Direct Cellular Delivery of Human Proteasomes to Delay Tau Aggregation

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Abstract

The 26S proteasome, a ~2.5 MDa holoenzyme complex, is the primary machinery that degrade ubiquitin (Ub)-conjugated proteins, including many proteotoxic proteins implicated in neurodegenerative processes. It has been suggested that the elevation of proteasomal activity is tolerable to cells and may be beneficial to prevent the accumulation of protein aggregates.[3-5] Here, we show that purified proteasomes can be directly transported to cells through mesoporous silica nanoparticle-mediated endocytosis. Proteasomes were loaded onto nanoparticles through noncovalent interactions between histidine (His) tags and nickel ions, and retained their proteolytic activity when complexed with nanoparticles. Cells with exogenous proteasomes appeared to be more efficient in degrading induced full-length human tau, instead of engaging in detrimental nonspecific proteolysis, resulting in decreased levels of tau aggregates. Moreover, exogenous proteasome delivery significantly promoted cell survival against proteotoxic stress caused by overexpressed tau and reactive oxygen species (ROS). These data demonstrate that increasing cellular proteasome activity through the direct delivery of purified proteasomes may be an effective strategy to reduce cellular levels of proteotoxic proteins.