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NOVEL IMMUNE REGULATORY PROPERTIES OF NAD+ AND ITS BENEFITS IN DISEASE SCENARIOS

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It is well known that MHC-TCR activation following pathogen invasion dictates CD4+ T cell differentiation. More recently, a second mechanism involving TLRs and NLRs pathways have been shown to regulate CD4+ T cell differentiation as well. Both pathways require antigen presenting cells in particular dendritic cells (DCs). Moreover, CD4+ T cell fate is tightly regulated by cytokine milieu (produced by DCs) and major transcription factors that give rise to specific T helper subset (Th1, Th2, Th17 and regulatory T cells (Tregs)). Alterations in DC-mediated CD4+ T cell regulation pathway leads to a myriad of diseases including atopic disorders, autoimmune, primary immunodeficiency, infections and cancer. In our studies, we demonstrated that NAD+ regulates CD4+ T cell differentiation independently of cytokine milieu and well established transcription factors. It is well established that the transcription factor T-bet is critical for Th1 differentiation. Our results demonstrated that in the presence of NAD+, the frequency of T-bet−/− CD4+IFNγ+ T cells was twofold higher than wild-type CD4+ T cells cultured in conventional T helper 1 polarizing conditions. Moreover, we showed a robust and unique immunoregulatory property of NAD+ that are independent of CD4+CD25+Foxp3+ Tregs, a unique T cell lineage that is essential for maintaining immune tolerance and homeostasis. Finally, our findings indicate that following NAD+ administration MCs, exclusively, promote CD4+ T cell differentiation, both in absence of antigen and independently of major APCs. Moreover, we found that MCs mediated CD4+ T cell differentiation independently of MHC-II and TCR signaling machinery. Collectively, our study unravels a novel cellular and molecular pathway that regulates innate and adaptive immunity via MCs, exclusively. This untapped novel and distinct pathway may serve as an alternative to bypass certain inflammatory conditions and pave the way for novel therapeutic approaches in the context of autoimmune diseases, transplantation, primary immunodeficiencies and antimicrobial resistance.

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