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Epigenetic mediators and consequences of excessive alcohol consumption

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Alcohol has pleiotropic effects across multiple organ systems, including brain, cardio-vascular, endocrine, immune, musculoskeletal, and gastrointestinal systems. Moreover, some effects, such as intoxication, can be brief, but others, such as the development of Alcohol Use Disorders (AUDs), cardiovascular disease, and liver damage, can persist for a lifetime. Effects resulting in encoding of endocrine and other dysfunctions can also persist across generations. This complexity creates a barrier to the creation of therapeutics and discovery of biomarkers. However, we know that environmental factors, which can include drugs of abuse such as alcohol, can have short- and long-term effects on gene expression through epigenetic mechanisms (Holliday, 2006; Shukla et al., 2008). Epigenetic mechanisms affect the transcription and translation of many genes simultaneously. Therefore, by understanding the mechanics of these epigenetic changes, we will have the ability to craft powerful new therapeutics to offset negative effects of alcohol exposure.

Epigenetic modifications commonly occur through three mechanisms: methylation of DNA, histone post-translational modifications, and the interactions of non-coding RNA with transcriptional and translational cellular machinery (Fig. 1). Modifications that open the tightly wound chromatin structure are thought to increase gene expression, while modifications that condense chromatin structure are thought to inhibit gene expression. DNA methylation, which usually occurs at groupings of cytosine and guanine nucleotides referred to as “CpG islands”, represses gene transcription. This repression occurs with the binding of methyl-CpG binding domain proteins, the subsequent recruitment transcription inhibitory complexes, and chromatin condensation (Cedar & Bergman, 2012). Post-translational modifications of histones, by covalent addition of functional groups to histone tails, can also regulate chromatin access. These modifications include commonly studied acetylation and methylation, as well as many other modifications, including ubiquitinylation, phosphorylation, and ADP ribosylation, to name a few (Bannister & Kouzarides, 2011; Kouzarides, 2007; Strahl & Allis, 2000). Histone acetylation relaxes chromatin, which facilitates gene transcription. Histone methylation can bidirectionallly affect gene expression depending on the amino acid location on the histone tail and quantity of methylation, i.e., whether singly, di-, or tri-methylated (Zhou, Goren, & Bernstein, 2011). Non-coding RNAs (ncRNAs) can affect both gene transcription and translation. For example, long non-coding RNAs (lncRNAs, >200 nucleotides in length) can interact with transcription machinery to trigger chromatin compaction at commonly imprinted regions, including the H19 locus and X chromosome (Nagano & Fraser, 2011; Rinn & Guttman, 2014). MicroRNAs (miRNAs, ~21 nucleotides in length) affect translation by binding the 3′-untranslated region (3′-UTR) of mRNA transcripts and, along with the miRNA-induced silencing complex, inhibit translation and enhance mRNA degradation (Fabian & Sonenberg, 2012). miRNAs can bind to many related transcripts and regulate the expression of gene networks as a whole (reviewed in Miranda, 2014).

Commonly researched epigenetic modifications include covalently bonded groups attached to DNA and histones, as well as interactions with non-coding RNAs (ncRNAs). DNA methylation, via methyl-CpG binding domain proteins (MBDs), recruits repressor

