Mouse models for proteasome insufficiency: tools in the study of neurodegenerative disease

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Intracellular accumulation of misfolded or aberrant proteins is a common characteristic of many neurodegenerative diseases, indicating a loss of protein quality control. For instance, in Alzheimer's disease tau accumulates to form tangles, in Huntington's disease polyglutamine repeats accumulate in intranuclear neuronal aggregates, and in Parkinson's disease alpha-synuclein forms Lewy bodies. A reduction in the activity of the ubiquitin-proteasome system concomitant with the accumulation of these proteins has been reported. We hypothesize that failure of the ubiquitin-proteasome system underlies the accumulation of aberrant proteins in neurodegenerative disease, but also that some of these proteins may clog the proteasome themselves.
UBB+1 is an aberrant form of ubiquitin, which accumulates in many neurodegenerative diseases (Fischer *et al*. 2003, FASEB J 17:2014-24). UBB+1 is very efficiently targeted to the proteasome and degraded, but at higher levels it can inhibit the ubiquitin-proteasome system.
We have generated several UBB+1 transgenic mouse lines which can be used either to 1) measure the effects of aberrant proteins on the ubiquitin-proteasome system, or to 2) create long-term ubiquitin-proteasome insufficiency in the brain. These lines are valuable tools in the study of neurodegenerative disease.

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