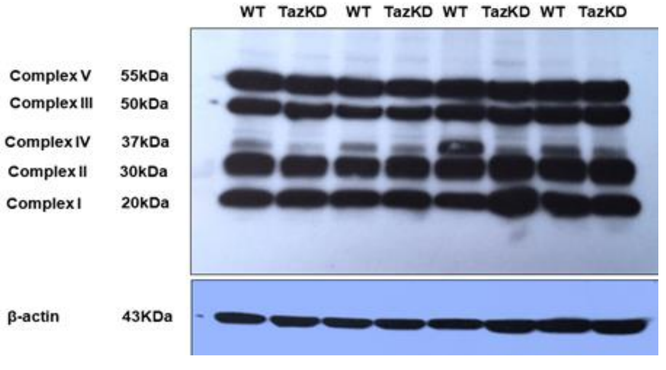


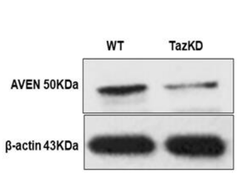


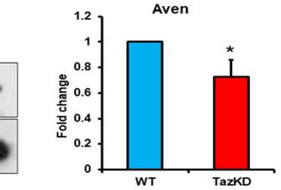


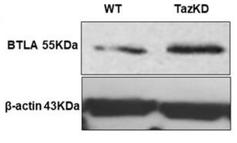


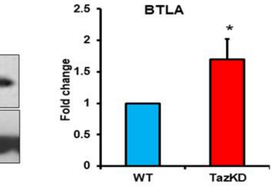


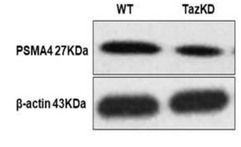


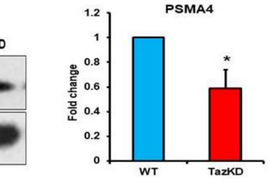


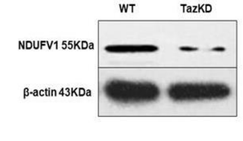


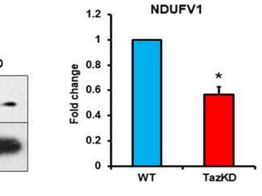












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