Breast Cancer

Major finding: Inhibition of RANKL signaling may prevent breast tumorigenesis in *BRCA1*-mutation carriers.

Concept: In *BRCA1*-mutant breast tissue, RANK$^+$ cells are highly proliferative and vulnerable to DNA damage.

Impact: RANKL inhibition has potential in breast cancer prevention therapy in patients with *BRCA1* mutations.

RANKL BLOCKADE MAY AID BREAST CANCER PREVENTION IN HIGH-RISK PATIENTS

Individuals who harbor germline mutations in the breast-cancer-susceptibility gene *BRCA1* have an increased risk of developing breast cancer. The resulting tumors are often hormone receptor–negative basal-like tumors with deregulated progesterone signaling that have a poor prognosis. Patients carrying *BRCA1* mutations often undergo prophylactic mastectomy to reduce the risk of breast cancer, and effective preventative therapies are needed. The receptor activator of nuclear factor kappa-B ligand (RANKL) is an important mediator of progesterone signaling in mammary gland development and tumorigenesis, prompting Nolan and colleagues to investigate the role of RANK–RANKL signaling in the initiation of breast tumorigenesis in patients carrying *BRCA1* mutations. Breast tissue from normal, *BRCA1*-mutation, or *BRCA2*-mutation women revealed that RANK expression was restricted to normal luminal progenitor (LP) cells in wild-type and *BRCA1*-mutant breast tissue, with a larger fraction of RANK$^+$ LP cells in *BRCA1*-mutant tissue, suggesting that enhanced RANK expression indicates a perturbed LP population in *BRCA1*-mutation carriers. RANK$^+$ LP cells from *BRCA1*-mutation carriers exhibited increased clonogenic capacity and proliferation compared to RANK$^-$ cells and RANK$^+$ cells from wild-type *BRCA1* tissue. RANK$^+$ LP cells exhibited enrichment of genes involved in cell cycle, proliferation, and DNA repair. Further, RANK$^+$ progenitor cells from *BRCA1*-mutant tissue were more susceptible to DNA damage than RANK$^-$ progenitor cells. Data from The Cancer Genome Atlas revealed that RANK$^+$ LP cells exhibited a basal-like gene signature, whereas RANK$^-$ cells were more similar to other subtypes, suggesting that RANK$^+$ LP cells might be a target for breast cancer prevention therapy. The RANKL inhibitor, denosumab, blocked progesterone-induced proliferation in BRCA1-mutant organoids. Further, in a pilot window study, three *BRCA1*-mutation carriers treated with denosumab exhibited reduced breast epithelial cell proliferation. Finally, in BRCA1-deficient mouse models, RANKL inhibition resulted in delayed tumor onset. Altogether, these data imply that RANK signaling promotes tumorigenesis in *BRCA1*-mutation carriers, and suggest the potential for RANKL targeting in breast cancer prevention. ■

Nolan E, Vaillant F, Branstetter D, Pal B, Giner G, Whitehead L, et al. RANK ligand as a potential target for breast cancer prevention in BRCA1-mutation carriers. Nat Med 2016 Jun 20 [Epub ahead of print].

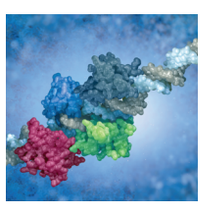
DNA Repair

Major finding: H4K20me0 recruits the TONSL–MMS22L DNA repair complex to postreplicative chromatin.

Concept: H4K20me0 distinguishes newly synthesized unmethylated histones from recycled methylated histones.

Impact: TONSL–MMS22L may have a tumor suppressor role in recognizing H4K20me0 and promoting genomic stability.

THE TONSL–MMS22L DNA REPAIR COMPLEX IS A H4K20me0 READER



The mechanisms by which cells distinguish and recognize prereplicative and postreplicative chromatin states are poorly understood. The TONSL–MMS22L homologous recombination complex has been shown to interact not only with nucleosomal histones in chromatin but also with newly synthesized histone H3 and H4, the histone chaperone ASF1, and the replication factor MCM2, suggesting functions for TONSL–MMS22L as both a histone code reader and a histone chaperone during DNA replication. Finding that the TONSL ankyrin repeat domain (ARD) alone bound directly to histones H3 and H4, Saredi, Huang, and colleagues solved the crystal structure of the TONSL ARD in complex with an H3–H4 tetramer and the MCM2 histone-binding domain and observed that the TONSL ARD interacted with the H4 tail. Of note, the structure predicted that H4K20 methylation would disrupt essential hydrogen bonds between the TONSL ARD and H4 tails. Consistent with this prediction, TONSL-bound nucleosomes did not exhibit H4K20 methylation, and depletion of the H4K20 methyltransferase SET8 increased TONSL binding to chromatin sites that normally exhibit H4K20 methylation, providing further evidence that TONSL binds to unmethylated H4K20 (H4K20me0). Altogether, these findings suggest a role for the TONSL ARD as a histone-reading domain for H4K20me0 as well as a role for the TONSL–MMS22L complex in recognizing postreplicative chromatin, as the majority of newly synthesized histones, but not recycled histones, are unmethylated at H4K20. TONSL was recruited to DNA repair sites and damaged replication forks during S and G2 phases, but was excluded from chromatin in G1 phase, further indicating that TONSL is recruited to replication forks and postreplicative chromatin by recognition of H4K20me0. Additionally, TONSL ARD mutants induced replication-associated DNA damage, whereas the recruitment of wild-type TONSL–MMS22L to chromatin maintained genome stability in the presence of DNA damaging agents. In addition to suggesting a tumor-suppressive function of TONSL–MMS22L in recognizing H4K20me0, these findings provide a histone-based mechanism for recognizing postreplicative chromatin. ■

Saredi G, Huang H, Hammond CM, Alabert C, Bekker-Jensen S, Forne I, et al. H4K20me0 marks post-replicative chromatin and recruits the TONSL-MMS22L DNA repair complex. Nature 2016;534:714–8.