



Autophagy: Chapter 13. Induction of Autophagic Cell Death by Anticancer Agents

Karin Eberhart, Ozlem Oral, Devrim Gozuacik

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Autophagy is a cellular degradation and recycling pathway contributing to cell survival under stressful conditions (e.g., starvation and growth factor deprivation). Depending on the cellular context, excessive autophagy might sometimes lead to a non-apoptotic programmed death, namely autophagic cell death. Studies using various pharmacological agents and substances with anticancer properties revealed a role for autophagy in cancer cell elimination. In this chapter, we will document and analyze the contribution of autophagy to cell death activated by various anticancer agents. The chapter will be limited to cases where blockage of autophagy using chemical inhibitors or genetic approaches resulted in the survival of cancer cells during drug treatment – hence, to examples of autophagy-related or autophagic cell death (ACD). In other words, in studies that will be discussed here, autophagy seemed to play a rate-limiting role in cellular demise, irrespective of the downstream executionary event. Paradoxically, autophagy was reported to play a prosurvival role (i.e., inhibition of autophagy potentiated cell death) in other cancer cell types treated with similar drugs, underlining the cellular context dependence of ACD. Usage of drugs downregulating anti-autophagic pathways (e.g., mTORC1 and AKT pathways) or stimulating dissociation of the key autophagy protein BECN1 (Beclin 1 protein) from an inhibitory complex with BCL-2 proteins as monotherapy or combination treatment seemed to strongly activate ACD and to overcome the death resistance of cancer cells in several cases. Yet death execution mechanisms downstream of autophagy have been revealed to be multiple. In addition to lysosomal degradation-mediated mechanisms, apoptosis, necroptosis, or lysosomal membrane permeabilization were involved in autophagy-related cell death. Nevertheless, the study and exploitation of autophagy and ACD certainly has the potential to give rise to novel and effective treatment strategies, especially in cancer types that are refractory to conventional chemotherapy and associated with poor prognosis.

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