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The symphony of autophagy and calcium signaling

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Posttranslational regulation of macroautophagy (hereafter autophagy), including phosphorylating and dephosphorylating components of the autophagy-related (Atg) core machinery and the corresponding upstream transcriptional factors, is important for the precise modulation of autophagy levels. Several kinases that are involved in phosphorylating autophagy-related proteins have been identified in both yeast and mammalian cells. However, there has been much less research published with regard to the identification of the complementary phosphatases that function in autophagy. A recent study identified PPP3/calcineurin, a calcium-dependent phosphatase, as a regulator of autophagy, and demonstrated that one of the key targets of PPP3/calcineurin is TFEB, a master transcriptional factor that controls autophagy and lysosomal function in mammalian cells.

Previous studies indicated that phosphorylated TFEB is trapped in the cytosol and remains inactive in nutrient-rich conditions, whereas the dephosphorylated protein translocates to the nucleus during starvation.[1,2] In the paper by Medina et al. the authors started with a phosphatase screen using an siRNA library,[3] and identified PPP3/calcineurin as a candidate phosphatase that regulates the cytosol-to-nuclear-shuttling of TFEB (see the Commentary in this issue of the journal). Inhibition of PPP3/calcineurin results in decreased nuclear localization of TFEB in starvation conditions. Conversely, constitutively active PPP3/calcineurin induces TFEB translocation in fed cells. Both coimmuprecipitation and a proximity ligation assay demonstrate an interaction between the 2 proteins. In addition, PPP3/calcineurin dephosphorylates Ser142 and Ser211 of immunoprecipitated TFEB. Previous work indicated that Ser211 of TFEB is phosphorylated by MTOR, resulting in TFEB cytoplasmic localization.[2] Thus, the study by Medina et al. connects MTOR-dependent regulation of TFEB translocation into the nucleus with PPP3/calcineurin-dependent activation of autophagy.

Considering that PPP3/calcineurin is a calcium-dependent phosphatase, the authors next focused on the role of calcium signaling in the regulation of TFEB. The chelation of Ca^{2+} leads to decreased TFEB nuclear translocation, whereas elevation of intracellular Ca^{2+} causes an increase in the nuclear pool of TFEB. Moreover, dephosphorylation of Ser142 and Ser211 of TFEB is seen with an increase in the level of intracellular Ca^{2+}, suggesting that Ca^{2+} regulates the TFEB phosphorylation status through the activation of PPP3/calcineurin. Next, the authors sought to identify the source of this Ca^{2+}. After excluding a role for other organelles and plasma membrane Ca^{2+} channels, they postulated that the lysosome might be responsible for modulating the Ca^{2+} signal. Accordingly, they linked a Ca^{2+} sensor to MCOLN1, a lysosomal calcium channel located on the lysosomal surface. The calcium imaging results showed a transient elevation of the Ca^{2+} signal after starvation that was sensitive to lysosomal Ca^{2+}-depletion, indicating that the lysosome releases a Ca^{2+} pulse through MCOLN1. Furthermore, MCOLN1 inhibition reduces the nuclear translocation of TFEB, whereas overexpression of MCOLN1 has the opposite effect. These results suggest that the Ca^{2+} signal released from the lysosome is the source that activates TFEB translocation.

Finally, the authors tested whether the expression level of PPP3/calcineurin and MCOLN1 affect autophagy. A transcriptome analysis indicated a general reduction in lysosomal and autophagy gene expression in cells that do not express the essential regulatory subunit of PPP3/calcineurin, PPP3R1. In addition, the PPP3R1-depleted cells show a reduced LC3-II level after starvation, indicating that the induction of autophagy is repressed. Conversely, overexpression of PPP3/calcineurin or MCOLN1 increases LC3-II levels in a TFEB-dependent manner.

Thus, the authors identified PPP3/calcineurin as a novel phosphatase involved in autophagy regulation, adding to our understanding of the regulatory network involving TFEB. Moreover, they established the MCOLN1-Ca^{2+}-PPP3/calcineurin-TFEB pathway, bridging autophagy and calcium signaling. This work elucidates details of autophagy regulation as well as providing insights into

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the crosstalk of different signaling pathways. Although this paper reveals the mechanism of TFEB dephosphorylation, most phosphatases that are responsible for modifying the Atg/ATG core machinery remain unclear. More research aimed at identifying phosphatases and uncovering their role in autophagy regulation will help elucidate the complex regulatory network that controls this process.

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