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ON THE COVER
Using a multiomics approach to analyze 347 cases of diffuse large B-cell lymphoma (DLBCL), Ennishi, Takata, and colleagues observed that loss of MHC expression defines a molecular subgroup of germinal center B cell-like DLBCL with reduced T-cell infiltration, an immune-suppressed microenvironment, and poor survival. EZH2 was the most frequently mutated gene in MHC-deficient DLBCL, and Ezh2 mutation in mouse models reduced MHC levels and amounts of T-cell infiltrates and resulted in shorter survival. EZH2 inhibition restored MHC expression in DLBCL cells by reducing repressive histone methylation at the promoters of MHC transactivator genes. These findings identify an EZH2-mediated epigenetic mechanism of immune escape in DLBCL and suggest that EZH2 inhibition could be used to improve responses to immunotherapy. For details, please see the article by Ennishi, Takata, and colleagues on page 546.