SEMINAR

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Mechanism of growth factor deprivation-induced autophagy

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Different from unicellular organisms, metazoan cells require the presence of extracellular growth factors to utilize environmental nutrients. However, the underlying mechanism was unclear. We have delineated a pathway, in which glycogen synthase kinase 3 (GSK3) in cells deprived of growth factors phosphorylates and activates the acetyltransferase TIP60, which in turn stimulates the protein kinase ULK1 to elicit autophagy. Cells with the Tip60 gene replaced with TIP60S86A that cannot be phosphorylated by GSK3 are resistant to serum starvation-induced autophagy. Acetylation sites on ULK1 were mapped to K162 and K606, and the acetylation-defective mutant ULK1K162,606R displays reduced kinase activity and fails to rescue autophagy in Ulk1-/- mouse embryonic fibroblasts, indicating that acetylation is vital to the activation of ULK1. The GSK3-TIP60-ULK1 cascade seems to be specific for cells to sense growth factors, as TIP60 phosphorylation is not enhanced under glucose deprivation. Thus, the growth factor deprivation response pathway is perhaps unique to metazoan organisms, and the glucose starvation-autophagy pathway is conserved in all eukaryotic organisms.

Artwork by Ann Nee, DBS, NUS