A loss of branched-chain aminotransferase (BCAT) enzyme function enhances T regulatory cell lineage commitment

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Amino acid availability strengthens T cell-driven immunity. The branched-chain amino acids (BCAAs) are essential for T cell activation. The cytosolic and mitochondrial branched-chain aminotransferases (BCATc and BCATm), which catabolize BCAAs, are implicated as T cell immunosuppressive enzymes. While BCAT enzymes are well characterized in tumor growth, their impact on $CD4^+$ T cell lineage commitment remains unknown. The objective of this study was to decipher the role of BCATc and BCATm in the differentiation of $CD4^+$ T cells into regulatory T cells (Tregs), which are known to maintain peripheral immunotolerance. $CD4^+$ T cells were isolated from the spleens of wild type (WT) mice or mice with T cells deficient in BCATc (T-$BCATc^{KO}$) or BCATm (T-$BCATm^{KO}$) followed by activation with anti-CD3/CD28 in the absence (undifferenced control) or the presence of transforming growth factor (TGFβ), cytokine-IL2, anti-IFNy and anti-IL4 for 4 days to induce Treg lineage commitment. RT-PCR was performed to analyze expression levels of the Treg lineage specific transcription factors: forkhead box protein 3 (FOXp3) and TGFβ. WT $CD4^+$ T cells, induced to Tregs, significantly downregulated BCATc and BCATm. Further, a loss of expression of BCATc or BCATm significantly increased Foxp3 and TGFβ expression in Tregs compared to undifferenced controls. Pharmacological treatment with n-acetyl leucine amide (NALA), an antagonist of the BCAA, leucine, reversed the effect of a loss of function of BCAT. Taken together, these results indicate a loss of BCAT enzymes enhances Treg differentiation and point toward a role of BCAA metabolism in the regulation of immunotolerance.