Institut Pasteur
Microbes and Infection 17 (2015) 493–504
www.elsevier.com/locate/micinf

# RNA regulators of host immunity and pathogen adaptive responses in the oral cavity

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Received 2 February 2015; accepted 7 March 2015
Available online 17 March 2015

**Abstract**

The recent explosion of RNA-seq studies has resulted in a newfound appreciation for the importance of riboregulatory RNAs in the post-transcriptional control of eukaryotic and prokaryotic genetic networks. The current review will explore the role of *trans*-riboregulatory RNAs in various adaptive responses of host and pathogen in the oral cavity.
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*Keywords:* Small RNA; Noncoding RNA; MicroRNA; Host pathogen interactions; Gene expression regulation

## 1. Introduction

Recent improvements in sequencing technology have revealed a surprising diversity of noncoding RNAs expressed in nearly all cell types that have been examined thus far. In bacteria, noncoding RNAs constitute at least 10–20% of all expressed genes [86], yet despite their ubiquity and abundance, only a minute fraction of these molecules actually have assigned functions. Similarly, most of what is currently known about bacterial noncoding RNAs has been derived from studies in just a handful of species. The situation is substantially more daunting when considering human noncoding RNAs. Nearly 15,000 unique long noncoding RNA (lncRNA) transcripts have been recently annotated from the human genome [23]. As this number does not account for *any* of the plethora of <200 nt noncoding RNA species, such as microRNAs (miRNA) or small-interfering RNAs (siRNA), the true breadth of the human noncoding transcriptome must be astounding. However, as more attention has been focused upon deciphering the roles of noncoding RNAs, it is becoming increasingly evident that many of these molecules are likely to be riboregulatory RNAs involved in posttranscriptional control of gene expression [15]. Within the next decade, it would not be surprising to discover that riboregulatory RNAs play an even greater role than transcription factors for the regulation of genetic networks. Posttranscriptional mechanisms also have a variety of characteristics that make them particularly suited for highly dynamic genetic pathways like many of the major cellular adaptive responses. This includes the regulation of accessory genes and virulence factors in pathogens [29,34,54,79,86] as well as the corresponding immune responses of their infected hosts [5,75,105]. Posttranscriptional mechanisms offer a faster response time at a reduced energetic cost compared to most transcriptional mechanisms [34]. Perhaps of even greater importance is the fact that

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http://dx.doi.org/10.1016/j.micinf.2015.03.003
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posttranscriptional mechanisms also provide the option of directly overriding existing genetic programs in response to environmental signals [34]. For example, preexisting mRNA pools transcribed during a previous growth condition can be rapidly inhibited from further translation or even selectively degraded in response to new environmental stimuli. This will prevent these mRNAs from yielding proteins that would otherwise provide little or no utility in the current environment. This is a key distinction from transcriptional mechanisms, which are clearly essential for the production of new transcripts, but are typically incapable of inactivating them once they are transcribed.

There are several basic mechanisms of posttranscriptional control employed by both bacterial and human cells that can be broadly classified via control by either *cis* elements within mRNAs, *trans* riboregulators, or via sequestration of regulatory RNAs/proteins. Frequently, genes are regulated using a combination of these mechanisms as well. Regulation in *cis* often involves mRNA secondary structures within the 5′ and/or 3′ untranslated regions (UTRs) of mRNAs [8,34,35,91]. These structures ultimately influence the translation efficiency and mRNA stability of the molecules to which they are attached. In contrast, *trans* riboregulators perform a similar function, but do so via direct hybridization (seed pairing) to heterologous target mRNAs [4,27,97]. Since *trans* riboregulation typically occurs through imperfect complementarity between the regulator and target, a single riboregulator may have numerous targets as part of a larger posttranscriptional regulon [78]. Posttranscriptional regulation by sequestration is an indirect mechanism by which an RNA molecule serves as a sink to titrate other regulatory RNAs or proteins away from target mRNAs [1,6,25,32]. Such RNAs are commonly referred to as "decoys" or "sponges". A substantial body of recent research in both human and bacterial cells exists for each of these aforementioned regulatory mechanisms. Therefore, due to space limitations, this review will be specifically focused upon a comparison of the recent advances related to *trans* riboregulation in the host and bacterial pathogen with an emphasis on the human oral cavity. Although not considered here, we would also like to highlight the importance of microRNAs that play crucial roles in viral pathogenesis. Viral modulation of the host miRNA machinery can promote viral replication, while the expression of viral miRNAs in host cells may play critical roles in viral pathogenesis. The reader is referred to several comprehensive reviews for additional information on the subject [36,31,103,41].

