REPLY TO HAFFNER ET AL.:

DNA hypomethylation renders tumors more immunogenic

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In the letter by Haffner et al. (1), they report that seminoma cell-intrinsic DNA hypomethylation is associated with endogenous retroviral expression, an IFN response, and lymphocytic infiltration. Their data complement and support our recent therapeutic study in a mouse model of ovarian cancer (2) and support our observations that low doses of the DNA methyltransferase (DNMT) inhibitor azacytidine (AZA), in combination with the histone deacetylase inhibitor, givinostat, activate type 1 IFN signaling in ovarian (2) and lung (3) cancer cells to increase numbers and activation of immune cells in the tumor microenvironment and to increase sensitivity to the immune checkpoint inhibitor anti-PD1. We and others have shown that this AZA-induced immunogenic response is dependent on the reexpression of endogenous retroviruses (ERVs) and an innate immune response (4). However, our study does not eliminate the possibility that activation of IFN signaling by AZA might be due to more than hypomethylation and reexpression of ERVs. For example, AZA acts to degrade DNMTs (5), which also serve as DNA scaffolding proteins, and this loss could have significant implications for chromatin remodeling and gene expression beyond hypomethylation.

The chromatin of seminomas is intrinsically demethylated (6–8), which distinguishes them from other testicular germ cell tumors and most other hypermethylated solid tumors. Moreover, seminomas exhibit a significant immune cell infiltrate (8–10), and ERV (ERV-K)-specific T cells have been shown to be important in seminomas (11). Haffner et al. (1) cleverly use this tumor model to demonstrate that ERVs and IFN signaling are naturally elevated in the tumor cells that exhibit DNA hypomethylation in the absence of treatment with epigenetic modifiers. They also present elegant data that extend our study to suggest that DNA hypomethylation may be sufficient to render tumors more immunogenic. When coupled with expression of checkpoint markers, DNA hypomethylation may predict response to checkpoint inhibitors or other immunotherapy. Moreover, these studies suggest that global hypomethylation may induce a common mechanism shared among numerous tumor types to regulate the tumor immune response. Taken together, these data suggest that a combination of DNA demethylation and immunotherapy may be a therapeutically attractive strategy, for which clinical trials are already in progress.

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