Alcohol 60 (2017) 31–39

Contents lists available at ScienceDirect

Alcohol

journal homepage: http://www.alcoholjournal.org/

Emerging roles for ncRNAs in alcohol use disorders

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ARTICLE INFO

Article history:
Received 15 October 2016
Received in revised form
4 January 2017
Accepted 4 January 2017

Keywords:
Alcohol
Non-coding RNA
microRNA
Long noncoding RNA
Transcriptome
Gene regulation
Next generation sequencing

ABSTRACT

Chronic alcohol exposure produces widespread neuroadaptations and alterations in gene expression in human alcoholics and animal models. Technological advances in the past decade have increasingly highlighted the role of non-protein-coding RNAs (ncRNAs) in the regulation of gene expression and function. These recently characterized molecules were discovered to mediate diverse processes in the central nervous system, from normal development and physiology to regulation of disease, including alcoholism and other psychiatric disorders. This review will investigate the recent studies in human alcoholics and rodent models that have profiled different classes of ncRNAs and their dynamic alcohol-dependent regulation in brain.

Introduction

Non-coding RNA

Protein-coding genes have traditionally been the most well studied sequences in the human genome; however, these genes account for less than 2% of known structural and regulatory molecular elements (Alexander, Fang, Rozowsky, Snyder, & Gerstein, 2010). In recent years, it has become increasingly clear that the non-protein-coding portion of the genome is functionally important and is required for normal development and physiology, and is also linked with a number of diseases (Cech & Steitz, 2014; Mercer, Dinger, & Mattick, 2009). This fundamental change in our understanding of the complexity of the transcriptome has been the result of improved RNA sequencing (RNA-seq) technologies, which allow exploration of gene structure and regulation in unprecedented detail (Fig. 1). Data generated from these advanced techniques have transformed our view of the central dogma that DNA is transcribed into RNA, which is translated into protein. Non-coding RNAs (ncRNAs) are emerging as key transcriptional and post-translational regulators, representing a large and diverse class of regulatory molecules (Alexander et al., 2010). ncRNAs make up a sizeable portion of the transcriptional landscape of the cell (Carninci & Hayashizaki, 2007; Carninci et al., 2005), but the precise functions of many non-coding elements remain largely unknown. Defining the biological roles carried out by multiple classes of ncRNAs is an expanding area of transcriptomics that will likely rival the large number and diversity represented by the proteome. Currently, ncRNAs are grouped into three general subclasses based on nucleotide number (small, 18–31 nt; medium, 31–200 nt; and long, >200 nt), with each class having regulatory potential and specific subcellular localization (Alexander et al., 2010; Costa, 2005; Dozmorov, Giles, Koelsch, & Wren, 2013). These ncRNAs include transfer and ribosomal RNA (tRNA and rRNA, respectively), small nucleolar RNA (snoRNA), microRNA (miRNA), small interfering RNA (siRNA), small nuclear (snRNA), extracellular RNA (exRNA), piRNAs, and small Cajal body-specific RNA (scaRNA), as well as different classes of long ncRNA (lncRNA), including intergenic (lincRNA) and intronic RNA. Identifying roles for ncRNAs will provide a better understanding of cellular function, as well as new insight into gene regulation of disease.

Genomic studies based on DNA and RNA sequencing have identified thousands of ncRNAs in diverse animal genomes. Until recently, the conservation of ncRNAs between human and nonhuman primates was limited compared to human-mouse conservation, due to limitations in the quality of nonhuman primate genome annotations. However, sequencing technology has resulted in more complete and correct assemblies, thus greatly improving genome annotation quality. Systematic curation efforts

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http://dx.doi.org/10.1016/j.alcohol.2017.01.004
0741-8329/

