Autophagy ›

Volume 8, 2012 - Issue 10

Free access

Autophagic Punctum

Curbing autophagy and histone deacetylases to kill cancer cells

Noor Gammoh, Paul A. Marks & Xuejun Jiang

Pages 1521-1522 | Received 01 Jun 2012, Accepted 18 Jun 2012, Published online: 16 Aug 2012

Cite this article https://doi.org/10.4161/auto.21151

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 deacetylase (HDAC) inhibitors, such as the anticancer agent suberoylanilide hydroxamic acid (SAHA, Vorinostat), can induce autophagy. In this study, we show that HDAC inhibition triggers autophagy by suppressing MTOR and activating the autophagic kinase ULK1. Furthermore, autophagy inhibition can sensitize cells to both apoptotic and nonapoptotic cell death induced by SAHA, suggesting the therapeutic potential of autophagy targeting in combination with SAHA therapy. This study also raised a series of questions: What is the role of HDACs in regulating autophagy? Do individual HDACs have distinct functions in autophagy? How do HDACs regulate the nutrient-sensing kinase MTOR? Since SAHA-induced nonapoptotic cell death is not driven by autophagy, what then is the mechanism underlying the apoptosis-independent death? Tackling

these questions should lead to a better understanding of autophagy and HDAC biology and contribute to the development of novel therapeutic strategies.

Keywords: :

HDAC inhibitors | autophagy | apoptosis | nonapoptotic cell death | MTOR | ULK1 | SAHA

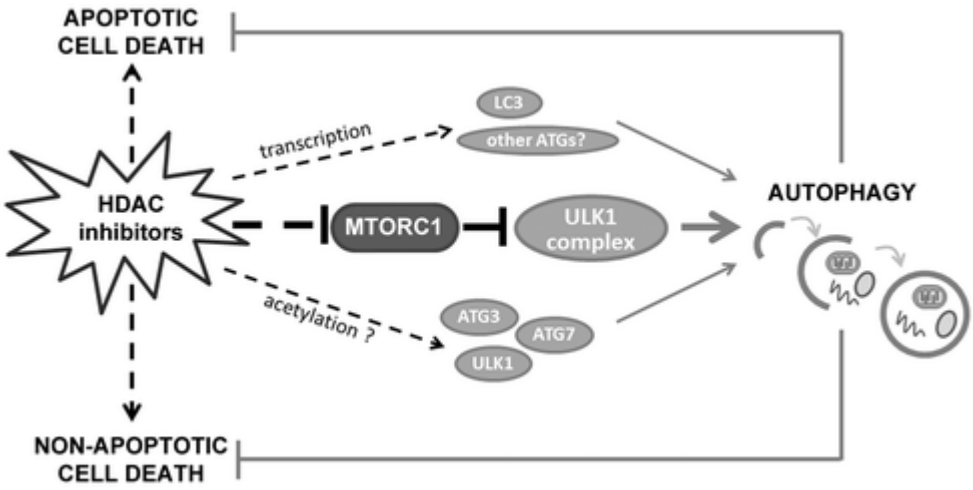
This article refers to:

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 importance of the ULK1 complex in relaying HDAC inhibition-mediated signaling to induce autophagy. Indeed, SAHA cannot trigger autophagy in cells that are deficient in ULK1 expression (as well as its homolog, ULK2). The mechanism by which SAHA inactivates MTOR, however, remains largely unknown. We have not observed an effect of SAHA on the transcription of the core components of MTOR or upstream regulators of MTOR, thus it is formally possible that SAHA suppresses MTORC1 via modulating the acetylation of certain relevant nonhistone protein(s). On the other hand, unlike MTOR or its regulators, the transcription of LC3, an essential autophagy gene, is upregulated by

SAHA. While LC3 upregulation per se cannot trigger autophagy, it can further fuel autophagy when MTORC1 activity is inhibited by SAHA.

Figure 1. HDAC inhibitor-induced autophagy and cell death. HDAC inhibitors 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.



Display full size

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 deacetylase(s) should also be localized in the cytoplasm. Indeed, many HDACs can shuttle between the nucleus and cytoplasm. Particularly, HDAC6 is thought to be a strictly cytosolic enzyme, acting only upon selective nonhistone substrates. Furthermore, considering the diverse substrate spectra of HDACs, can individual HDACs play distinct roles in autophagy? This is possible because different ATG proteins might utilize their own specific HDACs for deacetylation. It is also likely that different HDACs might even play opposing functions in autophagy. Indeed, HDAC6 is required for autophagy that targets certain specific cargos, such as aggresomes and damaged

mitochondria. In conclusion, to further dissect the specific role of individual HDACs in autophagy, approaches such as targeting each HDAC genetically, pharmacologically, or by RNAi should be employed.

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 recently identified necrotic proteins, or does it represent a novel nonapoptotic cell death pathway, be it necrosis or not? Regardless, SAHA-induced nonapoptotic cell death might be a feasible paradigm for identifying novel nonapoptotic death pathways. Obviously as well, the ability of SAHA to induce both apoptotic and nonapoptotic death, and the effect of autophagy-targeting on sensitizing SAHA-induced cancer cell death, point to a potential combination therapy for cancer treatment.