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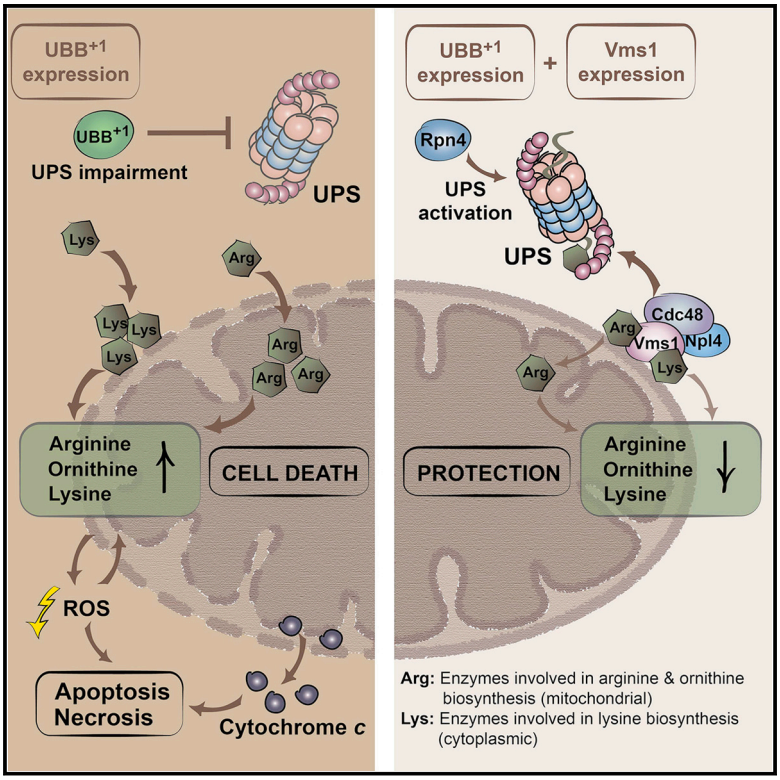
Cell Reports

Accumulation of Basic Amino Acids at Mitochondria Dictates the Cytotoxicity of Aberrant Ubiquitin

Graphical Abstract



Highlights

- UBB^{+1} co-exists with the UPS component VMS1 in neurofibrillary tangles
- UBB^{+1} accumulation impairs the UPS and mitochondria, triggering cell death
- UBB^{+1} causes accumulation of basic amino acids at mitochondria
- Vms1 reverts UBB^{+1}-triggered basic amino acid accumulation and cell death

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In Brief

Braun et al. demonstrate that basic amino acid accumulation at mitochondria is a decisive toxic event upon cellular accumulation of UBB^{+1}, an Alzheimer's-disease-associated ubiquitin variant. Triggering the mitochondrion-specific branch of the ubiquitin-proteasome system is sufficient to prevent UBB^{+1}-triggered cytotoxicity, which has potentially far-reaching pathophysiological implications.

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Accumulation of Basic Amino Acids at Mitochondria Dictates the Cytotoxicity of Aberrant Ubiquitin

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SUMMARY

Neuronal accumulation of UBB^{+1}, a frameshift variant of ubiquitin B, is a hallmark of Alzheimer's disease (AD). How UBB^{+1} contributes to neuronal dysfunction remains elusive. Here, we show that in brain regions of AD patients with neurofibrillary tangles UBB^{+1} co-exists with VMS1, the mitochondrion-specific component of the ubiquitin-proteasome system (UPS). Expression of UBB^{+1} in yeast disturbs the UPS, leading to mitochondrial stress and apoptosis. Inhibiting UPS activity exacerbates while stimulating UPS by the transcription activator Rpn4 reduces UBB^{+1}-triggered cytotoxicity. High levels of the Rpn4 target protein Cdc48 and its cofactor Vms1 are sufficient to relieve programmed cell death. We identified the UBB^{+1}-induced enhancement of the basic amino acids arginine, ornithine, and lysine at mitochondria as a decisive toxic event, which can be reversed by Cdc48/Vms1-mediated proteolysis. The fact that AD-induced cellular dysfunctions can be avoided by UPS activity at mitochondria has potentially far-reaching pathophysiological implications.

INTRODUCTION

UBB^{+1}, a loss-of-function variant of ubiquitin B (UBB), accumulates in neurofibrillary tangles, a pathological hallmark in Alzheimer's disease (AD) (van Leeuwen et al., 1998). UBB^{+1} is translated from an aberrant mRNA encoding a +1 frameshift protein in which the C-terminal glycine residue required for ubiquitylation is replaced by an extension of 20 amino acids (Dennissen et al., 2010). The detrimental impact of UBB^{+1} has been studied in neuronal cell cultures, transgenic mice, and yeast (De Vrij et al., 2001; Fischer et al., 2009; Tank and True, 2009). UBB^{+1} is a substrate for truncation, ubiquitylation, and proteasomal degradation (Dennissen et al., 2011; Lindsten et al., 2002; van Tijn et al., 2007, 2010). Whereas the ubiquitin-proteasome system (UPS) can assure the degradation of low levels of UBB^{+1}, higher levels impair the UPS and subvert the homeostatic mechanisms allowing for its elimination (Fischer et al., 2009; Lindsten et al., 2002; van Tijn et al., 2007, 2010). At high levels, UBB^{+1} affects mitochondrial dynamics and triggers neuronal cell death (De Vrij et al., 2001; Tan et al., 2007) through as-yet elusive mechanisms.

Yeast is an established model for studying programmed cell death mechanisms that are often shared with animal cells, including the contribution of caspases and mitochondrion-associated cell death proteins, such as cytochrome *c* (Carmona-Gutierrez et al., 2010). Yeast models have been used to explore cell killing by neurotoxic proteins, such as Parkinson-disease-associated α-synuclein, and the outcome could be successfully translated to fly, worm, and murine disease models, as well as to human disease (Braun et al., 2010; Büttner et al., 2013).

Driven by these premises, we established a yeast cell death model for UBB^{+1}-triggered neurotoxicity. Our findings revealed that UBB^{+1} interfered with the UPS and triggered the perturbation of the mitochondrion-associated basic amino acid synthesis executing cell death. The mitochondrion-associated UPS subroutine, depending on the AAA-ATPase Cdc48 and its co-factor Vms1, strongly antagonized UBB^{+1} cytotoxicity. Since VMS1,