Supplemental Methods S1. Nanodroplet FAIRE assay

Tissue deparaffinization and rehydration

1. Remove paraffin by placing the FFPE tissue slides on a slide holder and transferring to a coupling jar containing 200 mL of fresh xylene (Epredia 6615). Incubate for 3 minutes and blot dry on a paper towel. Repeat for a total of 3 xylene treatments.
2. While incubating in xylene, prepare 2 coupling jars containing 200 mL of 100% ethanol, 2 jars containing 85% ethanol, 1 jar containing 70% ethanol, 1 one jar containing double deionized water. After the third xylene treatment, incubate the slides sequentially for 3 minutes in the decreasingly concentrated ethanol baths and then water bath (Xylene→ 100% ethanol→ 85% ethanol→ 70% ethanol→ water).
3. Remove the slides from the double deionized water and blot the tissue dry with a paper towel. Carefully use a fine razor blade (VWR 55411-050) to scrape the tissue horizontally off the slide in one fluid motion. The tissue should remain intact and rest on top of the slide. use a tweezer to place inside 100 µL clear round bottom crimp vials (Triangle Biotechnology, Inc., PL101-BT100) on ice.
4. Add 90 µL of Lysis Buffer A (10 mM Tris-HCl, pH 8.0; 2% Triton-X-100; 1% SDS; 100 mM NaCl; and 1 mM EDTA) per tube and re-suspend tissue by pipetting up and down.
5. Add 10 µL of nanodroplets (Triangle Biotechnology, Inc., FF101-5000), for a total volume of 100 µL. Seal the tube with a crimp cap (ThermoFisher Scientific, C4008-6A), invert the tube horizontally in a circular motion to mix, and briefly spin a picofuge.

Sonication

1. Sonicate the tubes in the Covaris E110 sonicator at 4˚C with 20% duty factor; intensity of 8; 200 cycles per burst, or in a Covaris LE220 sonicator at 4°C with a peak incident power of 450; duty factor of 20%; 200 cycles per burst, for 2 - 16 minutes. Sonication time may need to be optimized for different tissue sizes, thickness, or type.
2. Briefly spin sonication tubes in a picofuge before removing caps.
3. Transfer samples to 1.7 mL tubes (Genesee Scientific, 22-282), making sure to re-suspend any remaining tissue fragments.
4. Centrifuge for 10 minutes at 4°C, 20,000 x g.
5. Transfer supernatant into PCR tubes (Genesee Scientific, 27-104), being careful not to aspirate any pellet.

FAIRE assay

1. Add 2 µL of [7,000 U/mL] RNase (Qiagen, 19101) to each sample and incubate at 37°C for 10 minutes in thermal cycler (Bio-Rad).
2. After incubation, transfer 10% (approximately 10 uL) of each sample to new PCR tubes and add 90 µL of Lysis Buffer A. These will be the input samples. Add 2 µL of [20 mg/mL] Proteinase K (Worthington) and incubate at 55°C for 1 hour, followed by 80°C for 2 hours in thermal cycler (Bio-Rad). After incubation, purify input DNA on a silica matrix column according to manufacturer's instructions (Zymo Research ChIP DNA Clean & Concentrate kit, D5201). DNA is eluted in a 25 µL volume.
3. The FAIRE assay is performed by purification of remaining 90 µL of chromatin on a silica matrix column according to manufacturer's instructions (Zymo Research ChIP DNA Clean & Concentrate kit, D5201). DNA is eluted in a 25 µL volume.
4. Quantify DNA by fluorometry (Qubit Fluorometer with Qubit dsDNA High Sensitivity Assay Kit, Invitrogen, Q33231).