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Cross-talk between apoptosis and autophagy: the role of suppressed translation

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Macroautophagy/autophagy inhibition under stress conditions is often associated with increased cell death. Recent data demonstrate a transcriptional regulation of several autophagy genes as a mechanism that controls autophagy in response to starvation. We found that despite the significant upregulation of mRNA of the essential autophagy initiation gene *ULK1*, its protein level is rapidly reduced under starvation. Although both autophagic and proteasomal systems contribute to the degradation of ULK1, under prolonged nitrogen deprivation, its level was still reduced in *ATG*7 knockout cells, and only initially stabilized in cells treated with the lysosomal or proteasomal inhibitors. Under starvation, protein translation is rapidly diminished and, similar to treatments with the proteosynthesis inhibitors, is associated with a significant reduction of ULK1. Inhibiting the mitochondrial respiratory complexes or the mitochondrial ATP synthase leads to upregulation of the ULK1 mRNA and protein expression in an AMPK-dependent manner. These inhibitors could also drastically increase the ULK1 protein in lung adenocarcinoma cells (LACC) with knockout of the *ATG13*, where the ULK1 expression is significantly diminished. We also found that under nutrient limitation, activation of caspase-8 was significantly increased in autophagy-deficient lung cancer cells, which precedes mitochondria outer membrane permeabilization, cytochrome *c* release, and activation of caspase-9, indicating that under such conditions the activation of caspase-8 is a primary event in the initiation of apoptosis as well as essential to reduce clonogenic survival of autophagy-deficient cells. As expected overexpression of inhibitor of FLICE reduces caspase-8 activation and apoptosis during starvation, while its silencing promotes efficient activation of caspase-8 and apoptosis in autophagy-deficient LACC even under nutrient-rich conditions. Similar to starvation, inhibition of protein translation leads to efficient activation of caspase-8 and cell death in autophagy-deficient LACC. Thus, here for the first time we report that suppressed translation leads to activation of caspase-8-dependent apoptosis in autophagy-deficient LACC under conditions of nutrient limitation. Our data suggest that targeting translational machinery can be beneficial for elimination of autophagy-deficient cells via the caspase-8-dependent apoptotic pathway.
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