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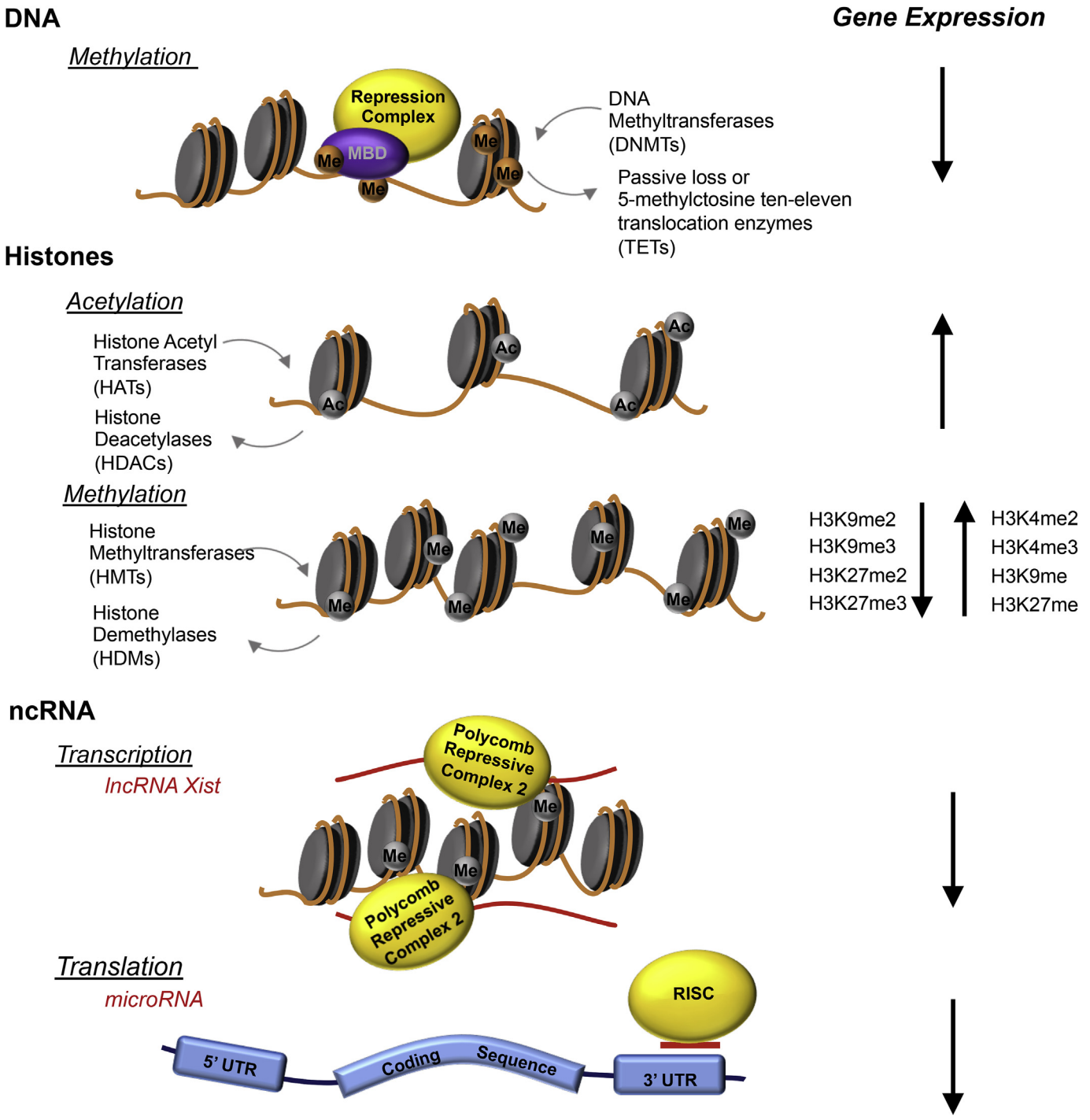

Fig. 1. Commonly researched epigenetic modifications.

complexes to inhibit transcription and to encourage chromatin condensation. Histone acetylation opens chromatin to allow access to transcription machinery, while histone methylation can either condense or open chromatin, depending on the localization and degree of methyl group attachment. ncRNAs can interact at the chromatin level (e.g., long non-coding RNAs that act during imprinting to silence an allele) or at the translation level (e.g., microRNAs that bind to the 3′-UTR of mRNAs), along with the RNA-Induced Silencing Complex (RISC), to trigger mRNA degradation.

DNA methylation, histone modification, and ncRNAs interact with each other to coordinate and regulate overall gene expression. The aim of this special edition of *Alcohol* is not only to provide background on what we currently know about epigenetic modifications in response to alcohol exposure, but also to further examine the impact of these changes throughout the lifespan and across generations. Additionally, we highlight, by targeting epigenetic mediators, how we can create novel therapeutics for both AUDs in adult populations and for Fetal Alcohol Spectrum Disorders (FASD).