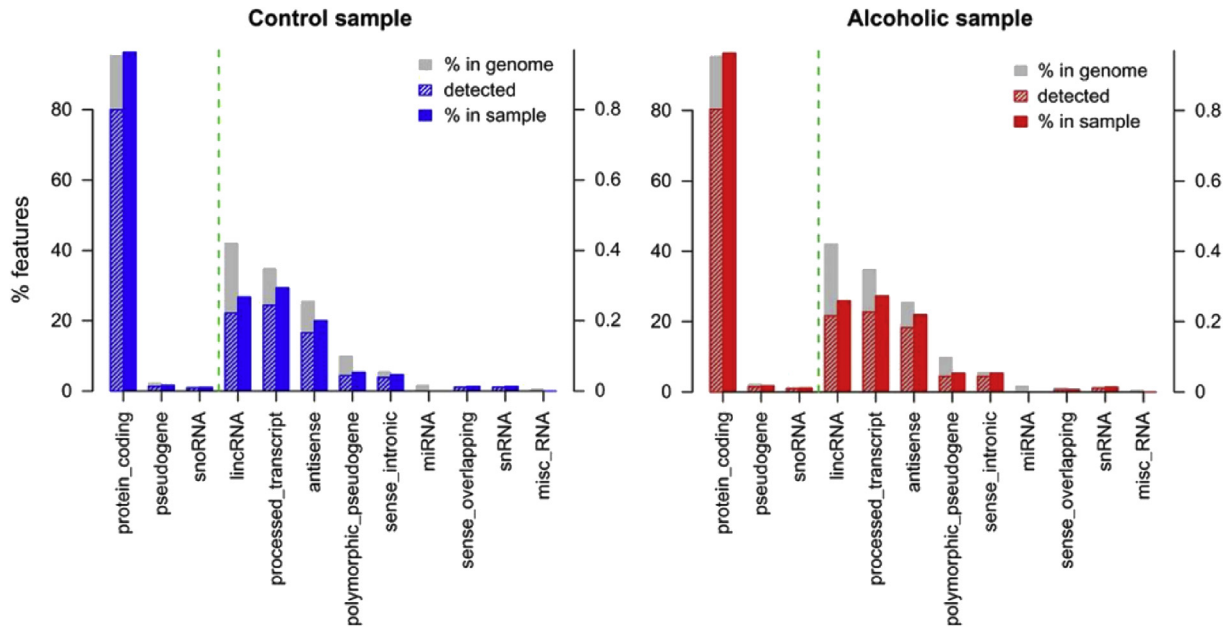

Fig. 1. RNA features detected by RNA-seq in the prefrontal cortex of alcoholic and matched control samples. Bar plots depict the percentage of features detected in representative control (blue) and alcoholic (red) samples. The left axis shows the percentage of features for the top three biotypes and the right axis shows the percentage of remaining biotypes (separated by dotted green vertical line). Protein-coding transcripts were the predominant feature detected in both groups.

have enabled the development of several cross-species ncRNA databases (Ulitsky, 2016). Identification of cross-species conservation is a key question when evaluating the functional impact of specific ncRNAs. For example, if a ncRNA is associated with a human condition, it is important to know the extent to which it can be studied in model organisms. Conversely, if a ncRNA is discovered in a model organism, evidence of conservation will be critical for establishing relevance to a human condition.

Distinct ncRNA mechanisms in brain are thought to influence the development of psychiatric diseases (Kocerha, Dwivedi, & Brennand, 2015; Sartor, St Laurent, & Wahlestedt, 2012), including alcoholism (Farris & Mayfield, 2014). Rapid advances in this field have largely come from next-generation sequencing technologies such as RNA-seq that have been critical for genome-wide identification of novel transcripts (Fig. 1). Previous review articles have focused on ncRNAs (primarily miRNAs) that are altered in response to alcohol administration (Balaraman, Tingling, Tsai, & Miranda, 2013; Farris & Mayfield, 2014; Most, Workman, & Harris, 2014; Nunez & Mayfield, 2012; Pietrzykowski, 2010). This review focuses on the effects of alcohol on ncRNAs from studies published since 2012. It should be noted that there are few studies focusing on the association of genetic risk to ncRNAs in animal models, representing an area of future research.

MicroRNA

The expanding fields of genetics and genomics over the previous 15 years have highlighted the growing number of genes that can potentially influence alcohol-drinking behavior in humans and animal models. In particular, the discovery of miRNAs (Lee, Feinbaum, & Ambros, 1993) and their mechanisms of action are revolutionizing our understanding of gene regulation in physiology and disease (Mattick & Makunin, 2006; Morris & Mattick, 2014). These short (~17–24 nt) ncRNAs act as post-transcriptional modulators of gene expression by binding to miRNA-recognition elements in their numerous target genes. miRNA-mediated gene suppression occurs through multiple mechanisms, including interruption of translational initiation, 5′ decapping, alternative splicing, 3′ deadenylation, and exonuclease degradation (Fabian & Sonenberg, 2012; Krol, Loedige, & Filipowicz, 2010). miRNA biogenesis includes gene transcription by RNA polymerase II that typically binds to promoters near DNA sequences encoding precursor miRNAs (pre-miRNA). The resulting transcript is capped, polyadenylated, and spliced (Hammond, 2015). Many pre-miRNAs are derived from intronic transcriptional regions; however, novel mechanisms have been identified demonstrating that traditional RNA splicing events can negatively regulate the processing of pre-miRNAs that overlap exon-intron junctions (Melamed et al., 2013). These distinctly different RNA processing mechanisms (miRNA processing and RNA splicing) underscore the regulatory potential of these short ncRNAs.

miRNAs play important roles in neuronal differentiation, developmental timing, synapse function, and neurogenesis (Fiorenza & Barco, 2016). miRNAs are thought to act as 'master regulators' of gene expression, and a recent RNA-seq study of 13 different types of human tissue identified over 3700 mature miRNAs (Londin et al., 2015), compared to the >2700 listed in release 20 of miRBase (Kozomara & Griffiths-Jones, 2014). In addition, the sequence conservation across human and nonhuman primate-specific lineage is quite high (>94% of the newly discovered miRNAs). Given the vast number of miRNAs identified to date and the expression silencing of large collections of target genes, there is considerable regulatory potential of these molecules.

Alcohol-responsive miRNAs in human postmortem brain

Because of their regulatory functions, it is reasonable to expect that miRNAs are also critical mediators of alcohol's effects. Early studies demonstrated that alcohol alters miRNA levels and miRNA-regulated systems that are associated with tolerance, gut leakiness,