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Benefits of blocking the immunoproteasome

Kirk, Groettrup and colleagues describe a new small-molecule inhibitor that selectively blocks immunoproteasome activity and reveals a previously unappreciated role for the immunoproteasome in cytokine production. Analysis of the inhibitor in mouse models of rheumatoid arthritis provides promise that selective inhibition of the immunoproteasome could be a useful approach to treat autoimmune disorders.

The immunoproteasome is a specialized type of proteasome that is mainly found in monocytes and lymphocytes and is known to be important for generating certain peptide antigens for MHC class I presentation. The inhibitor used in this study — known as PR-957 — was identified on the basis of its potent ability to block the *in vitro* activity of the chymotrypsin-like immunoproteasome subunit low-molecular mass polypeptide 7 (LMP7; also known as PSMB8). PR-957 treatment of splenocytes from wild-type mice lowered the cell surface expression of MHC class I molecules to levels similar to those seen in splenocytes from LMP7-deficient mice. Specificity of the inhibitor was confirmed by the observation that MHC class I-restricted presentation of known LMP7-dependent epitopes from lymphocytic choriomeningitis virus and the male antigen HY was selectively decreased following exposure to PR-957 *in vitro* and *in vivo*.

> “…PR-957 inhibits cytokine production through specific inhibition of LMP7.”

CORBIS

Surprisingly, the authors observed that cytokine production by endotoxin-stimulated monocytes was also inhibited by PR-957 treatment, with specific reductions in the production of interleukin-23 (IL-23), tumour necrosis factor (TNF) and IL-6. The release of interferon-γ and IL-2 by activated T cells, as well as the differentiation of $CD4^+$ T cells into T helper 17 cells in the presence of polarizing cytokines, were also reduced following exposure to PR-957. By contrast, cytokine production was not inhibited following incubation with a selective inhibitor of the constitutive proteasome component β5 or PR-957 treatment of LMP7-deficient cells. This indicates that PR-957 inhibits cytokine production through specific inhibition of LMP7.

These observations led the authors to test whether PR-957 could ameliorate inflammatory disease. Indeed, PR-957 treatment significantly reduced disease progression in two models of rheumatoid arthritis, showing more rapid resolution of clinical symptoms and more efficacy than TNF blockade by the drug etanercept. The superior efficacy of PR-957 in treating experimental arthritis is probably a result of the pleiotropic effects of LMP7 inhibition on various cell types and cytokines.

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ORIGINAL RESEARCH PAPER Muchamuel, T. *et al.* A selective inhibitor of the immunoproteasome subunit LMP7 blocks cytokine production and attenuates progression of experimental arthritis. *Nature Med.* 14 Jun 2009 (doi:10.1038/nm.1978)