Regulation of HDAC Inhibitor-Triggered Autophagy

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Autophagy is an essential process of the eukaryotic cell allowing degradation and recycling of dysfunctional or non-functional cellular components either in response to physiological or pathological changes [1]. Beside proteasome-mediated degradation, baseline autophagy serves as a major cellular pathway for long-lived protein and organelle turnover maintaining a well-balanced equilibrium between anabolism and catabolism.

Inhibition of autophagy in combination with chemotherapeutic treatment has emerged as a novel approach in cancer treatment. As a consequence, the question whether autophagy benefits or suppresses tumorigenesis has been highly debated and is a matter of ongoing research. Varying results have been obtained depending on the model system used in each study. Thus, on the one hand, inuction of autophagy could promote tumor cell survival [2]. Here, autophagy may aid in the degradation of organelles that were activated by initiation of apoptosis or have accumulated free radical-induced damage, such as mitochondria (i.e. mitophagy), or could furthermore serve to optimize nutrient utilization in fast growing tumor cells. On the other hand, autophagy could protect the cell against cancer by taking over a tumor suppressor function [3]. In this case, major autophagosomal degradation of the cellular content could finally result in cell death, if it proceeds to completion, or even ignite a decisive cell death signal.

Recent evidences emphasize coexistent tumor suppressing as well as tumor-promoting functions of autophagy that could depend on the cellular context settings and type of tumor [4]. Nevertheless, this issue gets particularly important when it comes to decide the choice of pharmacological interference that can be applied to fight the tumor. Thus, to increase the number of killed cancer cells, inhibitors of autophagy can be applied to cells that use autophagy to survive, while autophagy-inducing drugs should be used in cells where autophagy protects the cell from malignant transformation.

Inhibitors (HDACi) of histone deacetylases (HDAC) are a promising new class of cytostatic anticancer agents in this context that inhibit the proliferation of tumor cells by inducing cell cycle arrest, differentiation, and apoptosis [5]. Suberoyl hydroxamic acid (SAHA; also called vorinostat) belongs equivalent to trichostatin A and panobinostat to the category of broadspectrum inhibitors that inhibit family members in multiple HDAC classes [6]. Increasing evidence indicates that SAHA other HDACi can in addition to mitochondria-mediated apoptosis also promote caspase-independent autophagy [7-11]. Moreover, SAHA-induced autophagy was found to act as a prosurvival mechanism that counteracts the cytotoxic activity of SAHA thereby delaying the initiation of apoptosis via clearance of reactive oxygen species, p62/SQSTM1-containing protein aggregates or of damaged mitochondria that are generated during SAHA treatment [12,13]. Vice versa, it has been observed that SAHA-induced apoptosis can also be significantly upregulated by genetically or pharmacologically blocking autophagy [14,15]. Although the contribution of autophagy to HDACi-induced cell death is still considered questionable by some researchers, the use of the expression “autophagic cell death” has been strongly discouraged in scientific reports anyway as in most cases inhibition of autophagy does not prevent cell death, but often accelerates it [4].

In general, HDACi-induced cell death in tumor cells occurs via modulation of deacetylation leading to indirect or direct expression changes of histones or other target proteins such as transcription factors, oncogenes, and tumor suppressors [16]. However, as even the biological functions of different HDACs isozymes that are targeted by individual HDACi are incompletely understood, the selectivity of corresponding altered gene transcription and signaling pathways involved in HDACi-induced autophagy are unclear. Increasing evidence suggests that several molecular levels contribute to the regulation of HDACi-mediated autophagic process.

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With respect to the regulation of autophagy, class I and IIa HDAC and their inhibitors appear to modulate the nutrient-sensing kinase mammalian target of rapamycin (mTOR) pathway while class IIb HDAC and HDACi seem to modify acetylation of the cytoplasmic proteins of the HSP70 family and of LC3-II [17]. The inactivation of mTOR upon SAHA treatment is by far the most reported pathway in several tumor models [17-21] as mTor is a major regulator of autophagy that activates the remaining downstream core machinery of autophagy by restoring the ULK-1 complex. ULK-1 then initiates autophagosomal formation leading to the recruitment of LC3-II to autophagosomal membranes. Nevertheless, single reports implicate also ROS production in Jurkat T-leukemia cells and the stimulation of NF-κB activity in prostate cancer cells in SAHA-induced autophagy [19,22].

With regard to the mTOR signaling pathway, the question which upstream mechanisms regulate SAHA-induced mTOR inactivation that consequently initiate autophagy were mainly left unexplored. Mechanistically, this could involve the inhibition of deacetylation of transcription factors or of nonhistone proteins affecting mTOR regulation. To elucidate this issue, we recently initiated a study clarifying different modes of SAHA-induced cell death in two human uterine sarcoma cell lines [18]. We identified a mutation in TP53, the gene encoding the tumor suppressor protein p53 provoking the absence of p53 expression in the endometrial stroma sarcoma cell line ESS-1. Rescue of p53-deficiency by re-introduction of wildtype p53 in ESS-1 cells re-shifted the balance between previous predominant autophagy and apoptosis towards prevailing apoptosis and basic autophagy. Therefore, this finding led to the conclusion that p53 could act as a molecular switch between SAHA-triggered autophagic or apoptotic cell death. General validation of these experimental results in several other p53-deficient tumor cell lines undergoing SAHA-induced autophagy and by RNAi-silenced p53 expression suggested an inhibitory role for the functional wildtype p53 protein in the autophagic pathway in response to SAHA treatment.

Supporting evidence for such an anticipated regulatory mechanism comes from physiological studies indicating that p53 can both, promote and inhibit the autophagic process, depending on its subcellular localization [23]. On the one hand, nuclear p53 transactivates TSC2 (tuberous sclerosis) and AMPK (AMP-activated protein kinase) thus indirectly promoting autophagy. On the other hand, Tasdemir et al. discovered that cytoplasmic p53 is mainly responsible for autophagy inhibition and that its inactivation consequently induces autophagy in mammalian cells. Nuclear as well as cytoplasmic actions of p53 employ, for induction or inhibition of autophagy, the same canonical pathway of either downregulating or activating mTOR activity, respectively. Thus, nuclear p53 promotes autophagy, while cytoplasmic p53 inhibits it. However, the exact underlying molecular mechanisms of SAHA-induced autophagic inhibition still remain to be verified. Nevertheless, it is very tempting to speculate that direct acetylation of p53 by histone acetyl transferases upon suppression of the corresponding HDAC activity by SAHA could be held responsible as found applicable in a previous study of HDACi-induced apoptosis in HepG2 cells [24].

Accordingly, such a mechanism of SAHA- provoked cell death regulation induced via p53- dependant autophagy would implicate immediate applications in the choice of cancer therapeutics. The development of isozyme-specific HDACi that specifically target the autophagy machinery and a better understanding of the context-dependent effects of the individual HDAC isozymes on autophagic flux will provide more efficient options to eliminate tumor cells. Potential combination treatments with potential synergistic or additive antitumor effects might furthermore offer an advantage in overcoming apoptosis resistant tumor cells for cancer therapy. Conclusively, investigating the importance of acetylation in the regulation of autophagy and its corresponding pathways is emerging as a new and exciting field.

References


