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EC PHARMACOLOGY AND TOXICOLOGY
Editorial

# From Bench to Bedside: Role of 3-AWA (3-Azido Withaferin A) to Override Drug Resistance in Cancer by Switching Autophagy to Apoptosis

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**Received:** February 25, 2017; **Published:** July 28, 2017

Autophagy is a homeostatic catabolic degradation mechanism whereby cellular proteins and organelles are engulfed into autophagosomes, digested in lysosomes and recycled to sustain cellular metabolism. Tumor cells turn on autophagy in response to intrinsic cellular stress including hypoxia, acidosis and increased metabolic demands related to rapid cell proliferation. Autophagy-related stress tolerance can facilitate cell survival to a certain extent by maintaining energy production leading to tumor growth and therapeutic resistance. However, handfuls of evidences suggest that the inhibition of autophagy can restore chemosensitivity and accelerate tumor cell death ensuring autophagy as a therapeutic target [1]. This recent ideology has led to the development of multiple early phase clinical candidates in human by means of autophagy inhibition in combination with chemotherapy in the current decade.

Autophagy has been designated as a complex biological process. Termination of autophagy cascades substantially enhance the efficacy of currently used anticancer drugs and radiotherapy. In addition, triggering autophagy has proven benchmark to induce cancer cells death with a high threshold to apoptosis [2]. Therefore, both strategies have significant potential to be translated into ongoing clinical trials that may provide more valuable information regarding whether targeting autophagic pathways in tumor cells would be a promising leap towards development for potential therapeutics. An active medicinal component of plant origin with an ability to overcome autophagy by inducing apoptosis should be considered as therapeutically lead pharmacophore to control malignancies. Majority of cytotoxic chemotherapeutics fail to proof efficacy due to multiple reasons including autophagy mediated chemo-resistant or protective autophagy [1]. In a recent report from our group, Rah., *et al*. studied the effects of concentration-dependent 3-AWA (3-azido withaferin A) sensitization to androgen-independent prostate cancer (CaP) cells revealing a distinct switching of two interrelated conserved biological processes, i.e. autophagy and apoptosis [3]. 3-azido-withaferin A, a novel derivative of plant natural product withaferin A, induces ER stress-mediated protective autophagy at sub-toxic doses and reprograms these autophagic cells to apoptosis at a higher concentration (above its $IC_{50}$ value) in a Par-4 dependent manner [3]. Par-4, a leucine zipper domain protein, is essential for apoptosis induction as a result of exogenous apoptotic insults [4]. Given that the expression as well as activity of Par-4 are perceivably down-modulated in a number of cancers, efforts to trigger Par-4 levels and activity, to ensure the susceptibility of cancers to apoptotic agents *in vitro* and *in vivo*, have been emerged [5]. Rah., *et al*. have observed that 3-AWA induced Par-4 induction prompted two distinct cell death parameters which are hallmarks of autophagy in their studies [3]. First, subtoxic concentration of 3-AWA triggers an autophagic phenotype with a steady amplification of autophagy markers LC3-I/II leading to a massive accumulation of MAP1LC3B and EGFP-LC3B puncta along with gradual degradation of specific autophagy indicator sequestosome-1 (SQSTM1). Second, higher lethal concentrations of 3-AWA stimulates ER stress in CaP cells to turn on apoptosis within 12h by elevating the expression of the proapoptotic protein Par-4, which in turn sharply attenuates the autophagy-related proteins BCL2 and Beclin-1 [3].

However, a better understanding of the autophagic protein-protein interaction network has provided useful insights into how these hub proteins and autophagy related signaling pathways can be exploited as potential therapeutic targets for treatment of cancer and other human diseases. In that study, Rah., *et al*. have specifically pointed out that at the optimum concentration of 3-AWA, pro-survival candidate BCL2 interacts to autophagic protein Beclin-1 to abrogate autophagy. Beyond this concentration of 3-AWA, at the switchover point (1.0 μM

of 3-AWA), where the BCL2:Beclin-1 interaction is distorted by stimulation of pro-apoptotic protein Par-4 [3]. This inhibition of Beclin-1 in CaP cells, leading to the disruption of the BCL2- Beclin-1 interaction has widened the therapeutic window of 3-AWA. This study provides a firsthand evidences that 3-AWA is a strong anticancer candidate to abrogate protective autophagy via enhancing chemosensitivity as well as sensitizing prostate cancer cells to apoptosis through induction of Par-4 endorsing its therapeutic potential.

Cytoprotective autophagy often bestows shielding effects and strongly neutralizes drug induction [6]. Thus, successful termination of this protecting mechanism leading to a more meaningful cell fate would be considered as a promising dive toward the development of anticancer therapeutics. Thus, this kind of classical approach concerning the therapeutic perspective of Par-4 by natural product derivative 3-AWA, might ensure the investigation of its (Par-4) preclinical to clinical trial therapeutic potential.

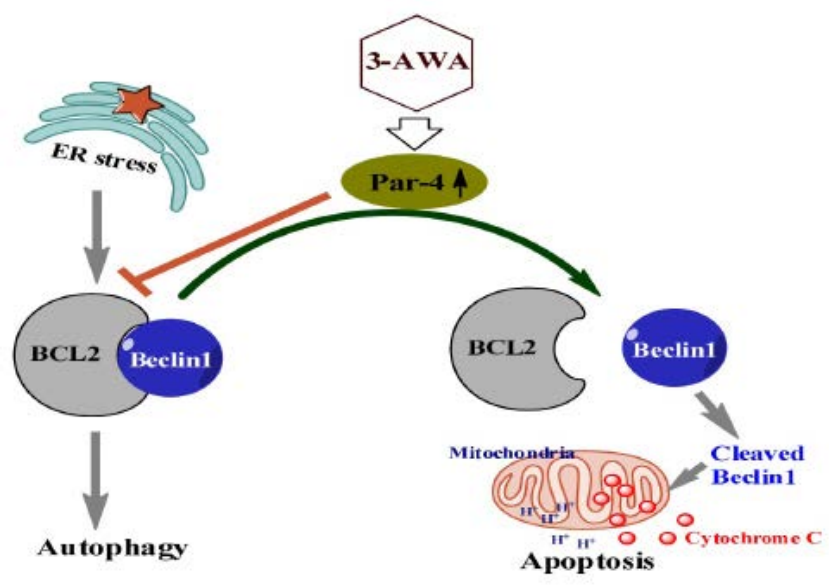


***Figure:*** *Schematic diagram shows switching of autophagy to apoptosis in the presence of 3-AWA through stimulation of intracellular Par-4 and subsequent Par-4 mediated disruption of BCL2-Beclin 1 interaction.*

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**Volume 4 Issue 2 July 2017**