

## Ubiquitin-independent proteosomal degradation of myelin basic protein contributes to development of neurodegenerative autoimmunity

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### Abstract

© The Author(s). Recent findings indicate that the ubiquitin-proteasome system is involved in the pathogenesis of cancer as well as autoimmune and several neurodegenerative diseases, and is thus a target for novel therapeutics. One disease that is related to aberrant protein degradation is multiple sclerosis, an autoimmune disorder involving the processing and presentation of myelin autoantigens that leads to the destruction of axons. Here, we show that brain-derived proteasomes from SJL mice with experimental autoimmune encephalomyelitis (EAE) in an ubiquitin-independent manner generate significantly increased amounts of myelin basic protein peptides that induces cytotoxic lymphocytes to target mature oligodendrocytes *ex vivo*. Ten times enhanced release of immunogenic peptides by cerebral proteasomes from EAE-SJL mice is caused by a dramatic shift in the balance between constitutive and  $\beta 1^{\text{high}}$  immunoproteasomes in the CNS of SJL mice with EAE. We found that during EAE,  $\beta 1$  is increased in resident CNS cells, whereas  $\beta 5$  is imported by infiltrating lymphocytes through the blood-brain barrier. Peptidyl epoxyketone specifically inhibits brain-derived  $\beta 1^{\text{high}}$  immunoproteasomes *in vitro* ( $k_{\text{obs}}/[I] = 240 \text{ M}^{-1}\text{s}^{-1}$ ), and at a dose of 0.5 mg/kg, it ameliorates ongoing EAE *in vivo*. Therefore, our findings provide novel insights into myelin metabolism in pathophysiologic conditions and reveal that the  $\beta 1$  subunit of the immunoproteasome is a potential target to treat autoimmune neurologic diseases.

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### Keywords

Antigen presentation, Experimental autoimmune encephalomyelitis, Immunoproteasome, Multiple sclerosis, Oligodendrocytes