Oxidative Stress Regulator NRF2 Controls Inflammatory T-helper 1 (Th1) Subset Differentiation by Modulating Glycolysis and Protects against Colitis Progression in Mice

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Introduction. CD4 T cells are the orchestrators of adaptive immunity and a disbalance in their effector responses is implicated in multiple inflammatory diseases, like Ulcerative Colitis (UC). In this project, we aim to identify if/how Nrf2 (nuclear factor erythroid 2–related factor 2), an oxidative stress regulator controlled by Keap1 (Kelch-like ECH-associated protein1), impacts the differentiation of inflammatory (Th1) or regulatory (Treg) T-cell subsets and in turn, the disease outcome of Colitis.

Methods. To answer this, we used mice with T-cell specific knock outs (KO) of Nrf2 (N-KO) or Keap1 (K-KO). We performed *in vitro* assays in KO mice and validated results *in vivo* using OTII mice (with OVA antigen specific T-cell receptor). IFN-γ and T-bet expression were measured for Th1 and Foxp3 for Tregs differentiation, respectively. To dissect metabolic mechanisms, levels of glycolysis intermediates lactate and pyruvate were measured (Th1 differentiation is Glycolysis dependent). Further, to elucidate if/how NRF2 in T cells plays a protective role in Colitis, we performed T cell specific adoptive transfer experiment in immunodeficient RAG1 KO mice.

Results. Our data overall depicts lower Th1 differentiation *in vitro* as well as *in vivo* in K-KO mice along with lower glycolysis compared to Wild type (WT) and N-KO CD4 T-cells. Conversely, we observed increased Foxp3 expression indicative of Nrf2 promoting Treg cell differentiation. We also observed better disease outcomes in RAG1 KO mice adoptively transferred with K-KO T cells.

Conclusions. These results suggested the protective role of NRF2 in UC, making it an attractive therapeutic target for the same.

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