## 2. *Trans*-riboregulatory control of the host immune response

### 2.1. Sources of host riboregulatory molecules

Recently, there has been considerable interest in the central roles of microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) for the control of many diverse processes such as oncogenesis [118], cell differentiation [44,93], and more recently the immune response [105]. For miRNAs, mature riboregulators generally range in size between 20 and 22 nt in length and are typically derived from larger immature transcripts produced by RNA polymerase II [37,119]. The immature primary miRNA transcripts are converted into miRNAs via a variety of pathways, but the two best-studied mechanisms are via the canonical miRNA pathway and the mirtron pathway (Fig. 1A). The canonical pathway begins with the production of the primary miRNA transcript, which forms a hairpin structure of about 55–70 nt [37,88,119]. This hairpin is processed in the nucleus by the Drosha enzyme in complex with the RNA binding protein DGCR8 [37,88,119]. Drosha is an RNase III-type endoribonuclease that is specific for double stranded RNA. The processed hairpin is then exported to the cytoplasm via the exportin-5 protein and further processed by another RNase III enzyme (Dicer) in

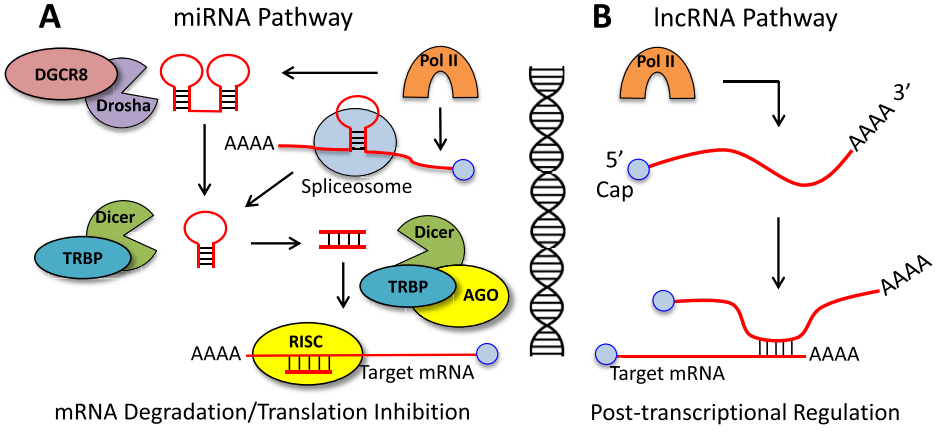


Fig. 1. General overview of riboregulation by miRNA and lncRNA. A) RNA polymerase II transcripts of primary miRNAs are processed by the RNase III family enzyme Drosha, whereas immature mirtrons are derived from intron splicing. After transport to the cytoplasm, the RNAs are further processed by the RNase III family enzyme Dicer in conjunction with accessory proteins required for cellular localization and mRNA targeting (TRBP and AGO). Seed pairing with miRNAs occurs in the 3′ UTR of target mRNAs leading to translation inhibition and mRNA degradation. B) lncRNAs are transcribed by RNA polymerase II and are capped and polyadenylated similar to mRNAs. Posttranscriptional regulation by lncRNAs includes regulation of translation, RNA turnover, and mRNA splicing. No additional proteins are required for the regulatory function of lncRNAs, but lncRNAs may interact with other regulatory proteins.

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