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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 brainderived proteasomes from SJL mice with experimental autoimmune encephalomyelitis (EAE) in an ubiquitinindependent 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 $\beta 1i^{high}$ immunoproteasomes in the CNS of SJL mice with EAE. We found that during EAE, β1i is increased in resident CNS cells, whereas β5i is imported by infiltrating lymphocytes through the blood-brain barrier. Peptidyl epoxyketone specifically inhibits brain-derived $\beta 1i^{high}$ immunoproteasomes in vitro ($kobs/[I] = 240\ M^{-1}s^{-1}$), 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 β1i 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