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Opening the core particle gate of mammalian proteasomes to enhance their degradatory activity

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The proteasome core particle (CP) has the substrate translocation channel that is topologically blocked by the N-termini of the alpha subunits when it is in the closed form. For substrate degradation, the gate of CP channels is opened upon association with the regulatory particle (RP) or other proteasome activators. Here we show that deletion of the N-terminal tails of the alpha3 subunits (alpha3deltaN) constitutively opens the CP gate of mammalian proteasomes without affecting their structural integrity. The hyperactivity of open-gated alpha3deltaN proteasomes was observed both in 20S and 26S measured by small fluorogenic peptide substrates and polyubiquitinated Sic1 (Ub-Sic1). The cells, which express alpha3deltaN proteasomes showed significantly facilitated degradation of various proteasome substrates. Delayed aggregation formation of tau proteins, and promoted cell survival against oxidative stress. These data demonstrate that the regulation of CP gate function as a rate-limiting step of proteasomal degradation and opening the CP gate may be an effective strategy to increase proteasome activity and to reduce levels of aberrantly overexpressed proteins in cells.

Biography

Min Jae Lee has earned his PhD on Pharmaceutical Sciences from University of Pittsburgh, USA and completed his Postdoctoral at the Harvard Medical School, USA. He is currently an Assistant Professor at the Seoul National University College of Medicine, Department of Biochemisty. His main interests are on the ubiquitin-proteasome system and its implication in many neurodegenerative diseases. He has published more than 35 research papers in reputed journals, including *Nature, Nature Communications, Nature Structural & Molecular Biology, and PNAS,* and has been serving as an Editorial Board Member of Scientific Reports since 2014.

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