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Curbing autophagy and histone deacetylases to kill cancer cells

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Cells res... ...athways. One path... ...ophagy (hereafte... ...-histone deace... ...e hydroxamic acid ... ...HDAC inhibitio... ...phagic kinase U... ...apoptotic and non... ...otential of autopha... ...ed a series of quest... ...ual HDACs have dis... ...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

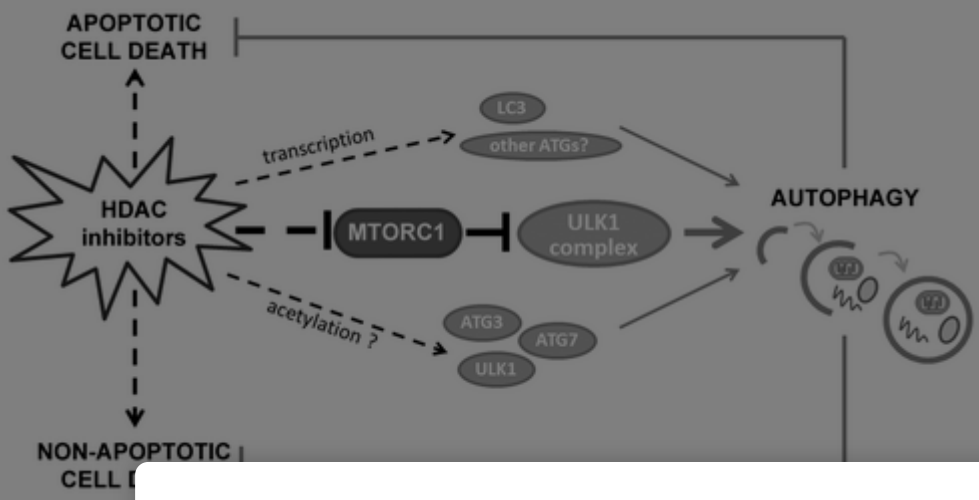
This article refers to:

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

In additi we found that HDA s highly implicat shows that SAHA do ulator of cellular R suppress ex, an upstr A restores the f lights the importa aling to induce a deficient in ULK1 ex AHA inactivat ed an effect of SAHA regulators of MTOR, t ating 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.



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Intriguin related (Atg) gene pro ovided further r utophagy. Presuma egative modul moting autop ir deacetyl ACs can shuttle b to be a strictly c Furtherm idual HDACs play dist eins might utilize th ent 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, a ophagy plays a similar poptotic cell death ob se inhibitor zVAD re eactive oxygen s n nonapop the necrotic factor RI poptotic cell deat ependent on other p poptotic cell death pa tic cell death m h pathways. Obvious ptotic death, and the cell death, point to

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