ABSTRACTS

Nuclear Receptor Co-repressor NCoR1 governs immune tolerance in conventional dendritic cells by fine-tuning glycolysis and fatty acid oxidation

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Dendritic cells (DCs) undergo rapid metabolic reprogramming events to induce signal-specific immune responses. The transcriptional control of energy metabolism in tolerogenic-DCs remains elusive. We have recently reported that NCoR1 ablation in DCs leads to immune tolerance by altering the balance of naive T helper cells towards T-regs. Here, comprehensive metabolic profiling of these tolerogenic DCs identified that they meet their anabolic requirements through enhanced glycolysis and OxPhos, supported by FAO-driven oxygen consumption. Mechanistically, AKT, mTOR, and HIF-1α-axis mediated glycolysis and CPT1a-driven β-oxidation were found to be enhanced in the NCoR1-depleted DCs. In addition, reduced pyruvate and glutamine oxidation, with a broken TCA cycle, and PPAR-γ-induced β-oxidation maintain the tolerogenic state of the cells. Additionally, we showed how the tolerogenic cytokines IL-10 and IL-27 and the overall transcriptional signature of immunological tolerance were considerably compromised by the combined suppression of HIF-1α and CPT1a using KC7F2 and Etomoxir respectively. Interestingly, this combined treatment further cleared the *Mycobacterium tuberculosis* (Mtb) burden in BMcDC1s *ex-vivo* and in $CD103^{+}$ lung DCs in $NCoR1DC^{-/-}$ mice *in-vivo*. Furthermore, the spleen of these infected mice also showed treatment-induced increased Th1-mediated IFN-γ responses. Ultimately, to validate the findings in the human system, we demonstrated that dexamethasone-derived primary human tolerogenic moDCs showed significantly reduced NCoR1 expression, which in turn suppressed the CD4 T-cell proliferation and Th1 phenotype at the expense of T-regs. Here, the combined treatment rescued the T-cell proliferative capacity and the Th1 phenotype. Our findings demonstrate that increased glycolysis and fatty acid oxidation fine-tune immune tolerance versus inflammation in murine and human DCs.

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