IDO-targeting intervention in autoimmune diabetes by proteasome inhibition

C. Orabona[†], C. Volpi[†], F. Fallarino[†], M.L. Belladonna[†], M.T. Pallotta[†], C. Vacca[†], R. Bianchi[†], U. Grohmann[†],Puccetti P[†]

[†] Dept. Experimental Medicine and Biochemical Sciences, via Gambuli, 06132 Perugia, ITALY

Indoleamine 2,3-dioxygenase 1 (IDO1) is a metabolic enzyme involved in the catabolism of tryptophan. Its metabolic activity has become pivotal in the regulation of both innate and adaptive immune responses. The functional expression of the IDO1 enzyme confers a tolerogenic phenotype to different subsets of dendritic cells (DCs), the most professional antigen-presenting cells. Our previous data suggest that, in autoimmune diabetes, IDO1-expressing DCs may represent an optimal instrument in the control of immune responses against diabetogenic autoantigens. Given our recent identification of a proteasome-mediated IDO1 degradation, an innovative strategy in autoimmune diabetes would consist of using selective proteasome inhibitors to restore and maintain optimal levels of IDO1 function in DCs, which, when contextualized to a proinflammatory milieu (prediabetes), would otherwise lose their IDO1-dependent tolerogenic properties. Bortezomib (also known as PS-341 or Velcade®) is the first proteasome inhibitor clinically approved as an antitumor drug. The boronic acid dipeptide structure of bortezomib is a reversible proteasome inhibitor that selectively inhibits the chymotrypsin-like activity of the proteasome 20S subunit. In the present study, we characterized the effects induced by Bortezomib in plasmacytoid dendritic cells (pDCs) purified from the spleen of nonobese diabetic (NOD) mice, a prototypic model of human type 1 diabetes. In vitro conditioning of NOD pDCs by bortezomib increased the functional expression of the IDO1 enzyme, conferring those cells an immunoregulatory phenotype. NOD female mice in prediabetes were thus sensitized with syngeneic splenic pDCs pretreated with bortezomib and pre-pulsed with the diabetogenic antigen IGRP. After two weeks from sensitization, mice were challenged intrafootpad with the IGRP peptide alone. We found that in vitro pretreatment of pDCs with bortezomib strongly inhibited the immunostimulating potential of pDCs presenting IGRP in vivo, an effect accompanied by an increase of IGRP-specific regulatory T cells in pancreatic lymph nodes. The observed immunoregulatory effects were IDO1-dependent, as revealed by the use of 1-methyl tryptophan (MT), the gold inhibitor of IDO1, which abolished the bortezomib-induced effect in pDCs. Overall, these data suggest that proteasome inhibitors are druggable molecules in halting autoimmune diabetes (T1D), behaving as IDO1 mimetic compounds.