

**Online Resource 4.** Endogenous PrP<sup>C</sup> cleavage profiles in N2a cells used for PrP-Myc transient transfections in Figure 3A. Whole cell lysates from naïve N2a cells, either untreated (-) or digested (+) with PNGaseF prior to PAGE and western blotting with the various anti-PrP antibodies as indicated. Results reveal these N2a cells undergo extensive endoproteolytic processing, in particular  $\beta$ -cleavage as indicated by the large amount of C2 detected. Under normal conditions, these N2a cells express proportionately very little full-length (un-cleaved) PrP<sup>C</sup> species.

