THE IMPORTANCE OF REGULATORY UBIQUITINATION IN NEURODEGENERATIVE DISEASE

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Introduction. Dysregulation of protease activity underlies many diseases and pathological conditions, including cancer, inflammation and infection. In all tissues, the majority of intracellular proteins are degraded by the ubiquitin (Ub)–proteasome pathway (UPP). Alzheimer's disease and Parkinson's disease are the most common neurodegenerative conditions associated with the ageing process. The pathology of these and other neurodegenerative disorders, including polyglutamine diseases, is characterised by the presence of inclusion bodies in brain tissue of affected patients. In general, these inclusion bodies consist of insoluble, unfolded proteins that are commonly tagged with the small protein, ubiquitin. Covalent tagging of proteins with chains of ubiquitin generally targets them for degradation.

Aim. Carry out an analytical review of the role of Protein Degradation by the Ubiquitin–Proteasome Pathway in the development of neurodegenerative diseases.

Materials and methods. Data analysis of literature and Internet sources.

Results and discussion. The ubiquitin/proteasome system (UPS) is the major route through which intracellular proteolysis is regulated. This strongly implicates the UPS in these disease-associated inclusions, either due to malfunction (of specific UPS components) or overload of the system (due to aggregation of unfolded/mutant proteins), resulting in subsequent cellular toxicity. Protein targeting for degradation is a highly regulated process. It relies on transfer of ubiquitin molecules to the target protein via an enzyme cascade and specific recognition of a substrate protein by ubiquitin-protein ligases (E3s). The discovery that parkin, mutations in which are found in at least 50% of patients with autosomal recessive juvenile parkinsonism, is an E3 further highlights the importance of the UPS in neurological disease. To date, parkin is the only E3 confirmed to have a direct causal role in neurodegenerative disorders. However, a number of other (putative) E3s have now been identified that may cause disease directly or interact with neurological disease-associated proteins. Many of these are either lost or mutated in a given disease or fail to process disease-associated mutant proteins correctly.

Conclusions. The study may be helpful in drug discovery and its application to alleviate the neurodegenerative disorders. However, detailed molecular mechanisms and its precise roles in neurodegenerative diseases remain to be defined.