IMMUNOREGULATORY SYNERGISM BETWEEN ARGININE AND TRYPTOPHAN CATABOLISM IN DENDRITIC CELLS

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Indoleamine 2,3-dioxygenase 1 (IDO1) and arginase 1 (Arg1) are two different enzymes that preside over the catabolism of tryptophan and arginine, respectively. Arg1 is mainly expressed in myeloid cells and it is induced by T helper 2 cytokines, such as interleukin-4 (IL-4). In contrast, high levels of IDO1 can be found in professional antigen-presenting cells such as dendritic cells (DCs), mainly in response to type I and type II interferons (IFN). Moreover, autocrine or paracrine TGF-β has been found to induce long-term IDO-dependent effects that imply a novel signaling function for IDO1. Although much is known about the biological properties of IDO1 and Arg1 at the individual level, no study has thus far examined a possible integrated function of the two enzymes in DCs. In the present study, we investigated whether Arg1 and IDO1 could be co-expressed in DCs and which could be the functional meaning of their co-expression. Therefore, conventional DCs from wild type, Ido 1 -/- and Itgax-Cre;Argfl/fl mice were stimulated with the main cytokines capable of inducing IDO1 and Arg1 (i.e., IFN-γ, IL-4, and TGF-β) to evaluate the expression and activity of these metabolic enzymes. We found that TGF-β can induce both Arg1 and IDO1 in DCs, with Arg1 being upregulated much more rapidly than IDO1, suggesting that Arg1 activity is required for the induction of IDO1. Moreover, Ornithine, the main Arg1 product, can activate the IDO1 signaling and confers IDO1-dependent immunosuppressive properties in DCs. However, this activity is strictly dependent on the decarboxylation of ornithine into polyamines, since it is blunted in the presence of a pharmacological inhibitor of ornithine decarboxylase. Polyamines are bioactive polycations well known for their role in tumor progression. Here we showed that these metabolites are also able to promote IDO1 phosphorylation and signaling events in DCs. This circuit, turned on by TGF-β, can occur not only between DCs, but also between DCs and MDSCs (myeloid-derived suppressor cells). Therefore, the network established by TGF-β, Arg1, and IDO1 could be very important in the context of cancer since tumors are very apt to co-opt metabolic and immunosuppressive networks, such as the one established between IDO1 and Arg1. Therefore, our data suggest that the simultaneous inhibition of the Arg1 and IDO1 activities, and/or TGF-β signaling, may provide a powerful strategy in tumor immunotherapy.