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Titel des Beitrags: Tryptophan deprivation induces inhibitory receptors ILT3 and ILT4 on dendritic cells favoring the induction of human CD4+CD25+ Foxp3+ T regulatory cells.

Abstract: Tryptophan catabolism through IDO activity can cause nonresponsiveness and tolerance acting on T cells. Given the crucial importance of dendritic cells (DCs) in the initiation of a T cell response, surprisingly little is known about the impact of IDO activity and tryptophan deprivation on DCs themselves. In the present study, we show that human DCs differentiated under low-tryptophan conditions acquire strong tolerogenic capacity. This effect is associated with a markedly decreased Ag uptake as well as the down-regulation of costimulatory molecules (CD40, CD80). In contrast, the inhibitory receptors ILT3 and ILT4 are significantly increased. Functionally, tryptophan-deprived DCs show a reduced capacity to stimulate T cells, which can be restored by blockade of ILT3. Moreover, ILT3(high)/ILT4(high) DCs lead to the induction of CD4(+)CD25(+) Foxp3(+) T regulatory cells with suppressive activity from CD4(+)CD25(-) T cells. The generation of ILT3(high)/ILT4(high) DCs with tolerogenic properties by tryptophan deprivation is linked to a stress response pathway mediated by the GCN2 kinase. These results demonstrate that tryptophan degradation establishes a regulatory microenvironment for DCs, enabling these cells to induce T regulatory cells. The impact of IDO thus extends beyond local immune suppression to a
systemic control of the immune response.