

## Regulation and function of autophagy in retinoic acid mediated therapy of myeloid leukemia and breast cancer

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Autophagy is a lysosomal degradation process that removes and recycles cytoplasmic constituents. Autophagy is characterized by the formation of double-membraned autophagosomes. Autophagosomes engulf bulk cytoplasm or selected contents thereof and transfer them to lysosomes for degradation. At basal activity autophagy ensures cellular homeostasis. Moreover, autophagy is an essential cytoprotective stress response to a variety of stimuli. In tumorigenesis the effects of autophagy are clearly context-dependent. Autophagy may act as tumor suppressor by clearing cells from damaged organelles/aggregated proteins or may promote cancer progression by enabling cancer cell survival under metabolic stress. Furthermore, autophagy frequently protects cancer cells from cytotoxic therapeutic agents and also functions in cellular differentiation and development (1). Therefore, modulating autophagy holds great promises for novel treatment options in cytotoxic and differentiation therapies.

Retinoids are naturally occurring vitamin A derivatives, which exert their functions via activation of nuclear retinoid acid receptor mediated gene expression. Due to their cyto-differentiating, pro-apoptotic and anti-proliferating capacity they represent promising anti-tumor agents. The predominant form of retinoids, all-trans retinoic acid (ATRA), is successfully used to treat acute promyelocytic leukemia (APL) where it induces neutrophil differentiation of leukemic blast cells. We observed increased autophagic activity during neutrophil differentiation as well as impaired differentiation upon pharmacological inhibition of autophagy in APL cells. Next, we found significantly decreased expression of key autophagy genes in primary AML patients as compared to normal neutrophils. Moreover, knocking down key autophagy genes significantly attenuated neutrophil differentiation of APL cells (2,3). Importantly, pharmacological activation of autophagy in combination with ATRA treatment significantly boosted APL differentiation (1).

*In vitro* data using ATRA showed promising anti-proliferative and cytotoxic effect in breast cancer cells, but clinical studies failed to show a therapeutic benefit. Since ATRA induces autophagy in AML cells, we asked if ATRA also triggers an autophagic response in breast cancer cells. Indeed, retinoids induce autophagy in ATRA-sensitive breast cancer cells and autophagy inhibition significantly augmented cell death.

Although, autophagy is induced in both tumor types, our data clearly suggest that inhibition of autophagy augments cytotoxicity in breast cancer, whereas inhibiting autophagy attenuates neutrophil differentiation of APL cells and thereby lowers therapy efficiency. In summary, a combination of ATRA therapy with autophagy

modulating agents is beneficial, but one needs to consider autophagy inhibition when intending to increase cytotoxicity and autophagy activation when aiming at enhanced differentiation.

This work was supported by grants from the Swiss National Science Foundation (31003A\_143739), Swiss Cancer Research (KFS-3409-02-2014), and "Stiftung für Klinisch-Experimentelle Tumorforschung Bern".

## References

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## Keywords

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Autophagy; Acute myeloid leukemia; Breast cancer; Retinoic acid.