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Induction of leukemic myeloid progenitor cell death by a combination of ER and oxidative 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 characterized by the expression of fusion or mutant proteins that cause impaired differentiation and enhanced proliferation and survival. We previously showed that APL cell lines and primary blasts induced to differentiate by RA become highly sensitive to amounts of ER stress not detrimental for the same cells in the absence of Retinoic Acid (RA) [1]. Furthermore the same cells resulted sensitive to a combination of ER stress inducers with Arsenic Trioxide (ATO) that generates oxidative stress. Importantly we observed that ER stress caused increased amounts of disulphide-bound high molecular weight aggregates of PML-RARα and PML, exacerbating the alteration of cellular proteostasis already generated by induction of ER stress. This observation provides the rationale to translate the findings we observed in APL to other types of AML characterized by fusion or mutant proteins. The presence of mutant proteins that are easily prone to aggregation or mis-folding, because of their mutant structure or because of mis-localization, could render the cells sensitive to levels of ER and oxidative stress that could be recovered in their absence. We first tested a panel of AML cell lines characterized by different oncogenic fusion or mutant proteins and we found that ML-2 cells, bearing the MLL-AF6 fusion protein, and MV-4-11 cells, expressing the fusion protein MLL-AF4 and FLT3-ITD are highly sensitive to the combination of sub-lethal amounts of RA, Tm and ATO. In the cells undergoing ER and oxidative stress in combination, we found prolonged activation of the antioxidant response and of the unfolded protein response (UPR), activated by ER stress, as indicated by the expression of HMOX, CHOP, BiP and sXBP1. Importantly, the combination of ER and oxidative stress significantly reduces the colony forming capacity of primary leukemic blasts isolated from the bone marrow of FLT3-ITD positive patients. Altogether our data suggest that the combination of ER and oxidative stress leads to apoptosis rather than recovery, achieved instead when the same stresses are induced alone.

References

[1] Masciarelli et al. (2018) Retinoic acid and arsenic trioxide sensitize acute promyelocytic leukemia cells to ER stress. Leukemia 32(2): 285-294

Key words

ER stress, oxidative stress, myeloid progenitors.

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