Stressing the stem cell in acute myeloid leukemia

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Mitigation of cell intrinsic and cell extrinsic stress is critical for survival of leukemia stem cells (LSC) in acute myeloid leukemia (AML). Unfolded protein response (UPR) is an endoplasmic reticulum (ER)-regulated adaptive stress mitigation response and is regulated by protein kinase RNA-like ER kinase (PERK), inositol requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6). Li *et al.*[1] identified DNAJC10, an ER chaperone protein of the Hsp70 family of proteins, as a vulnerability in AML LSC in an MLL-AF9 model of AML. DNAJC10 (ERdj5) participates in the ER-associated degradation (ERAD) process.[2] *DNAJC10* knockdown (KD) resulted in dilated ER and improved mouse survival in serial transplants, indicating impact on LSC. Mechanistically, *DNAJC10*-KD activated PERK arm of UPR and PERK inhibition reversed the effect of DNAJC10-KD in the MLL model of mouse AML. DNAJVC10-KD increased the sensitivity of AML cell to cytarabine and daunorubicin. Interestingly, the impact of *Dnajc10*-KO in the MLL-AF9 mouse model was more evident in secondary and tertiary transplants, suggesting that *Dnajc10* is not essential for the initiation of leukemia in this model and that attrition of the LSC compartment happens over time. Interestingly, DNAJC10 is a transcriptional target of Hoxa9,[3] and, knowing the impact of Hoxa9 on LSC maintenance, the finding of LSC attrition with DNAJC10 silencing may not be surprising. However, Li *et al.*[1] do not explore the mechanistic link with Hoxa9 in any detail.

While the data are exciting, several questions remain. First is whether this mechanism is operative in the MLL-AF9 model only. Second is the mechanistic link with activation of PERK with DNAJC10 silencing. Following on from that, the next question will be is this the result of general activation of UPR with impaired chaperone function of DNAJC10 or is this a specific response that involves the PERK arm of UPR? Loss of *Dnajc10* in mice results in increased reactive oxygen (ROS) production in mouse hepatocytes.[4] Given the critical need of ROS mitigation in maintenance of AML LSC, the impact of DNAJC10 silencing on AML LSC could be linked to impaired ROS mitigation. Irrespective of the underlying mechanism, Li *et al.*[1] have clearly identified a promising target for eliminating AML LSC.

Disclosures

No conflicts of interest to disclose.

References

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