

Distinct TP73–DAPK2–ATG5 pathway involvement in ATO - mediated cell death versus ATRA - mediated autophagy responses in APLMagali Humbert , Elena A. Federzoni, ... [See all authors](#) >

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Abstract

We have previously demonstrated that the death - associated protein kinase 2 (DAPK2) expression is significantly reduced in acute myeloid leukemia (AML), particularly in acute promyelocytic leukemia (APL) blast cells. In this study, we aimed at further understanding DAPK2 function and regulation during arsenic trioxide (ATO) cytotoxic or all - trans retinoic acid (ATRA) differentiation therapy in APL cells. We found that the p53 family member transactivation domain - p73 isoform (TAp73) binds to and activates the *DAPK2* promoter, whereas the dominant - negative Δ Np73 isoform inhibits *DAPK2* transcription. Furthermore, the knocking down of tumor protein p73 (*TP73*) in NB4 cells resulted in reduced DAPK2 expression associated with decreased cell death and autophagy upon ATO and ATRA treatment, respectively. Moreover, the silencing of *DAPK2* revealed that DAPK2 is an important downstream effector of p73 in ATO - induced apoptosis but not autophagy responses of APL cells. In contrast, the p73–DAPK2 pathway is essential for ATRA - induced autophagy that is mediated by an interaction of DAPK2 with the key autophagy - related protein (ATG)5. Lastly, we show that DAPK2 binds and stabilizes the p73 protein; thus, we propose a novel mechanism by which ATO - or ATRA - induced therapy responses initiate a positive p73–DAPK2 feedback loop.

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