

## Epigenetics

**Major Finding:** The histone modification H3K36me2 recruits DNMT3A, a DNA methyltransferase associated with cancer.

**Mechanism:** The histone methyltransferase NSD1 dimethylates H3K36, which is read by DNMT3A's PWWP domain.

**Impact:** These findings lay a foundation for understanding the role of DNMT3A and DNA methylation in disease.

### CANCER-ASSOCIATED DNMT3A IS RECRUITED BY H3K36me2 TO METHYLATE DNA

The DNA methyltransferase DNMT3A, which methylates CpG dinucleotides, has been implicated in a variety of cancers. Weinberg, Papillon-Cavanagh, and colleagues report that DNMT3A colocalized with regions bearing high levels of CpG methylation and histone H3 dimethylated at lysine residue 36 (H3K36me2), an epigenetic mark associated with active transcription and neighboring intergenic regions, in mouse mesenchymal stem cells (MSC). Experiments in mouse embryonic stem cells lacking DNA methylation in which reexpression of the predominant DNMT3A isoform (DNMT3A2) had been established revealed that *de novo* methylation activity of DNMT3A correlated with the level of H3K36me2. Additionally, maintenance of CpG methylation and the intergenic localization of DNMT3A required H3K36me2 deposited by the histone methyltransferase NSD1. Biochemical experiments showed that the PWWP “reader” domain of DNMT3A (DNMT3A<sub>PWWP</sub>) exhibited preferential binding of H3K36me2 compared with other modified histones; this binding occurred with high affinity, and DNMT3A<sub>PWWP</sub> also exhibited weaker affinity for trimethylated H3K36 (H3K36me3). In mouse MSCs in which

*Nsd1* and the related histone methyltransferase-encoding gene *Nsd2* had been genetically ablated, DNMT3A was redistributed from intergenic regions to gene bodies containing high levels of H3K36me3, suggesting that the localization of DNMT3A is guided by its PWWP domain's affinity for H3K36me2 (and, to a smaller degree, H3K36me3). Illustrating the relevance of these findings in human cancer, profiling of H3K36me2 and CpG methylation in patient-derived head and neck squamous cell carcinoma cell lines indicated that low CpG methylation levels correlated with genome-wide reductions (primarily at intergenic regions) in *NSD1*-mutant lines compared with an *NSD1*-wild-type line. Together, these results provide a basis for understanding the role of DNMT3A in disease and, more broadly, for learning how the DNA-methylation landscape is established and maintained. ■

Weinberg DN, Papillon-Cavanagh S, Chen H, Yue Y, Chen X, Rajagopalan KN, et al. The histone mark H3K36me2 recruits DNMT3A and shapes the intergenic DNA methylation landscape. *Nature* 2019;573:281–6.

## Clinical Trials

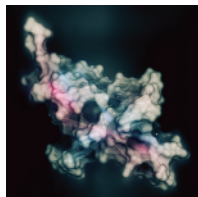
**Major Finding:** Pegilodecakin plus anti-PD-1 showed tolerability and efficacy in some advanced solid tumors.

**Concept:** The best objective response rates were seen in non-small cell lung cancer and renal-cell carcinoma.

**Impact:** Larger, randomized trials of pegilodecakin with pembrolizumab or nivolumab are warranted.

### PEGILODECAKIN PLUS ANTI-PD-1 IS TOLERABLE AND EFFECTIVE

Combination of the anti-inflammatory and CD8<sup>+</sup> T-cell stimulating cytokine IL10 with anti-PD-1 therapy has been suggested as a means to increase antitumor activity of both agents. In an open-label, dose-escalation, phase Ib clinical trial, Naing and colleagues investigated treatment of advanced solid tumors with the combination of anti-PD-1 therapies (pembrolizumab or nivolumab) and pegilodecakin, a PEGylated form of IL10 that has a greater *in vivo* half-life than IL10. In total, 111 patients were enrolled, with 53 being assigned to pembrolizumab plus pegilodecakin (P+P) and 58 being assigned to nivolumab plus pegilodecakin (N+P); most patients had been treated with at least one previous therapy. In the P+P cohort, nine patients had renal-cell carcinoma, five had non-small cell lung cancer (NSCLC), 37 had melanoma, one had bladder cancer, and one had triple-negative breast cancer. In the N+P cohort, 29 patients had renal-cell carcinoma and 29 patients had NSCLC. Six patients died over the course of the trial, though no deaths were determined to be due to study treatment. Toxicity profiles were similar between the cohorts, with 103 (93%) patients experiencing one or more treatment-related adverse events and 73 (66%) experiencing



at least one grade 3 or 4 treatment-related adverse event. The most common grade 3 or 4 adverse events were anemia, thrombocytopenia, fatigue, and hypertriglyceridemia. The objective response rate in the 96 evaluable patients was 43% (12 of 28 patients) for NSCLC, 10% (three of 31 patients) for melanoma, and 40% (14 of 35 patients) for renal-cell carcinoma. One patient with NSCLC in the N+P cohort attained a complete response. Pre-specified exploratory analyses of blood samples from a subset of patients receiving pegilodecakin with anti-PD-1 revealed an expansion of T-cell clones after treatment. Limitations of the study include small sample sizes and the absence of comparator groups. Together, the tolerability and efficacy data support continued investigation of the combination of pegilodecakin with anti-PD-1 therapies in larger, randomized trials. ■

Naing A, Wong DJ, Infante JR, Korn WM, Aljumaily R, Papadopoulos KP, et al. Pegilodecakin combined with pembrolizumab or nivolumab for patients with advanced solid tumours (IVY): a multicentre, multicohort, open-label, phase 1b trial. *Lancet Oncol* 2019 Sep 25 [Epub ahead of print].