

Prion protein (PrP<sup>C</sup>) modulates many cellular functions including the secretion of trophic factors by astrocytes. Some of these factors are found in exosomes, which are formed within multivesicular bodies (MVBs) and secreted into the extracellular space to modulate cell-cell communication. The mechanisms underlying exosome biogenesis and release remain unclear. Here, we demonstrate that primary astrocytes and fibroblasts from PrP<sup>C</sup>-null mice secreted lower levels of exosomes than wild-type cells. The reconstitution of PrP<sup>C</sup> expression at the cell membrane restored exosome secretion in PrP<sup>C</sup>-deficient astrocytes. PrP<sup>C</sup>-null astrocytes exhibited reduced MVB formation and increased autophagosome formation, whereas autophagy inhibition via Beclin-1 depletion restored exosome release. Moreover, the PrP<sup>C</sup> octapeptide repeat domain was necessary to promote exosome secretion and to impair the formation of the caveolin-1-dependent ATG12-ATG5 cytoplasmic complex that drives autophagy induction. Accordingly, higher levels of caveolin-1 were found in lipid raft domains. These findings demonstrate that PrP<sup>C</sup> supports caveolin-1-suppressed autophagy to protect MVBs from sequestration to autophagosomes and thus facilitate exosome secretion.