Chromatin

Major Finding: Whole-genome doubling (WGD) induces loss of chromatin segregation, which promotes cancer development.

Concept: Loss of chromatin segregation leads to nuclear compartment repositioning and deregulated transcription.

Impact: This study reveals a potential mechanism behind how WGD predisposes cells to a malignant phenotype.

GENOME DOUBLING WEAKENS DNA ORGANIZATION AND SUPPORTS TUMORIGENESIS

Whole-genome doubling (WGD) occurs in approximately 30% of human tumors, during which the entire set of chromosomes within a cell is duplicated. While WGD can promote chromosomal instability that leads to the generation and selection of oncogenic genetic alterations, the impact of WGD on the 3D organization of chromatin and how subsequent changes in DNA organization may contribute to tumorigenesis have not been well characterized. To investigate the effects of WGD on chromatin structure, Lambuta, Nanni, and colleagues chemically induced WGD via mitotic slippage or cytokinesis failure in permissive p53-deficient diploid and triploid cell lines. Whereas DNA is organized within the nucleus at the level of interacting chromosomes, active and inactive nuclear subcompartments, and topologically associated domains (TAD), high-throughput chromatin conformation capture (Hi-C) analysis revealed that WGD induction consistently led to an increased proportion of contacts between long and short chromosomes, active and inactive subcompartments, and TADs, culminating in an overall loss of chromatin segregation (LCS). WGD-induced cells exhibited a reduction in the abundance of the insulator protein CTCF and the trimethylation of lysine 9 at histone 3 (H3K9me3), which are important for the maintenance of insulation at TAD boundaries and segregation between subcompartments, respectively, suggesting that WGD gives rise to LCS by triggering a shortage of regulatory DNA proteins. Single-cell Hi-C confirmed the occurrence of LCS in individual cells following WGD and highlighted chromosome 1–chromosome 16 interactions as some of the most frequent interchromosomal contacts. After 6 or 20 weeks of *in vitro* culture following WGD, cells were injected into mice, and tumors developed within 2.5 and 1.5 months, respectively, with no tumor engraftment following injection of noninduced control cells. Genomic and chromatin conformation analysis indicated that tumors derived from post-WGD cells altered transcription by repositioning specific oncogenes and tumor suppressor genes in active or inactive compartments. Together, these findings demonstrate that, in parallel with genetic alterations, WGD can support oncogenic transcriptional deregulation through LCS and subcompartment repositioning. ■

Lambuta RA, Nanni L, Liu Y, Diaz-Miyar J, Iyer A, Tavernari D, et al. Whole-genome doubling drives oncogenic loss of chromatin segregation. Nature 2023;615:925–33.

doi: 10.1158/2159-8290.CD-RW2023-044

Immunology

Major Finding: Gut bacteria translocation augments T-cell activity and tumor control in response to immunotherapy.

Concept: Dendritic cells mediate the translocation of gut bacteria into remodeled secondary lymphoid organs.

Impact: Supplementation with specific probiotics may help improve the clinical response to immunotherapy.

TRANSLOCATION OF GUT BACTERIA ENHANCES THE RESPONSE TO IMMUNOTHERAPY

Gut microbiota, especially gut bacteria, have been associated with clinical response to immune checkpoint inhibitor therapy (ICT), but how these gut bacteria modulate the immune response to tumors outside the intestine and which species are involved remain unclear. To determine the effects of gut microbiota on extraintestinal antitumor immune responses and immunotherapy response, Choi and colleagues used an immunocompetent mouse model of melanoma and showed that, upon combination anti–CTLA-4 and anti–PD-1 treatment, tumor-bearing mice had bacterial translocation into tumors and secondary lymphoid organs, most notably the mesenteric lymph nodes (MLN). The dominant taxa identified in these tissues were *Enterococcus faecalis* during early phases of ICT treatment and *Lactobacillus johnsonii* after the second ICT dose, with neither species being highly abundant in the gut prior to treatment, suggesting ICT induced their specific translocation. Both species of bacteria, but not the common commensal gut bacteria *Lactobacillus acidophilus*, significantly activated mouse dendritic cells (DC) *ex vivo*, leading to high levels of $CD8^+$ T-cell priming and activation. Removal of the MLN, but not the tumor-draining lymph node or spleen, reduced extraintestinal bacterial load, leukocyte infiltration of tumors, as well as DC and T-cell activation, which subsequently led to increased tumor growth and reduced survival in mice treated with ICT. Moreover, depletion of DCs or the chemokine receptor CCR7 abolished bacterial translocation into the MLN, and DCs isolated from the MLN of ICT-treated mice not only were more numerous but also carried higher bacterial loads compared to untreated mice. Furthermore, ICT was found to increase lymphangiogenesis and dilation of high endothelial venules in the MLN, which led to increased bacterial translocation. Finally, mice treated with antibiotics prior to tumor implantation exhibited reduced DC and $CD8^+$ T-cell activation in response to ICT. In summary, this study shows that the translocation of gut bacteria can alter the effects of ICT, providing insight into why different taxa of the gut microbiome may be critical for ICT efficacy, and suggests that therapeutically targeting this phenotype could improve outcomes after treatment with ICT. ■

Choi Y, Lichterman JN, Coughlin LA, Poulides N, Li W, Del Valle P, et al. Immune checkpoint blockade induces gut microbiota translocation that augments extraintestinal antitumor immunity. Sci Immunol 2023;8:eabo2003.

doi: 10.1158/2159-8290.CD-RW2023-045