Angelman syndrome protein Ube3a regulates synaptic growth and endocytosis by inhibiting bone morphogenetic protein signaling *in Drosophila*

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Short title: Ube3a regulates synapse development by inhibiting BMP signaling

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Abstract

Altered expression of the E3 ubiquitin ligase UBE3A, which is involved in protein degradation through the proteasome-mediated pathway, is associated with neurodevelopmental and behavioral defects observed in Angelman syndrome (AS) and autism. However, little is known about the neuronal function of UBE3A and the pathogenesis of UBE3A-associated disorders. To understand the *in vivo* function of UBE3A in the nervous system, we generated multiple mutations of *ube3a*, the *Drosophila* ortholog of *UBE3A*. We found a significantly increased number of total boutons and satellite boutons in conjunction with compromised endocytosis in the neuromuscular junctions (NMJs) of *ube3a* mutants compared to the wild type. Genetic and biochemical analysis showed an upregulation of bone morphogenetic protein (BMP) signaling in the nervous system of *ube3a* mutants. An immunochemical study revealed a specific increase in the protein level of Thickveins (Tkv), a type I BMP receptor, but not other BMP receptors Wishful thinking (Wit) and Saxophone (Sax), in *ube3a* mutants. Ube3a was associated with and specifically ubiquitinated lysine 227 within the cytoplasmic tail of Tkv, and promoted its proteasomal degradation in Schneider 2 cells. Negative regulation of Tkv by Ube3a was conserved in mammalian cells. These results reveal a critical role for Ube3a in regulating NMJ synapse development by repressing BMP signaling. This study sheds new light onto the neuronal functions of UBE3A and provides novel perspectives for understanding the pathogenesis of UBE3A-associated disorders.