The proteasome inhibitor bortezomib controls IDO1 breakdown and restores immune regulation in autoimmune diabetes

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Bortezomib is a first-in-class proteasome inhibitor approved for the therapy of multiple myeloma that also displays unique regulatory activities on immune cells (1). The enzyme indoleamine 2,3-dioxygenase 1 (IDO1) is a tryptophan metabolizing enzyme exerting potent immunoregulatory effects when expressed in dendritic cells (DCs), the most potent antigen presenting cells capable of promoting either immunity or tolerance. We previously demonstrated that, in inflammatory conditions, IDO1 is subjected to proteasomal degradation in DCs, turning these cells from immunoregulatory to immunostimulatory (2). In nonobese diabetic (NOD) mice, an experimental model of autoimmune diabetes, we also identified an IDO1 defect such that the DCs do not develop tolerance towards pancreatic islet autoantigens. We found that bortezomib rescues IDO1 protein expression in vitro in a particular subset of DCs, i.e. plasmacytoid DCs (pDCs) from NOD mice. When administered in vivo to prediabetic mice, the drug prevented diabetes onset through IDO1- and pDC-dependent mechanisms. Although the drug showed no therapeutic activity when administered alone to overtly diabetic mice, its combination with otherwise suboptimal dosages of autoimmune-preventive anti-CD3 antibody resulted in disease reversal in 70% diabetic mice, a therapeutic effect similarly afforded by full-dosage anti-CD3. Thus, our data indicate a potential for bortezomib in the immunotherapy of autoimmune diabetes and further underline the importance of IDO1-mediated immune regulation in such disease.

1. Fierabracci A. Proteasome inhibitors: a new perspective for treating autoimmune diseases. Current drug targets (2012) 13(13):1665-75.

2. Orabona C, Pallotta MT, Volpi C, Fallarino F, Vacca C, Bianchi R, et al. SOCS3 drives proteasomal degradation of indoleamine 2,3-dioxygenase (IDO) and antagonizes IDO-dependent tolerogenesis. Proceedings of the National Academy of Sciences of the United States of America (2008) 105(52):20828-33.