reference herein. Beyond DNA methylation, however, there is an unmet need for methods enabling sensitive characterization of epigenetic changes at targeted DNA loci. Chromatin accessibility (by ATAC-seq) and protein(s) associated with a DNA locus (by ChIP-seq) are examples of epigenetic elements that are difficult to target with existing hybrid capture technology. Commonly, assays that enrich for DNA sequences are associated with an epigenetic feature. However, as these sequences are not known *a priori*, it is challenging to design appropriate hybrid capture oligonucleotides to efficiently enrich the output of the epigenetic assay for a particular genomic region of interest (e.g., a genomic locus).

[0006] Prior methods of using deactivated Cas (dCas9) for targeted locus-specific protein isolation to identify histone gene regulators have been presented; see, e.g., Tsui et al., "dCas9-targeted locus-specific protein isolation method identifies histone gene regulators," PNAS 115(2): E2734-E2741 (2018), the entire contents of which are incorporated by reference herein. Such methods demonstrated that dCas9-based locus enrichment can isolate chromatin that can be subsequently assayed by mass spectrometry. However, this method only allows a single chromatin locus to be assayed in each experiment. Furthermore, this prior work provides two separate results, i.e. the sequence of the DNA locus, and mass spectrometry to identify DNA associated proteins. Improved methods for locus-targeted epigenetic analysis are needed.

SUMMARY

[0007] Genomic library preparation, and targeted epigenetic assays, using Cas-gRNA ribonucleoproteins (RNPs), are provided herein.

[0008] Some examples herein provide a method of treating a mixture of first double-stranded polynucleotides from a first species and second double-stranded polynucleotides from a second species, The method may include protecting ends of the first double-stranded polynucleotides and any ends of the second double-stranded polynucleotides. The method may include, after protecting the ends of the first and second double-stranded polynucleotides, selectively generating free ends within the first double-stranded polynucleotides. The method may include degrading the first double-stranded polynucleotides from the free ends toward the protected ends. In one aspect, the present disclosure refers to a method of treating a mixture of first double-stranded polynucleotides from a first species and second double-stranded polynucleotides from a second species, the method comprising: protecting ends of the first double-stranded polynucleotides and any ends of the second double-stranded polynucleotides; after protecting the ends of the first and second double-stranded polynucleotides, selectively generating free ends within the first double-stranded polynucleotides; and degrading the first double-stranded polynucleotides from the free ends toward the protected ends.

stranded DNA. In some examples, the second double-stranded polynucleotides include circular DNA.

[0015] In some examples, the Cas includes Cas9.

[0016] Some examples herein provide a composition. The composition may include first double-stranded polynucleotides from a first species. Ends of the first double-stranded polynucleotides may be protected. The composition may include second double-stranded polynucleotides from a second species. Any ends of the second double-stranded polynucleotides may be protected. The composition also may include CRISPR-associated protein guide RNA ribonucleoproteins (Cas-gRNA RNPs) hybridized to sequences that are present within the first double-stranded polynucleotides and that are not present within the second double-stranded polynucleotides. The Cas-gRNA RNPs may be for cutting the sequences so as to selectively generate free ends within the first double-stranded polynucleotides. In one aspect, the present disclosure refers to a composition, comprising: first double-stranded polynucleotides from a first species, wherein ends of the first double-stranded polynucleotides are protected; second double-stranded polynucleotides from a second species, wherein any ends of the second double-stranded polynucleotides are protected; and CRISPR-associated protein guide RNA ribonucleoproteins (Cas-gRNA RNPs) hybridized to sequences that are present within the first double-stranded polynucleotides and that are not present within the second double-stranded polynucleotides, the Cas-gRNA RNPs being for cutting the sequences so as to selectively generate free ends within the first double-stranded polynucleotides.

[0017] In some examples, the sequences include mammalian specific repetitive elements. In some examples, the mammalian specific repetitive elements include human repetitive elements. In some examples, the second species is bacterial, fungal, or viral.

[0018] In some examples, the ends of the first and second double-stranded polynucleotides are protected using hairpin adapters. In some examples, the ends of first and second double-stranded polynucleotides are protected using 5’-dephosphorylation. In some examples, the ends of the first and second double-stranded polynucleotides are protected using modified bases. In some examples, the modified bases include phosphorothioate bonds.

[0019] In some examples, the free ends include 3' ends. In some examples, the free ends include 5' ends.

[0020] In some examples, the first double-stranded polynucleotides include double-stranded DNA. In some examples, the second double-stranded polynucleotides include double-stranded DNA. In some examples, the second double-stranded polynucleotides include circular DNA.

[0021] In some examples, the Cas includes Cas9.