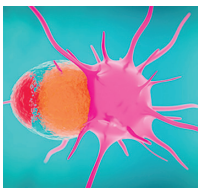
Obesity

Major Finding: DNA damage in normal breast epithelium of *BRCA* mutation carriers is enhanced by obesity.

Concept: Pharmacologic inhibition of estrogen biosynthesis and activity, leptin, or insulin reduced DNA damage.

Impact: This study reveals a link between elevated BMI and breast cancer development in patients with *BRCA* mutations.

OBESITY INCREASES BREAST EPITHELIUM DNA DAMAGE IN *BRCA* MUTATION CARRIERS



Germline mutations in *BRCA1* or *BRCA2*, which affect homologous recombination–mediated repair of DNA double-strand breaks, are causally linked to breast cancer development. There is also strong evidence that obesity, defined as a body mass index (BMI) at or above 30, is linked to hormone receptor–positive breast cancer development. However, the relationship between obesity and *BRCA1/2* mutation status has not been fully resolved. Bhardwaj and colleagues sought to elucidate the connection between obesity and DNA damage in breast epithelial cells and showed a positive correlation between elevated BMI and DNA damage in the normal breast epithelia of women carrying a *BRCA* mutation. RNA sequencing was used to identify obesity-related changes to the microenvironment that promote DNA damage and revealed altered gene expression between *BRCA1/2* carrier patients with high BMI versus those with low BMI, including activation of estrogen biosynthesis pathways in carrier patients with high BMI. Moreover, secreted factors, including β-estradiol, were found to be upregulated in *BRCA* mutation carriers with obesity, suggesting that endogenously produced factors in the microenvironment of women with obesity can induce gene expression changes as well as DNA damage in neighboring breast epithelial cells. Mechanistically, pharmacologic disruption of estrogen signaling and biosynthesis using fulvestrant or metformin indicated a reduction in DNA damage, with additional obesity-associated factors like leptin and insulin also demonstrating a positive correlation with DNA damage in cells with *BRCA* heterozygous mutations that could be mitigated by a leptin-neutralizing antibody or a PI3K inhibitor, respectively. Furthermore, mice with *BRCA* heterozygous mutations that were fed a high-fat diet exhibited elevated DNA damage in the mammary gland as well as early breast tumor penetrance. In summary, this study showed that BMI is positively correlated with DNA damage in the normal breast epithelium of *BRCA1/2* mutation carriers and suggests that maintaining a lower body weight or pharmacologically targeting estrogen or metabolic dysfunction in this patient population could reduce breast cancer risk. ■

Bhardwaj P, Iyengar NM, Zahid H, Carter KM, Byun DJ, Choi MH, et al. Obesity promotes breast epithelium DNA damage in women carrying a germline mutation in BRCA1 *or* BRCA2. *Sci Transl Med 2023;15:eade1857.*

doi: 10.1158/2159-8290.CD-RW2023-036

Prostate Cancer

Major Finding: Prostate tumor cell secretion of APOE promotes senescence of TREM2$^+$ immunosuppressive neutrophils.

Concept: Histone deacetylase inhibitors eliminate these neutrophils and improve current standard-of-care efficacy.

Impact: These results support the targeting of these senescent neutrophils to improve patient outcomes.

THE APOE–TREM2 AXIS MEDIATES SENESCENT NEUTROPHILS IN PROSTATE CANCER

Enhanced numbers of immunosuppressive neutrophils promote tumor proliferation, immune suppression, and treatment resistance in many cancer types, including prostate cancer. Typically, in healthy subjects, neutrophils are characterized by a short half-life, but it currently remains undetermined whether immunosuppressive neutrophils that are critical to tumorigenesis persist within the tumor microenvironment (TME). Bancaro and colleagues sought to address this issue and showed that tumor-infiltrating immunosuppressive neutrophils express markers of cellular senescence and persist in the TME, where they are especially high in castration-resistant disease. These senescent neutrophils demonstrated enhanced immunosuppressive activity and protumorigenic function, and investigation into factors secreted by tumor cells that can regulate this phenotype revealed that prostate tumor cell secretion of apolipoprotein E (APOE) binds to TREM2 on neutrophils and activates downstream ERK signaling to induce senescence. In patients with prostate cancer, TREM2 expression correlated with a senescent neutrophil signature, disease progression, and poor prognosis, with APOE expression also correlating with poor disease-free and overall survival. Elimination of these senescent neutrophils in murine models of prostate cancer reduced tumor progression, supporting the protumorigenic role of these cells. Moreover, histone deacetylase (HDAC) inhibitors demonstrated the ability to eliminate these pathogenic cells through reduction of TREM2, and combination of the HDAC inhibitor romidepsin with the androgen receptor signaling inhibitor enzalutamide significantly reduced the number of immunosuppressive senescent neutrophils as well as tumor cell proliferation. Use of this combination along with the CXCR2 inhibitors, which are currently under clinical evaluation in prostate cancer, showed an even greater inhibition of immunosuppressive senescent neutrophils and prostate cancer progression. In conclusion, this work shows that neutrophils can persist in the prostate cancer TME by acquiring markers of senescence and suggests that targeting this cell population can improve outcomes in patients with this disease. ■

Bancaro N, Calì B, Troiani M, Elia AR, Arzola RA, Attanasio G, et al. Apolipoprotein E induces pathogenic senescent-like myeloid cells in prostate cancer. Cancer Cell 2023;41:602–19.e11.

doi: 10.1158/2159-8290.CD-RW2023-037