

## Retinoic acid sensitizes acute myeloid leukemia cells to ER stress

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Acute myeloid leukemia (AML) is caused by the blockade of hematopoietic myeloid precursors at different stages of differentiation. A subtype of AML, acute promyelocytic leukemia (APL), is a paradigm of differentiation therapy since retinoic acid (RA) is able to induce leukemic blast terminal differentiation leading to cure rates exceeding 80% when administered in combination with chemotherapy. Although APL patients refractory to RA or who relapsed are very effectively treated with arsenic trioxide (ATO) in combination with RA, the elevated costs limit its use in developing countries and in first line therapy so that RA plus chemotherapy currently remain the standard of care (1, 2). Most importantly non-APL acute myeloid leukemia do not respond to RA indicating the need for novel strategies to sensitize AML cells to RA. Here we show that RA-triggered differentiation of APL cells induces endoplasmic reticulum (ER) stress slightly activating the unfolded protein response (UPR). This is sufficient to render leukemic cell lines and human primary blasts very sensitive to doses of ER stress inducing drugs, like tunicamycin (Tm), that are not toxic for the same cells in the absence of RA or for most cell types. Furthermore we observed that low doses of Tm, even in the absence of RA, are sufficient to strongly increase ATO toxicity. Indeed both RA-sensitive and RA-resistant APL cell lines resulted sensitive to Tm-ATO combined treatment at low doses of ATO that are ineffective in the absence of ER stress. The use of inhibitors targeting specific UPR branches indicate that the Protein Kinase RNA-like Endoplasmic Reticulum kinase (PERK) pathway protects differentiating APL cells from ER stress rendering it an interesting therapeutic molecular target. Finally, we extended our observations in a non-APL model, assessing that RA sensitize the non-APL cell line HL60 to ER stress. Altogether our data indicate ER stress as a possible target for designing novel combination therapeutic strategies in AML.

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### References

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### Keywords

AML; ER stress; RA; ATO.