frontiers in
GENETICS

EDITORIAL
published: 18 April 2012
doi: 10.3389/fgene.2012.00049

Connecting ncRNA cigarette smoking studies with tobacco use behaviors and health outcomes

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Many studies have demonstrated that smoking behavior is influenced by both genetic and environmental factors, and that these influences can change over time and during development (Swan et al., 1996; Han et al., 1999; Koopmans et al., 1999; Maes et al., 1999; Stallings et al., 1999; True et al., 1999; Kendler et al., 2000; McGue et al., 2000; Hopfer et al., 2001, 2003; Rhee et al., 2003). For example, most studies comparing heritability of age of initiation of smoking and regular use patterns suggest that age of initiation is more likely influenced by environmental factors, while progression to regular use and addiction are more heritable (Han et al., 1999; Koopmans et al., 1999; Stallings et al., 1999; McGue et al., 2000; Rhee et al., 2003). Until recently, most studies of smoking behaviors aimed at understanding mechanisms have been forced to examine genetic and environmental influences separately, because little was known about genetic features that were modified by environmental factors. Within recent years, two major areas of research have exploded to provide possible novel mechanisms that may help explain why behavioral disorders such as substance dependence "runs in families" beyond the separate entities of environmental exposure and common genes. The first is epigenetic reprogramming, whereby long-lasting changes to the DNA such as methylation on CpG islands (Kim et al., 2009) and histone tail modifications (Berger, 2007) are conferred upon environmental exposures. The second is the involvement of ncRNAs in regulation of gene expression (Li and van der Vaart, 2011), and the topic of the review article by Maccani and Knopik (2012).

Despite decreasing rates of smoking over the last several decades, maternal smoking during pregnancy (MSP) remains a major public health problem (Mathews, 2001). MSP has been associated with many behavioral problems including irritability in neonatal infants (Stroud et al., 2009), attention behavioral problems in children (Fried et al., 1992), disruptive behaviors in teenagers (Wakschlag et al., 2011), and increased risk of tobacco dependence in young adults (Buka et al., 2003). Furthermore, secondhand smoke (SHS) exposure during childhood has been associated with adverse behavioral and cognitive outcomes (reviewed in Niaura et al., 2001; Shenassa et al., 2003; Herrmann et al., 2008). Animal studies provide more evidence that *in utero* exposure to nicotine directly affects offspring behaviors. For example, mice exposed to nicotine or alcohol *in utero* showed impairment in anxiety and learning behaviors (Li and Wang, 2004). These findings have been replicated in an elegant study of nicotine exposure throughout early development where mice were allowed to orally self-administer nicotine during gestation and lactation. Exposed pups showed dramatic differences for multiple behaviors including nicotine self-administration, social interactions, and performance on a forced swim test (Chistyakov et al., 2010). However, as reviewed recently by Winzer-Serhan (2008), other animal studies examining the effects of nicotine, which does not contain all of the ingredients in tobacco, have been contradictory. As discussed by Maccani and Knopik, specific miRNAs were downregulated in placental cell lines exposed to nicotine and benzo[a]pyrene, but different miRNAs were dysregulated in lung and airway epithelium tissue. In general, the few studies examining the effects of various aspects of cigarette smoking on miRNA expression have revealed that responses are likely to be highly complex, with tissue, temporal, and type of exposure leading to differential responses.

As we consider possible effects of environmental exposure on long-lasting biological mechanisms such as epigenetic reprogramming and ncRNA regulation, it is important to remember that smoking may exert its effects in different ways throughout one's life course, including *in utero*, early childhood, adolescence, young adulthood, and adulthood. Most of the mechanistic work to date has examined *in utero* smoking exposure, but there is evidence for a continuum of effect. Most smokers begin smoking during adolescence, and several studies have shown that earlier age of initiation is associated with increased risk for later dependence (Khuder et al., 1999; Lando et al., 1999; Hu et al., 2006; Palmer et al., 2009). Interestingly, there is a genetic example that associations between *CHRN* genes (encoding the nicotinic receptor subunit genes) and nicotine dependence, may differ between subjects who started smoking early and those with later onset (Schlaepfer et al., 2008; Weiss et al., 2008; Ducci et al., 2011; Hartz et al., in press). The association between *CHRN* genes and tobacco behaviors is one of the most widely replicated findings among substance abuse genetics (Amos et al., 2008; Bierut et al., 2008; Thorgeirsson et al., 2008, 2010; Saccone et al., 2010), so this developmental aspect is of high interest. These results suggest the possibility of a "critical period" during adolescence where environmental effects may have stronger effects on certain genetic mechanisms.

In addition, many animal studies have shown that the nicotinic acetylcholine receptors (nAChRs) are likely to be targets for nicotine's effects during prenatal tobacco exposure. Numerous studies have shown upregulation of certain nAChR subtypes (e.g., $\alpha 2\beta 4$-containing) in various brain regions following postnatal (Marks et al., 1992; Lain et al., 2005) and prenatal exposure (Navarro et al., 1989; Popke et al., 1997; Tizabi et al., 1997). These findings have been replicated in rats (Lv et al., 2008). However, the global nAChR response to nicotine is complex, because certain receptor subtypes (e.g., $\alpha 6$-containing) are downregulated specifically in dopaminergic brain regions (Chen et al., 2005). The nAChRs are ligand-gated ion channels containing a central cation pore that act as the primary target for nicotine and the endogenous agonist acetylcholine.

nAChRs have been shown to activate release of dopamine, and are likely important in mediating the rewarding properties of abused drugs (Salminen et al., 2004; Gotti et al., 2006). More recently, work using a mouse model has shown that the effects of early nicotine exposure on later behaviors is "primarily due to the neuropharmacological effects of the drug and not due to effects of exposure on maternal behavior," and that the nAChRs play a critical role in mediating these effects (Heath et al., 2010a,b). Therefore, the nAChRs represent a possible key modulator of how MSP has long-term behavioral effects on offspring in both human and animal studies. Given the strong genetic associations between the *CHRN* genes and smoking behaviors, possible miRNA binding sites within these genes might represent feasible targets for study and intervention in the future.

In conclusion, the role of ncRNA in smoking exposure responses is in its infancy. As reported by Maccani and Knopik, fewer than 10 studies have been conducted in this area to date, but it is a high priority topic so we can expect to see new studies published frequently. Most of these studies are likely to be conducted using cell lines and animal models. Since not all ncRNAs are conserved across mammals, it will be important to foster collaborations and cross-talk between basic science investigators and human geneticists and clinicians to integrate the knowledge for greatest potential impact for human health.

ACKNOWLEDGMENTS

This work was supported by R01 AA017889, R21 DA026901, and P60 DA011015.

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Received: 28 February 2012; accepted: 20 March 2012; published online: 18 April 2012.

*Citation: Ehringer MA (2012) Connecting ncRNA cigarette smoking studies with tobacco use behaviors and health outcomes. Front. Gene. **3**:49. doi: 10.3389/fgene.2012.00049*

This article was submitted to Frontiers in Non-Coding RNA, a specialty of Frontiers in Genetics.