Role of endo-lysosomal ion channel TRPML3 in autophagy, neural development, and neurodegeneration

Abstract

Autophagy is an evolutionarily conserved process that involves regulated sorting and degradation of various cellular cargo via the endo-lysosomal system. In neurons, autophagy plays central roles in their homeostasis, survival, and development, with its dysregulation highly implicated in the pathology of neurodegenerative diseases. Transient Receptor Potential Mucolipin-3 (TRPML3) is an endo-lysosomal Ca+2 channel largely implicated in the mechanisms of autophagy and vesicular trafficking. TRPML3 has been reported to promote autophagy in cell-line models. However, its impact on the overall gene expression patterns, both before and during autophagy induction, is not clearly understood. Further, the expression and roles of TRPML3 in developing brain and neurodegenerative diseases have been unexplored. Using chicken embryo model, we present the first evidence of TRPML3 expression in the proliferative and expanding zones of developing brain, and in specific neurons of mature brain. Ectopic modulation of TRPML3 caused impaired development and lethality in chicken embryos. In an *in vitro* serum-starvation model, we show that TRPML3 promoted autophagy and remarkably suppressed neurodevelopmental markers, likely mediated by the transcription factors SOX2, TFEB, and FOXO1. Finally, by meta-analysis of public RNA-seq data, we identify TRPML3 as a key marker (among 40 ion channel genes investigated) in diverse familial neurodegenerative diseases, based on the underlying status of autophagy. Basically, we uncovered exciting and novel physiological roles of TRPML3 in neural development and neurodegenerative diseases via autophagy.