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Opening the proteasome gate and its proteostatic consequences in the cell

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The Proteasome Core Particle (CP) is a 28 subunit cylindrical structure, the ends of which are formed by hetero-heptameric rings of alpha subunits. When in the closed form, the axial substrate translocation channel of the CP is topologically blocked by the convergent N-termini of α subunits. To probe the role of channel gating in mammalian proteasomes, we have deleted the N-terminal tail of alpha 3. The resulting alpha 3 delta N proteasomes are intact but hyperactive in the hydrolysis of fluorogenic peptide substrates. This is true of both free CP and of the 26S proteasome in the presence of ATPgammaS, representing the substrate-engaged state. Polyubiquitinated Sic1 also showed enhanced degradation by purified alpha-3 delta N proteasomes. Cells expressing the hyperactive proteasomes showed markedly elevated degradation of established proteasome substrates and multiplexed quantitative proteomics revealed ~200 proteins with reduced levels in the mutant cells. Nonetheless the mutants were viable and highly resistant to oxidative stress. Potentially toxic proteins such as tau exhibited reduced accumulation and aggregate formation. These data demonstrate that the CP gate is a key negative regulator of proteasome function in mammals and that opening the CP gate may be an effective strategy to increase proteasome activity and reduce levels of toxic proteins in cells.

Biography

Jung Hoon Lee has completed her PhD from University of Pittsburgh and Postdoctoral studies from Harvard School of Public Health. She is the Research Assistant Professor of Seoul National University College of Medicine. She has published more than 28 papers in reputed journals.

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