

Ginet V, Puyal J, Rummel C, Aubry D, Breton C, Cloux AJ, Majjigapu SR, Sordat B, Vogel P, Bruzzone S, Nencioni A, Duchosal MA, Nahimana A (2014). A critical role of autophagy in antileukemia/lymphoma effects of APO866, an inhibitor of NAD biosynthesis. *Autophagy*. 2014 Jan 17;10(4). [Epub ahead of print] PMID:24487122.

APO866, an inhibitor of NAD biosynthesis, exhibits potent antitumor properties in various malignancies. Recently, it has been shown that APO866 induces apoptosis and autophagy in human hematological cancer cells, but the role of autophagy in APO866-induced cell death remains unclear. Here, we report studies on the molecular mechanisms underlying APO866-induced cell death with emphasis on autophagy. Treatment of leukemia and lymphoma cells with APO866 induced both autophagy, as evidenced by an increase in autophagosome formation and in SQSTM1/p62 degradation, but also increased caspase activation as revealed by CASP3/caspase 3 cleavage. As an underlying mechanism, APO866-mediated autophagy was found to deplete CAT/catalase, a reactive oxygen species (ROS) scavenger, thus promoting ROS production and cell death. Inhibition of autophagy by ATG5 or ATG7 silencing prevented CAT degradation, ROS production, caspase activation, and APO866-induced cell death. Finally, supplementation with exogenous CAT also abolished APO866 cytotoxic activity. Altogether, our results indicated that autophagy is essential for APO866 cytotoxic activity on cells from hematological malignancies and also indicate an autophagy-dependent CAT degradation, a novel mechanism for APO866-mediated cell killing. Autophagy-modulating approaches could be a new way to enhance the antitumor activity of APO866 and related agents.

KEYWORDS:

APO866, ATG, CATALASE, NAD, ROS, autophagy, leukemia, lymphoma, therapy