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Titel des Beitrags: Regulation of autophagy by ATF4 in response to severe hypoxia.

Abstract: Activating transcription factor 4 (ATF4) is a transcription factor induced under severe hypoxia and a component of the PERK pathway involved in the unfolded protein response (UPR), a process that protects cells from the negative consequences of endoplasmic reticulum (ER) stress. In this study, we have used small interfering RNA (siRNA) and microarray analysis to provide the first whole-genome analysis of genes regulated by ATF4 in cancer cells in response to severe and prolonged hypoxic stress. We show that ATF4 is required for ER stress and hypoxia-induced expansion of autophagy. MAP1LC3B (LC3B) is a key component of the autophagosomal membrane, and in this study we demonstrate that ATF4 facilitates autophagy through direct binding to a cyclic AMP response element binding site in the LC3B promoter, resulting in LC3B upregulation. Previously, we have shown that Bortezomib-induced ATF4 stabilization, which then upregulated LC3B expression and had a critical role in activating autophagy, protecting cells from Bortezomib-induced cell death. We also showed that severe hypoxia stabilizes ATF4. In this study, we demonstrate that severe hypoxia leads to ER stress and induces ATF4-dependent autophagy through LC3 as a survival mechanism. In summary, we show that ATF4 has a key role in the regulation of autophagy in response to ER stress and provide a direct mechanistic link between the
UPR and the autophagic machinery.

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