Prion diseases are fatal neurodegenerative and infectious disorders for which no therapeutic or prophylactic regimens exist. In search of cellular mechanisms that play a role in prion diseases and have the potential to interfere with accumulation of intracellular pathological prion protein (PrP(Sc)), we investigated the autophagic pathway and one of its recently published inducers, trehalose. Trehalose, an alpha-linked disaccharide, has been shown to accelerate clearance of mutant huntingtin and alpha-synuclein by activating autophagy, mainly in an mTOR-independent manner. Here, we demonstrate that trehalose can significantly reduce PrP(Sc) in a dose- and time-dependent manner while at the same time it induces autophagy in persistently prion-infected neuronal cells. Inhibition of autophagy, either pharmacologically by known autophagy inhibitors like 3-methyladenine, or genetically by siRNA targeting Atg5, counteracted the anti-prion effect of trehalose. Hence, we provide direct experimental evidence that induction of autophagy mediates enhanced cellular degradation of prions. Similar results were obtained with rapamycin, a known inducer of autophagy, and imatinib, which has been shown to activate autophagosome formation. While induction of autophagy resulted in reduction of PrP(Sc), inhibition of autophagy increased the amounts of cellular PrP(Sc), suggesting that autophagy is involved in the
physiological degradation process of cellular PrP(Sc). Preliminary in vivo studies with trehalose in intraperitoneally prion-infected mice did not result in prolongation of incubation times, but demonstrated delayed appearance of PrP(Sc) in the spleen. Overall, our study provides the first experimental evidence for the impact of autophagy in yet another type of neurodegenerative disease, namely prion disease.