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Autophagic Punctum

Curbing autophagy and histone deacetylases to kill cancer cells

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Abstract

Cells respond to cytotoxicity by activating a variety of signal transduction pathways. One pathway frequently upregulated during cytotoxic response is macroautophagy (hereafter referred to as autophagy). Previously, we demonstrated that pan-histone deacetyl… hydroxamic acid (SA… HDAC inhibitio… phagic kinase U… poptotic and non… otential of auto… ed a series of qu… ual HDACs have dis… sensing kinase M… autophagy, what the… Tackling these qu… DAC biology and contribute to the development of novel therapeutic strategies.

Keywords: : HDAC inhibitors autophagy apoptosis nonapoptotic cell death MTOR ULK1 SAHA

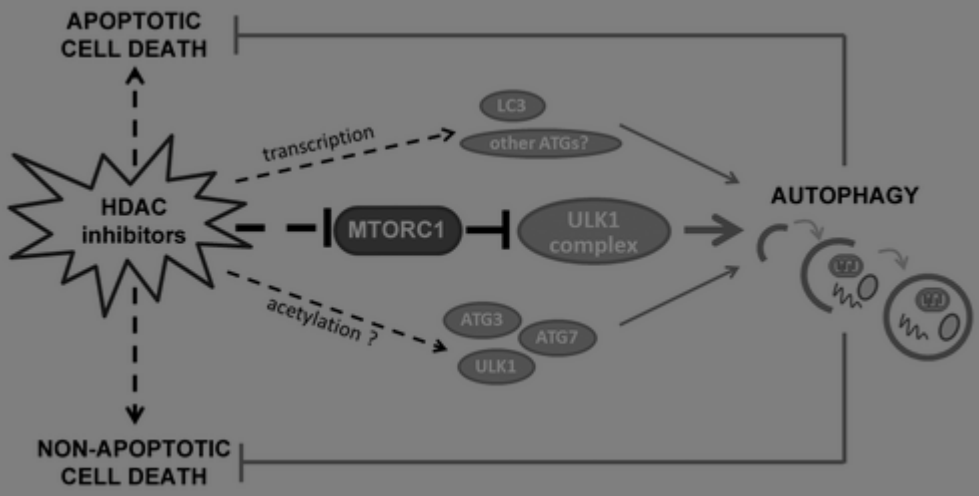
This article refers to:

HDAC expression is deregulated in a wide range of human cancer types. Targeting HDAC activity can impose antitumor effects, possibly through both chromatin-dependent and -independent mechanisms. Previous work by us and others demonstrates that HDAC inhibitors, including SAHA, can induce transcriptional upregulation of multiple genes that function to promote growth arrest or apoptosis, and downregulation of genes that may serve to facilitate cancer development. HDAC inhibitors can also enhance acetylation of various nonhistone proteins, and many of these proteins are involved in fundamental cellular processes whose malfunction can have an impact on tumorigenesis.

In addition to the induction of cell death preferentially in transformed cells, we found that HDAC inhibitors can also induce autophagy, a cellular catabolic process highly implicated in cancer development and treatment (Fig. 1). Our recent study shows that SAHA does so by suppressing the MTOR complex 1 (MTORC1), a master regulator of cellular metabolism and a therapeutic target for anticancer treatment. MTOR suppresses autophagy by phosphorylating and inactivating the ULK1 complex, an upstream component of the autophagy pathway. MTOR inactivation by SAHA restores the function of the ULK1 complex and thereby induces autophagy. This highlights the importa aling to induce a deficient in ULK1 ex AHA inactivat ed an effect of SAHA regulators of MTOR, t ating the acet like MTOR or its regu egulated by SAHA. W er fuel autopha

Figure 1. can induce autophagy by inactivating MTORC1 and consequently activating the upstream

component of the autophagy pathway, the ULK1 complex. Additionally, HDAC inhibition can also lead to the transcriptional upregulation of LC3, and possibly enhanced acetylation of autophagy proteins, such as ULK1, ATG3 and ATG7. These events may further augment autophagy once autophagy is activated through the ULK1 complex. Autophagy in turn plays a survival role in attenuating both apoptotic and nonapoptotic cell death induced by HDAC inhibitors.



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Intriguingly, the recent findings that acetylation of a number of autophagy-related (Atg) gene products, such as ULK1 and ATG3, can potentiate autophagy, have provided further mechanistic insights into the role of HDACs and HDAC inhibitors in autophagy. Presumably, by deacetylating these ATG proteins, HDACs can function as negative modulators of autophagy, consistent with the role of HDAC inhibitors in promoting autophagy. Importantly, because ULK1 and ATG3 are cytosolic proteins, their deacetyl ACs can shuttle b to be a strictly c Furtherm idual HDACs play dist eins might utilize th ent HDACs migh d for autopha maged mitocho HDACs in autopha ologically, or by RNAi

The obvious therapeutically relevant question is: Since HDAC inhibitors can trigger autophagy, what is the role of autophagy in HDAC inhibitor-induced cancer cell death? In our assays, HDAC inhibitors can induce robust caspase activity and apoptotic cell death in various cancer cells, including glioblastoma cells, which are resistant to multiple anticancer agents. We examined the effect of autophagy on SAHA-induced apoptosis in these malignant cells. Because specific inhibitors against autophagy are presently not available and all the currently used inhibitors affect both autophagy and endocytosis, we used an RNAi approach to tackle this question. Caspase activation and cell death are greatly increased when autophagy is impeded by RNAi. Because autophagy is a major survival mechanism upon stress, this result is not a surprise. However, mechanistically, how exactly autophagy protects cells from apoptosis (as well as nonapoptotic cell death as described below) is not well defined. This continues to be an important question, especially considering that under certain specific contexts, autophagy can be a cell death-promoting mechanism.

Perhaps the more interesting question concerns how SAHA triggers nonapoptotic cell death, and the role of autophagy in this death process. We found that autophagy plays a similar protective role in nonapoptotic cell death. The nature of this nonapoptotic cell death observed during combinational treatment using SAHA and the caspase inhibitor zVAD remains unknown. We have previously shown that the generation of reactive oxygen species, which is deliberately regulated by HDACs, may play a role in nonapoptotic cell death. However, our preliminary studies show that when the necrotic factor RIPK1/RIP1 kinase is inhibited using necrostatin-1, the induced nonapoptotic cell death still occurs. Therefore, is the SAHA-induced nonapoptotic cell death dependent on other re poptotic cell death pa tic cell death m h pathways. Obvious ptotic death, and the cell death, point

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