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Clozel and colleagues found that low-dose DNA methyltransferase (DNMT) inhibitor treatment induced DNA hypomethylation and a senescence-like phenotype in chemorefractory diffuse large B-cell lymphoma (DLBCL) cells and enhanced the sensitivity of these cells to doxorubicin. In addition, DNMT inhibition upregulated the expression of several hypermethylated genes including SMAD1 in refractory DLBCL cell lines and primary tumors, indicative of epigenetic reprogramming. SMAD1 reactivation sensitized resistant cells to growth inhibition by doxorubicin, whereas SMAD1 depletion augmented chemoresistance. Furthermore, in a phase I clinical trial of newly diagnosed, high-risk patients with DLBCL, DNMT inhibitor pretreatment prior to standard chemoimmunotherapy was well tolerated and resulted in a high rate of complete remission, supporting further investigation of this therapeutic combination in DLBCL. For details, please see the article by Clozel and colleagues on page 1002.