HYDROLYSIS OF THE MUTANT UBIQUITIN (UBB\textsuperscript{+1}) ASSOCIATED WITH NEURODEGENERATIVE DISORDERS BY UCH-L3

F. Dennissen\textsuperscript{1}, N. Kholod\textsuperscript{1}, H. Steinbusch\textsuperscript{1}, N. Dantuma\textsuperscript{2}, F. van Leeuwen\textsuperscript{1}

\textsuperscript{1}Neuroscience, Faculty for Health Medicine and Life Sciences (FHML), Maastricht University, Maastricht, The Netherlands, \textsuperscript{2}Cell and Molecular Biology (CMB), Karolinska Institutet, Stockholm, Sweden

Introduction: The mutant ubiquitin UBB\textsuperscript{+1} accumulates selectively in the hallmarks of tauopathies and polyglutamine diseases. UBB\textsuperscript{+1} lacks the C-terminal glycine of ubiquitin and has 20 amino acids added to its C-terminus. As a result, UBB\textsuperscript{+1} cannot be used for ubiquitination and impairs the ubiquitin-proteasome system (UPS). Furthermore, ubiquitinated UBB\textsuperscript{+1} is refractory to deubiquitination by isopeptidase T. Studies in yeast and human cells showed that expression of UBB\textsuperscript{+1} gives rise to an additional truncated product that corresponds in size with ubiquitin (FASEB J. 23, 123-33, 2009).

Aims: To identify the peptidase responsible for the C-terminal truncation of UBB\textsuperscript{+1}.

Methods: We performed a systematic screen with 175 yeast deletion strains. All strains were transformed to express \textsuperscript{myc}UBB\textsuperscript{+1}. Candidate genes from mouse and human were cloned from cDNA and co-transfected with \textsuperscript{myc}UBB\textsuperscript{+1} in HEK293 cells. Truncation of \textsuperscript{myc}UBB\textsuperscript{+1} was determined by immunoblotting using anti-myc antibodies.

Results: For yeast, we found the deubiquitylation enzyme YUH1 to be responsible for hydrolysis of the C-terminal extension of UBB\textsuperscript{+1}. Human and mouse homologue of YUH1, UCH-L3, were also able to hydrolyse the C-terminus of UBB\textsuperscript{+1}.

Conclusions: Human and mouse UCH-L3 are able to hydrolyse the C-terminal extension of UBB\textsuperscript{+1}. Hydrolysis of UBB\textsuperscript{+1}'s C-terminal tail prevents detection with the antibodies specific for this extension. Consequently, we hypothesize that full length UBB\textsuperscript{+1} is a marker for UCH-L3 dysfunction and that this is a common factor in tauopathies and polyglutamine diseases but not in synucleinopathies.