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Targeting Proteasome Homeostasis Mechanisms to Develop Novel Therapeutics for Solid Tumors

The 26S proteasome is a self-compartmentalized protease complex, one of whose crucial functions is protein quality control. Multiple layers of regulatory systems elaborately modulate proteasomal activity, i.e., hydrolysis of polyubiquitinated proteins. However, the mechanism of destruction of mammalian proteasomes is poorly understood. We found that inactive 26S proteasomes are concentrated into an insoluble aggresome. These proteasomes were colocalized with autophagic receptor SQSTM1/p62 in a large perinuclear inclusion body and were cleared through selective macroautophagy, linking aggresomal segregation to proteaphagic degradation. This pathway might be counterbalanced with recovery of proteasomal activity and critical for reducing cellular proteasomal stress. The amount and activity of proteasomes are also subject to structural alteration and transcriptional regulation. More specifically, glucose starvation uncouples 26S holoenzymes into 20S and 19S subcomplexes. These are cellular response mechanisms to adapt hostile environments for cell survival. Thus, 26S proteasomes are controlled by transcriptional and post-translational mechanisms, which is crucial for not only proteasome quality control and but also for developing novel anti-tumor drugs.

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