OMICS Group Conferences
Accelerating Scientific Discovery

3rd World Congress on
Cell Science & Stem Cell Research
November 20-22, 2013 DoubleTree by Hilton Baltimore-BWI Airport, MD, USA

Treatment with proteasome inhibitors induces coordinate expression of proteasome subunits and autophagy components via distinct mechanisms

Zhe Sha
Harvard Medical School, USA

Proteasome inhibition is toxic to all eukaryotic cells, especially multiple myeloma cells, and the inhibitor, bortezomib, is used worldwide to treat this cancer. Diminished proteasome function also may contribute to neurodegenerative diseases. To understand how myeloma and neuronal cells compensate for loss of proteasome function, we studied how proteasome inhibition affects the expression of proteasome subunits and autophagy genes. In both cell types, treatment with proteasome inhibitors caused induction within 4hrs of all 26S subunits, PA200, and p97 plus its cofactors, but suppression of mRNA for immunoproteasome subunits or PA28α/β. Proteasome inhibitors activate their induction by stimulating proteolytic processing of the endoplasmic reticulum-bound transcription factor Nrf1, which allows its translocation into the nucleus. Unlike other proteasome inhibitors, MG132 doesn't cause proteasome induction because it also inhibits the protease that processes Nrf1. Simultaneously, proteasome inhibition stimulates autophagy by causing dramatic induction of autophagy proteins involved in degrading poly-ubiquitinated proteins (p62, LC3B, GABARAPL1, but not others) by a distinct mechanism involving the transcription factor TFEB. Since p62, LC3B, and GABARAPL1 are consumed during autophagy, their induction enhances the capacity to degrade poly-ubiquitinated proteins. Consequently, p62 knock down increases the accumulation of poly-ubiquitinated proteins and toxicity of proteasome inhibitors. These mechanisms suggest new modes of enhancing cytotoxicity of proteasome inhibition.

Zhe_Sha@hms.harvard.edu