Abstract

Cellular homeostasis is a balance of several factors that keeps a cell healthy. It is a tightly regulated process involving; control of the rate of cell proliferation, modulation of cell differentiation and also regulation of the rate of cell death. In this study we focus on two different facets by which cellular homeostasis can be maintained. First is the clearance of apoptotic cells and the second involves clearance of intracellular misfolded protein aggregates.

Rapid clearance of apoptotic cells by phagocytes is crucial for organogenesis, tissue homeostasis and resolution of inflammation. Apoptotic cells expose certain ligands or *'eat me'* signals for their clearance. Among the several candidates reported, phosphatidylserine (PS) is the best recognized general recognition ligand till date. Several recent studies have however shown that phosphatidylserine exposure on cells is by itself not sufficient for effective removal of apoptotic cells. In this study we have identified GAPDH (Glyceraldehyde 3-phosphate dehydrogenase) as an *'eat me'* signal on apoptotic cell surface. Increased GAPDH on surface of apoptotic cells was found to interact with phagocytic receptor CD14 present on plasma membrane on phagocytes leading to their engulfment. This is the first study demonstrating the novel interaction between multifunctional GAPDH and the phagocytic receptor CD14 and its role in apoptotic cell clearance (efferocytosis). These findings provide a novel insight in understanding the unidentified mechanism of efferocytosis involving GAPDH. By studying the molecular mechanism of apoptotic cell clearance via GAPDH we hope to provide a new approach in understanding the inflammatory diseases associated with efferocytosis.

In order to maintain cellular protein homeostasis (proteostasis), eukaryotic cells must continuously synthesize new proteins, as well as eliminate unwanted and misfolded proteins. Accumulation of protein aggregates is a pathological hallmark of several neurodegenerative disorders. Autophagy has proven to be important for degradation of aggregate-prone proteins in neurodegenerative diseases like Huntington, Parkinson, Alzheimer's etc. In this study we have identified the novel role of the multifunctional glycolytic enzyme Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in clearance of

huntingtin mutant protein aggregates by autophagy. In the current study we have demonstrated that mutant huntingtin expressing cells, wherein GAPDH has been knocked down, have lowered levels of autophagy. We also observed that GAPDH regulates autophagy by the mTOR pathway. We have observed larger and more huntingtin protein aggregates in GAPDH knockdown cells as compared to empty vector control cells. This correlates with the decreased autophagy induction which is observed in GAPDH knockdown cells.

Our studies demonstrate that GAPDH assists in the clearance of protein aggregates by inducing autophagy. These findings provide a novel insight towards understanding the unidentified mechanism by which huntingtin aggregates are cleared inside cells. By studying the molecular mechanism of protein aggregate clearance via GAPDH we hope to provide a new approach in targeting and understanding several neurodegenerative disorders.