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# "A negative feedback regulation of MTORC1 activity by the lysosomal Ca2+ channel MCOLN1/mucolipin-1 in cellular homeostasis and human diseases"

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**Date :** 12 November 2018
**Time:** 11:00am to 12:30pm
**Venue:** Meeting Room 2-130, 1/F, Block 2, To Yuen Building

## Abstract

Autophagy is an evolutionarily conserved pathway that is required for cellular homeostasis, growth and survival. The lysosome plays an essential role in autophagy regulation. For example, the activity of MTORC1, a master regulator of autophagy, is regulated by nutrients within the lysosome. Starvation inhibits MTORC1 causing autophagy induction. Given that MTORC1 is critical for protein synthesis and cellular homeostasis, a feedback regulatory mechanism must exist to restore MTORC1 during starvation. In this study, we report that starvation activates the lysosomal Ca2+ release channel MCOLN1/mucolipin-1 by relieving MTORC1's inhibition of the channel. Activated MCOLN1 in turn facilitates MTORC1 activity that requires calmodulin. Our data suggest that lysosomal Ca2+ signaling is an essential component of the canonical MTORC1-dependent autophagy pathway and MCOLN1 provides a negative feedback regulation of MTORC1 to prevent MTORC1 from excess reduction during starvation. The feedback regulation may be important for maintaining cellular homeostasis during starvation, as well as many other stressful or disease conditions, such as sustained exercise, infection, lysosomal storage diseases, neurodegenerative diseases and cancer. In particularly, we have demonstrated that MCOLN1 promotes tumor development both in vitro and in vivo by maintaining MTORC1 activity. Because MCOLN1 is only activated by cellular stress which are prone to exist in tumor microenvironments, antagonists of MCOLN1 could represent anticancer drugs with more specificity and potency.

## Biography

Professor Dong's research interests include lysosome physiology and lysosome-related diseases. His primary interests are lysosomal ion channels and transporters. Investigation of these lysosomal channels and transporters will facilitate our understanding of the pathogenic mechanisms of many lysosomal storage diseases as well as neurodegenerative diseases.

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All are welcome!