UBB+1 transgenic mice: a novel in vivo model for proteasome research?

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Di-nucleotide deletions in the transcript for Ubiquitin B (UBB) lead to translation of this protein with an aberrant C-terminus, named UBB+1. In the human brain, UBB+1 accumulates in the neuropathological hallmarks of several neurodegenerative diseases, including Alzheimer's disease and Pick disease. The UBB+1 protein has two opposing activities; from in vitro experiments we know that UBB+1 is a substrate as well as an inhibitor of the 26S proteasome. In neuroblastoma cell lines, high UBB+1 expression eventually leads to apoptosis.
In vivo, the UBB+1 protein is rapidly degraded under non-pathological conditions. In rat and mouse hippocampus, lenti-virally delivered UBB+1 is degraded, whereas an undegradable form of UBB+1 accumulates. UBB+1 transcripts are expressed in neurological controls as well as demented subjects, the protein however only accumulates in pathological conditions in a subset of neurodegenerative diseases. As UBB+1 is normally targeted to the proteasome and degraded, this accumulation is an indication of proteasomal malfunctioning.
One of the goals of the present study is to find the exact mechanism by which UBB+1 accumulation is triggered in vivo. We have developed several mouse lines that postnatally express the UBB+1 transgene, including high- and low-expression lines for UBB+1 under the neuronal CaMKIIα or the Thy-1.2 promoter. In the high expression lines, the UBB+1 protein mainly accumulates in cortical and hippocampal neurons. Our results indicate that in these mice there is a significant inhibition of the of the 26S proteasome. These high expression lines can be used as a new mouse model for sustained proteasome insufficiency. In the low expression line, UBB+1 is mostly degraded and accumulates after inhibition of the proteasome. Thus the low-expression lines can be used as a reporter model in which the accumulation of UBB+1 functions as a marker for proteasome (dis-)functioning.

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