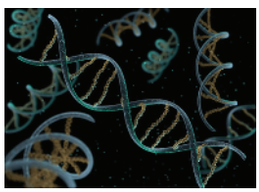
## Immune Evasion

**Major finding:** The TIM-3 receptor on dendritic cells inhibits nucleic acid–stimulated antitumor immunity.

**Mechanism:** TIM-3 binding to HMGB1 prevents nucleic acid trafficking necessary for innate immune signaling.

**Impact:** Targeting of TIM-3 may improve patient responses to cytotoxic chemotherapies.

### A DENDRITIC CELL-DERIVED RECEPTOR COUNTERACTS ANTITUMOR IMMUNITY



Dendritic cells (DC) are critical components of the innate immune system that are stimulated in response to pathogens and stressors, including tumor-derived factors. Nucleic acids, such as those released by dying cells, activate Toll-like receptors (TLR) on DCs and initiate immune responses that are in part mediated by high-mobility group box 1 (HMGB1) protein. Chiba and colleagues examined the mechanisms of how tumor-associated DCs regulate cancer immunity, in particular the role of the receptor T-cell immunoglobulin mucin 3 (TIM-3). Elevated TIM-3 expression was detected on tumor-associated DCs (TADC) within the microenvironment of mouse and human tumors. Expression of this receptor reduced cytokine production induced by TLR agonists or synthetic DNA, whereas inhibition of TIM-3 with the use of a monoclonal antibody enhanced cytokine levels in TADCs, suggesting that DC-derived TIM-3 suppresses nucleic acid–stimulated antitumor responses. In support of this idea, DC depletion or TIM-3 blockade enhanced the ability of DNA vaccination to inhibit tumor growth, and this protective effect was dependent on type I IFN and interleukin-12 signaling induced by DNA. Furthermore, TIM-3 impaired chemotherapy-triggered immunogenic cell death, as TIM-3 blockade synergized with cisplatin to augment cytokine production stimulated by dying tumor cells *in vitro* and significantly reduced tumor growth *in vivo*. TIM-3 attenuation of chemotherapeutic efficacy required the presence of functional DCs and HMGB1 detection of nucleic acids. Specifically, TIM-3 inhibited innate immune responses by competing with DNA for binding to the A-box domain of HMGB1, thereby preventing the HMGB1-mediated recruitment of DNA into endosomes that is required for innate immune signaling. Taken together, these results identify a mechanism by which TADCs negatively regulate chemotherapy-induced antitumor immune responses and suggest that TIM-3 inhibition may be useful in treating patients who do not respond to cytotoxic chemotherapy drugs. ■

*Chiba S, Baghdadi M, Akiba H, Yoshiyama H, Kinoshita I, Dosaka-Akita H, et al. Tumor-infiltrating DCs suppress nucleic acid–mediated innate immune responses through interactions between the receptor TIM-3 and the alarmin HMGB1. Nat Immunol 2012 July 29 [Epub ahead of print].*

## Drug Discovery

**Major finding:** A structure-guided approach identified a selective inhibitor of H3K27me3 demethylases.

**Clinical relevance:** Inhibition of H3K27me3 demethylation suppresses TNF-α production in primary macrophages.

**Impact:** These structural insights provide a framework for future development of histone demethylase inhibitors.

### A SELECTIVE H3K27me3 DEMETHYLASE INHIBITOR BLOCKS CYTOKINE PRODUCTION

Modulation of histone lysine methylation is crucial for regulation of chromatin structure and gene expression and is frequently deregulated in cancer. The lysine-specific demethylase 6 (KDM6) subfamily includes ubiquitously transcribed tetratricopeptide repeat, X chromosome (UTX, also known as KDM6A) and jumonji domain containing 3 (JMJD3, also known as KDM6B), which specifically remove the repressive histone H3 lysine 27 trimethyl (H3K27me3) mark. The identification of selective small-molecule inhibitors of histone demethylases would provide insight into the activity and cellular functions of these enzymes and also establish potential avenues for reversing pathologic epigenetic states. Kruidenier and colleagues solved the crystal structure of the JMJD3 catalytic domain in complex with an H3K27me3 peptide and used the insights into interactions required for substrate specificity and recognition to guide the optimization of weak inhibitors discovered in a screen of 2 million compounds. The lead compound, GSK-J1, competed with enzymatic cofactors and interacted with the catalytic metal ion at 2 sites to induce a shift in its position, suggesting potential approaches for the further development of selective demethylase inhibitors. GSK-J1 selectively bound and inhibited JMJD3 and UTX *in vitro* and in cell extracts, and masking of the polar acid groups in the derivate compound GSK-J4 allowed cell penetration and inhibition of JMJD3-induced H3K27me3 loss. In human macrophages, where JMJD3 participates in the transcriptional response to inflammatory stimuli, GSK-J4 significantly reduced the production of the proinflammatory cytokine TNF-α in association with sustained H3K27me3 occupancy and prevention of RNA polymerase II binding at the *TNFA* promoter. The identification and characterization of a selective H3K27me3 inhibitor thus provides insight into the structural determinants and cellular roles of demethylase activity, which may benefit cancer epigenetic drug discovery efforts. ■

*Kruidenier L, Chung C, Cheng Z, Liddle J, Che K, Joberty G, et al. A selective jumonji H3K27 demethylase inhibitor modulates the proinflammatory macrophage response. Nature 2012;488:404–8.*