INTERLEUKIN 4-INDUCED GENE-1 AS NOVEL IMMUNE REGULATORY PATHWAY

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Interleukin 4-induced gene-1 (IL4i1) is as L-phenylalanine oxidase initially described as an early IL-4-inducible gene in B cells [1]. Herein, we analyzed IL4I1 expression in different DC subsets and investigated the possible role of IL4I1 in T-cell regulation. By using a novel and highly specific antibody, reactive to mouse IL4I1, developed in our laboratory, we found that IL4i1 could be induced by IL-4 or CpG olognucleotides (CpGODN) only in classical DCs (cDC). IL4i1 induction, by IL-4 was prevented in cDCs isolated from AhR-/- mice. Moreover, IL-4–treated cDCs cultured with CD4+T cells favored the expansion of FoxP3+ CD4+ T cells (Treg) compared to untreated cDCs. This effect was abrogated in the presence of a small interfering RNA (siRNA) targeting IL4i1 but not by a control siRNA. Notably, IL-4-induced IL4i1 expression in cDCs required aryl hydrocarbon receptor (AhR) in these cells. IL4I1-mediated oxidative deamination of phenylalanine produces H2O2 and phenylpyruvate (PP). Recently we found that PP is a novel ligand of AhR. Phenylpyruvate administration in vivo significantly reduced disease severity in a murine model of multiple sclerosis, such effect was prevented in AhR-/- mice. Overall, these results point IL4i1 as a key enzyme in the regulation of immune responses.

1. Chu, C.C. and W.E. Paul, Fig1, an interleukin 4-induced mouse B cell gene isolated by cDNA representational difference analysis. Proc Natl Acad Sci U S A, 1997. 94(6): p. 2507-12.