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Retinoic Acid-induced differentiation sensitizes myeloid progenitors cells to ER stress

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The clonal expansion of hematopoietic myeloid precursors blocked at different stages of differentiation characterizes the acute myeloid leukemia (AML) phenotype. A subtype of AML, acute promyelocytic leukemia (APL), characterized by the chimeric protein PML-RARα is considered a paradigm of differentiation therapy. In this leukemia subtype the all-*trans*-retinoic acid (RA)-based treatments are able to induce PML-RARα degradation and leukemic blast terminal differentiation [1-2]. Granulocytic differentiation of APL cells driven by RA triggers a physiological Unfolded Protein Response (UPR), a series of pathways emanating from the ER in case of ER stress, which ensues when higher protein folding activity is required as during differentiation. We show here that, although mild, the ER stress induced by RA is sufficient to render human APL cell lines and primary blasts very sensitive to low doses of Tunicamycin (Tm), an ER stress inducing drug, at doses that are not toxic in the absence of RA. Importantly only human progenitors cells derived from APL patients resulted sensitive to the combined treatment with RA and Tm whereas those obtained from healthy donors were not affected. We also show that the UPR pathway downstream of PERK plays a major protective role against ER stress in differentiating cells and, by using a specific PERK inhibitor, we potentiated the toxic effect of the combination of RA and Tm. In conclusion, our findings identify the ER stress-related pathways as potential targets in the search for novel therapeutic strategies in AML.

References

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Keywords
Retinoic Acid, Myeloid differentiation, UPR, ER stress