Prion diseases are infectious and fatal neurodegenerative disorders of man and animals which are characterized by spongiform degeneration in the central nervous system. Prion propagation involves the endocytic pathway and endosomal and lysosomal compartments are implicated in trafficking and re-cycling as well as final degradation of prions. Shifting the equilibrium between propagation and lysosomal clearance to the latter impairs cellular prion load. This and earlier findings of autophagic vacuoles in correlation to prion infections both in in vitro and in vivo studies prompted us and others to analyze the role of autophagy in prion infection. Autophagy is a fundamental cellular bulk degradation process for e.g. organelles or cytoplasmic proteins which has many implications for physiology and pathophysiology of cells and whole organisms. In various neurodegenerative disease models mainly protective functions of autophagy were recently described. In this review, we focus on recent findings which correlate autophagy and its manipulations with prion infection scenarios, and discuss perspectives and future directions. The findings summarized here add to the knowledge of the role of autophagy in neurodegeneration and provide interesting new insight into how non-cytosolic aggregated proteins might be subjected to autophagic clearance.