High-resolution Chromosome Conformation Capture: Hi-C

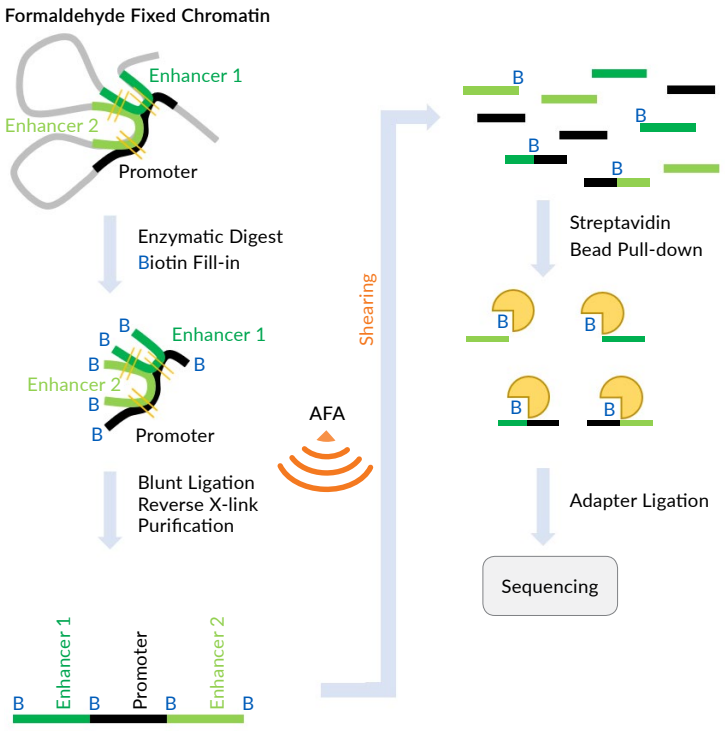
Scientific Relevance

- Three-dimensional chromatin organization regulates gene expression [1]
- Aberrant chromatin looping causes altered gene regulation in malignancies including solid tumors as well as hematologic neoplasms [2]
- Characterization of 3D-chromosomal conformations allows classification of cancer subtypes [3]
- Cancer progression can be alleviated by inhibiting certain chromatin loop formations [4,5,6]
- Hi-C provides a powerful tool to better characterize 3D chromatin organization and helps to uncover the impact of cancer risk-associated SNPs [7,8]

Challenges

- Protocol requires several replicates to retrieve reliable 3D-conformation data, good sets of controls, and optimizations are essential
- Unbiased, reproducible shearing with a tight DNA fragment size distribution is required to capture all chromosomal interactions especially in low input derivates [9] of the method

Workflow



Schematic representation of Hi-C workflow adapted from Davies *et al.*
Crosslinked chromatin is digested and the overhangs of the restriction enzymes are filled-in using biotin-labelled nucleotides following blunt-end ligation. Reproducible shearing followed by Streptavidin-bead pull-down allows the efficient and selective purification of chimeric DNA ligation junctions which are subjected to sequencing.

Advantages of Adaptive Focused Acoustics® (AFA®)

AFA technology is a very gentle, reproducible, and tuneable shearing method.

- Random shearing guarantees an unbiased fragmentation of ligation products
- The tight size distribution ensures comprehensive representation of all ligation junctions in the sequencing library
- Reproducible shearing allows reliable comparison of samples from different origins such as cancer subtypes or different stages of progressive diseases

Suggested Covaris Products

- Covaris Focused-ultrasonicator (M-Series, S-Series, E-Series, or LE-Series)

Citations

- Van Berkum et al. Hi-C: a method to study the three-dimensional architecture of genomes. Vis Exp., (2010)
- Ramani et al. Mapping three-dimensional genome architecture through in situ DNase Hi-C. Nat Protoc, (2016)
- Elphege et al. Targeted degradation of CTCF decouples local insulation of chromosome domains from genomic compartmentalization. Cell, (2017)

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