Ubiquitin-proteasome system

The ubiquitin-proteasome system (UPS) is a crucial cellular pathway responsible for protein degradation and regulation. It plays a vital role in maintaining protein homeostasis, controlling the levels of various proteins within the cell, and eliminating damaged, misfolded, or unnecessary proteins. The UPS is involved in numerous cellular processes, including cell cycle regulation, DNA repair, protein quality control, immune response, and signal transduction.

The UPS operates through a series of tightly regulated steps. The first step involves the covalent attachment of a small protein called ubiquitin to the target protein. This process, known as ubiquitination, is carried out by a cascade of enzymes. Initially, a ubiquitin-activating enzyme (E1) activates ubiquitin in an ATP-dependent manner. The activated ubiquitin is then transferred to a ubiquitin-conjugating enzyme (E2). Finally, a ubiquitin ligase enzyme (E3) recognizes the target protein and facilitates the transfer of ubiquitin from E2 to the target protein.

Once the target protein is tagged with a chain of ubiquitin molecules, it is recognized and degraded by the proteasome. The proteasome is a large protein complex with a barrel-shaped structure. It consists of a central catalytic core, known as the 20S proteasome, which contains proteolytic activities, and regulatory particles, such as the 19S regulatory particle. The 19S regulatory particle recognizes and binds to ubiquitin-tagged proteins, unfolds them, and translocates them into the 20S proteasome for degradation.

Within the 20S proteasome, the target protein is further degraded into smaller peptides by the proteolytic activity of the core subunits. These peptides can be recycled for the synthesis of new proteins or presented on the cell surface to the immune system for antigen presentation.

The UPS is highly regulated to ensure proper protein degradation and prevent the degradation of essential proteins. It allows cells to respond dynamically to changing conditions and maintain cellular integrity. Dysregulation of the UPS has been associated with various diseases, including cancer, neurodegenerative disorders, and autoimmune diseases. Consequently, the UPS has become an important target for therapeutic interventions, and research in this area continues to uncover its intricate mechanisms and potential therapeutic applications.

The ubiquitin-proteasome system (UPS) and autophagy are 2 major protein degradation pathways in eukaryotic cells. Liu et al. previously identified a switch from UPS to autophagy with changes in BAG3 (B-cell lymphoma 2-associated-athanogene 3) expression after cerebral ischemia in mice. BAG3 is an antiapoptotic-cochaperone that is directly involved in cellular protein quality control as a mediator for selective macroautophagy. Here, we aimed to investigate the role of BAG3 in ischemic stroke.

Methods: Middle cerebral artery occlusion/reperfusion (MCAO/R) and oxygen-glucose deprivation/reoxygenation were used to mimic cerebral ischemia in vivo and in vitro. The UPS inhibitor MG132 and autophagy inhibitor 3-MA (3-methyladenine) were administered to mice to identify how BAG3 was involved after MCAO/R. Adeno-associated virus and lentiviral vector were used to regulate BAG3 expression in vivo and in vitro, respectively. Behavioral tests, 2,3,5-triphenyltetrazolium chloride staining, and Hematoxylin & Eosin staining were performed to evaluate cerebral injury following MCAO/R, and a Cell Counting kit-8 assay was conducted to assess oxygen-glucose deprivation/reoxygenation-induced injury in cells. Brain tissues and cell lysates were collected and analyzed for UPS activation, autophagy, and apoptosis.

Results: The UPS inhibitor alleviated MCAO injury in mice and increased autophagy and BAG3 expression, whereas the autophagy inhibitor exacerbated MCAO/R-induced injury. In addition, BAG3 overexpression significantly improved neurological outcomes, reduced infarct volume in vivo, and enhanced cell survival by activating autophagy and suppressing apoptosis in vitro.

Conclusions: Our findings indicate that BAG3 overexpression activates autophagy and inhibits apoptosis to prevent cerebral ischemia/reperfusion and hypoxia/reoxygenation injury, suggesting a potential therapeutic benefit of BAG3 expression in cerebral ischemia [1)]

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Liu X, Ye Q, Huang Z, Li X, Zhang L, Liu X, Wu YC, Brockmeier U, Hermann DM, Wang YC, Ren L. BAG3 Overexpression Attenuates Ischemic Stroke Injury by Activating Autophagy and Inhibiting Apoptosis. Stroke. 2023 Jun 28. doi: 10.1161/STROKEAHA.123.041783. Epub ahead of print. PMID: 37377010.