Structural Biology

Major finding: Structures of PRC2 with its cofactors suggest context-dependent activation affected by cofactor binding.

Approach: Cryo-EM structures of PRC2 in complex with its cofactors AEBP2 and JARID2 reveal multiple active conformations.

Impact: JARID2 and AEBP2 may allow PRC2 activation in chromatin environments lacking activating histone marks.

JARID2 AND AEBP2 MIMIC HISTONE TAILS TO PROMOTE PRC2 ACTIVITY

The polycomb repressive complex 2 (PRC2) establishes H3K27 methylation to maintain heterochromatin and promote a transcriptionally repressive state, and PRC2 subunits are subject to mutations and misregulation in cancer. The core PRC2 complex is comprised of four proteins, the catalytic subunit EZH2, EED, SUZ12, and RBAP46/RBAP48. Cofactors such as AEBP2 and JARID2 are found to associate with the complex *in vivo*. However, the effect of these cofactors on the structure and activity of PRC2 has not been fully elucidated, prompting Kasinath, Faini, Poepsel, and colleagues to obtain high-resolution cryo-EM structures of PRC2 in complex with AEBP2 and JARID2. Two PRC2–AEBP2–JARID2 structures were obtained (at 3.5Å and 3.9Å) in different active conformations, termed the "compact active" and "extended active" states, both with methylated JARID2 bound to EED. In the absence of JARID2 containing K116, PRC2 adopted an inactive conformation termed the "extended basal state." Two JARID2 molecules bound simultaneously to PRC2 in the allosteric and active sites, supporting a model in which PRC2 methylates JARID2 at K116, resulting in methylated JARID2 binding to the allosteric site to promote PRC2 activity. The multiple conformational states along with the presence of large disordered regions in AEBP2 and JARID2 suggest an intrinsic conformational variability that may allow PRC2 to integrate diverse biological cues to regulate its activity in different contexts. JARID2 K116me2/3 binding mimicked histone H3 tails and is therefore able to stimulate PRC2 activity in the absence of H3K27me3. Similarly, AEBP2 mimicked unmethylated H3K4 binding to RBAP48, which may affect PRC2 activity in the presence of the inhibitory H3K4me3 mark. Further, AEBP2 established a structural bridge between RBAP48 and the EZH2 SET domain. Altogether, these findings suggest a structural mechanism by which JARID2 and AEBP2 can synergistically activate PRC2, and that by mimicking histone tails, JARID2 and AEBP2 may be able to stimulate PRC2 activity in diverse chromatin environments. ■

Kasinath V, Faini M, Poepsel S, Reif D, Feng XA, Stjepanovic G, et al. Structures of human PRC2 with its cofactors AEBP2 and JARID2. Science 2018 Jan 18 [Epub ahead of print].
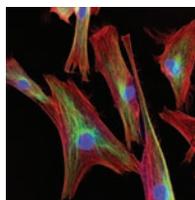
Stem Cells

Major finding: CD10 and GPR77 define a cancer-associated fibroblast (CAF) subset that sustains cancer stemness.

Mechanism: CAFs secrete IL6 and IL8 to create a cancer stem cell–supporting niche to promote breast cancer.

Impact: Targeting CD10+GPR77+ CAFs may be a strategy to restore chemosensitivity in patients with breast cancer.

CD10+GPR77+ CANCER-ASSOCIATED FIBROBLASTS PROMOTE CHEMORESISTANCE

Carcinoma-associated fibroblasts (CAF) are heterogeneous stromal cells in the tumor microenvironment thought to promote tumor progression. However, targeting CAFs promoted tumor progression in pancreatic cancer, suggesting that CAFs may have both tumor-promoting and tumor-suppressing roles. Su, Chen, Yao, and colleagues sought to identify specific cancer-promoting CAF subsets that might represent therapeutic targets. Analysis of paired tumor samples from patients with breast cancer before and after neo-adjuvant chemotherapy revealed no difference in the number of CAFs in chemosensitive versus chemoresistant patients. Microarray analysis of RNA from CAFs from 7 sensitive and 7 resistant patients found that the cell-surface markers CD10 and GPR77 were upregulated in the CAFs from chemoresistant tumors, a finding that was validated in an additional 24 patients. In patients with breast cancer or non–small cell lung cancer, high levels of CD10+GPR77+ CAFs were associated with chemoresistance and poor survival. In a breast cancer xenograft model, CD10+GPR77+ CAFs were themselves chemoresistant and also induced conferred chemoresistance to the tumor cells in their microenvironment. CD10+GPR77+ CAFs secreted IL6 and IL8, creating a niche that promoted cancer stem cell (CSC) chemoresistance and survival, and thereby enhancing the engraftment of breast cancer patient-derived xenografts (PDX). Mechanistically, GPR77 induced p65 phosphorylation that promoted P300-mediated p65 acetylation to drive persistent NF-κB activation that maintained the phenotypes and functions of CD10+GPR77+ CAFs. Inhibiting GPR77 with a neutralizing antibody blocked the establishment of breast cancer PDXs, and, in established PDXs, anti-GPR77 enhanced the efficacy of chemotherapy. In addition to identifying a CD10+GPR77+ tumor-promoting subset of CAFs, these findings suggest that targeting CD10+GPR77+ CAFs (as with an anti-GPR77 antibody) may suppress breast tumorigenesis and sensitize tumors to chemotherapy. ■

Su S, Chen J, Yao H, Liu J, Yu S, Lao L, et al. CD10+GPR77+ cancer-associated fibroblasts promote cancer formation and chemoresistance by sustaining cancer stemness. Cell 2018;172:841–56.e16.