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Breast Cancer

Major Finding: Loss of p53 caused increased neutrophil levels and systemic inflammation in mice with breast tumors.

Mechanism: p53-null tumors had increased secretion of WNT ligands, triggering macrophage IL1β production.

Impact: Tumors' p53 status may influence the extent of metastasis-promoting systemic inflammation.

p53 LOSS CAN PROMOTE NEUTROPHILIA, INCREASED WNT SIGNALING, AND METASTASIS

Recent evidence suggests that canonical driver mutations affect the local immune composition of primary tumors. Using 16 genetically engineered mouse models (GEMM) representing most subtypes of human breast cancer, Wellenstein, Coffelt, and colleagues showed that the mice had increased levels of circulating neutrophils—a condition that promotes metastasis. There was a large amount of variability in the degree of neutrophilia among the GEMMs, with p53-mutant mice having more circulating neutrophils. p53 loss was correlated with increased serum levels of CCL2, IL1β, and G-CSF, and systemic inflammation was correlated with tumor p53 status. Mice with tumors lacking p53 had increased neutrophil expansion compared to mice with size-matched p53-proficient tumors, implying a causal relationship between p53 loss and cancer-induced systemic neutrophilic inflammation. In cultured bone marrow–derived macrophages, conditioned medium from p53-mutant cells induced *Il1b* mRNA expression to a greater extent than medium from matched p53-proficient controls, and data from The Cancer Genome Atlas revealed that human breast tumors with *TP53* mutations had increased IL1B expression compared to tumors with wild-type *TP53*. In the GEMMs, there was an increase in WNT and β-catenin signaling in p53-null tumors, as indicated by upregulation of WNT-related genes and WNT ligands, downregulation of genes encoding negative regulators of WNT signaling, increased levels of WNT1 and WNT7A proteins, and increased expression of nonphosphorylated, active β-catenin. A similar effect was seen in *TP53*-mutant human tumors and p53-deficient cancer cell lines, which exhibited increased expression of WNT ligands. Depletion of *Porcn* mRNA or treatment with LGK974, an inhibitor of porcupine (a WNT-specific acetyltransferase responsible for regulating secretion of WNT ligands), reduced macrophages' expression of *Il1b* in the p53-null cells. Porcupine blockade reduced pulmonary metastases in mice, as did lack of p53, and LGK974 treatment decreased metastasis only in mice with p53-null tumors. These findings demonstrate that p53 mutations drive WNT-dependent metastasis, potentially in association with neutrophilia. ■

Wellenstein MD, Coffelt SB, Duits DEM, van Miltenburg MH, Slagter M, de Rink I, et al. Loss of p53 triggers WNT-dependent systemic inflammation to drive breast cancer metastasis. Nature 2019 Jul 31 [Epub ahead of print].

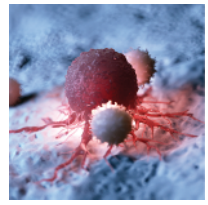
Immunotherapy

Major Finding: Tumor-expressed CD24 interacts with macrophage-expressed Siglec-10 to evade immune detection.

Concept: Blocking CD24–Siglec-10 interactions caused increased phagocytosis and reduced tumor growth in mice.

Impact: Targeting CD24 may be a worthwhile strategy, especially in TNBC and ovarian cancer.

CD24 IS A "DON'T EAT ME" SIGNAL THAT PROMOTES TUMOR IMMUNE ESCAPE



The cell-surface protein CD24 suppresses inflammatory responses and is expressed by several solid tumors, but whether it modulates the immune response to tumors is not known. Barkal and colleagues found that *CD24* expression was greatly elevated in triple-negative breast cancer (TNBC) and ovarian cancer; patients with breast cancers who had lower *CD24* expression in their bulk tumors had greater overall survival, and patients with ovarian cancer with lower *CD24* expression in their bulk tumors had improved relapse-free survival. Samples from primary TNBC tumors had high CD24 expression compared to other cell clusters; further, CD24 levels were elevated in breast and ovarian cancer cells from primary tumors. Additionally, tumor-associated macrophages from breast and ovarian cancers expressed Siglec-10, an inhibitory receptor known to interact with CD24. Co-culture of breast cancer cells with M2-like macrophages expressing Siglec-10 showed that *CD24* deletion was sufficient to trigger phagocytosis. Additionally, Siglec-10 blockade with monoclonal antibodies (mAb) increased phagocytosis, as did *SIGLEC10* knockout in donor-derived macrophages. Live-cell imaging revealed that treating breast cancer cells with a mAb against CD24 made them more vulnerable to engulfment into the low pH phagolysosome, and FACS analyses showed an increase in phagocytosis after treatment with a mAb against CD24. Deletion of *SIGLEC10* decreased the response to CD24 blockade. CD24 expression was correlated not only with response to CD24 blockade, but also with baseline phagocytosis levels, implying a significant role for CD24 as a "don't eat me" signal. Ovarian cancer cells from patients with metastatic ovarian cancer treated with a mAb against CD24 exhibited greater phagocytosis by M2-like macrophages than those treated with a mAb against the known "don't eat me" signal CD47, and cotreatment with both mAbs resulted in an even further increase in phagocytosis. In a mouse breast cancer model, tumors lacking CD24 grew significantly less than wild-type tumors, resulting in a survival advantage, and mice with tumors with wild-type CD24 exhibited reduced tumor growth with anti-CD24 therapy. Collectively, these results suggest that CD24 may be a useful target for immunotherapy, especially for breast and ovarian cancers. ■

Barkal AA, Brewer RE, Markovic M, Kowarsky M, Barkal SA, Zaro BW, et al. CD24 signalling through macrophage Siglec-10 is a target for cancer immunotherapy. Nature 2019 Jul 31 [Epub ahead of print].

AACR American Association for Cancer Research

CANCER DISCOVERY

p53 Loss Can Promote Neutrophilia, Increased WNT Signaling, and Metastasis

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