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Biotin deficiency induces Th1 and Th17 mediated inflammatory response in CD4+T lymphocytes via activation of mTOR signaling pathway

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Biotin (vitamin B7) is essential for normal human health due to its involvement, as a cofactor, in a variety of critical cellular metabolic reactions. Previous studies have shown that biotin deficiency enhances inflammation, and that certain chronic inflammatory diseases (like inflammatory bowel diseases) are associated with biotin deficiency. However, the mechanisms that mediate the association between biotin status and inflammation are not well understood. Here, we examined the effect of biotin deficiency on human CD4+ T cell responses to determine their role in biotin deficiency associated inflammation. Our investigations revealed that anti- CD3/CD28 stimulated human CD4+ T cells cultured in biotin deficient media secreted significantly enhanced levels of pro-inflammatory cytokines, IFN-γ, TNF-α, and IL-17. Expression of the transcription factors, T-bet and RORγt, was increased along with a decrease in Foxp3 expression in biotin deficient CD4+ T cells. The percentage of T regulatory cells was also decreased under biotin deficient condition. Further investigations indicated that the enhanced inflammatory response was not a consequence of increased T-cell differentiation towards Th1 and Th17 or increased proliferation. Instead deficiency of biotin enhanced the production of IFN-γ from already differentiated cells. Moreover, the results indicated that the increased inflammatory response was due to enhanced activation of the mTOR signaling pathway in biotin deficient CD4+ T cells. Similar increase in T-bet, RORγt and decrease in Foxp3 transcription factors was also observed in inguinal lymph nodes of mice fed with biotin deficient diet relative to pair-fed controls. Further, the level of IFN-γ, IL-17 cytokines and the expression of mTOR were found to be increased significantly in CD4+T cells isolated from inguinal lymph node of diet induced biotin deficient mice. These findings revealed that biotin deficiency leads to the upregulation of IFN-γ secreting Th1 and IL-17 secreting Th-17 cells via activation of mTOR signaling pathway which may contribute to inflammation associated with biotin deficiency

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