FEBS Letters xxx (2014) xxx–xxx

journal homepage: www.FEBSLetters.org

Review

Novel aspects of RNA regulation in *Staphylococcus aureus*

Pierre Fechter, Isabelle Caldelari, Efthimia Lioliou, Pascale Romby *

Architecture et Réactivité de l'ARN, Université de Strasbourg, CNRS, IBMC, 15 Rue René Descartes, 67084 Strasbourg, France

ARTICLE INFO

Article history:
Received 30 April 2014
Revised 16 May 2014
Accepted 19 May 2014
Available online xxxx

Edited by Wilhelm Just

Keywords:
Regulatory RNAs
Post-transcriptional regulation
Virulence
Staphylococcus aureus

ABSTRACT

A plethora of RNAs with regulatory functions has been discovered in many non-pathogenic and pathogenic bacteria. In *Staphylococcus aureus*, recent findings show that a large variety of RNAs control target gene expression by diverse mechanisms and many of them are expressed in response to specific internal or external signals. These RNAs comprise *trans*-acting RNAs, which regulate gene expression through binding with mRNAs, and *cis*-acting regulatory regions of mRNAs. Some of them possess multiple functions and encode small but functional peptides. In this review, we will present several examples of RNAs regulating pathogenesis, antibiotic resistance, and host-pathogen interactions and will illustrate how regulatory proteins and RNAs form complex regulatory circuits to express the virulence factors in a dynamic manner.
© 2014 Federation of European Biochemical Societies. Published by Elsevier B.V. All rights reserved.

1. Multiple roles of bacterial RNAs in gene regulation

Besides regulatory transcriptional proteins, RNA molecules are now recognized as key players of gene regulation in all living organisms (e.g. [1]). Mapping of the transcriptional start sites at the genome-wide scale revealed the complexity of the RNA landscape in numerous bacterial genomes, including non-pathogenic and pathogenic bacteria [2]. In bacteria, the small RNAs (sRNAs) often non-coding, accomplish a large variety of regulatory functions and can act at the levels of transcription, translation or RNA degradation. The large majority of them regulate pathways that sense and transfer the external signals, and adapt the cell population in response to stress and environmental changes [3] while others protect the core genome from foreign nucleic acids [4]. Among these sRNAs, many of them regulate gene expression by exploiting their ability to selectively bind to other nucleic acids. In addition, mRNAs also behave as regulatory RNAs or as reservoirs of sRNAs. Although the untranslated regions of mRNAs are in general of small size, mRNAs that encode proteins involved in virulence, stress responses and metabolism carry large 5′ or 3′ untranslated regions [2]. In these large UTRs, regulatory domains are often embedded that could function as direct sensor of physical cues like RNA thermosensors [5] or of intracellular concentration of metabolites, the so-called riboswitches [6]. Riboswitches exhibit a structured receptor domain specifically recognized by a small metabolite, which provokes premature transcription/anti-termination, translation repression/activation, or cleavage through a conformational switch of the mRNA. In general, riboswitches regulate the downstream mRNAs, which are involved in the uptake or metabolism of the sensed metabolite. Recent works have shown that riboswitches regulate gene expression in non-classical ways in *Listeria monocytogenes*: two S-adenosylmethionine (SAM) riboswitches function in *trans* to control the synthesis of the virulence regulator PrfA by binding to the 5′-untranslated region of its mRNA [7] while a B12-riboswitch regulates the transcription of an antisense RNA [8]. Because most of the riboswitches control essential genes and adopt specific binding pockets for small compounds, they have been considered as promising targets for the design of novel antibacterial compounds [9]. The advantageous properties of regulatory RNAs have been recently exploited in synthetic biology to rewire bacterial regulatory circuits [10].

In this short review, we will illustrate how several regulatory RNAs in *Staphylococcus aureus* fine tune the expression of key transcriptional factors and how they are embedded in complex regulatory circuits, which link virulence to stress adaptation and metabolism. For more detailed information, we refer to the recent reviews on *S. aureus* regulatory RNAs [11–14].

2. The quorum sensing dependent RNAIII, a multifaceted regulatory RNA

S. aureus is able to adapt to a wide variety of ecological niches. It is a commensal bacterium of skin and anterior nares of a large proportion of the human population but is responsible for numerous hospital- and community-acquired infections (e.g. [15]). This

* Corresponding author. Fax: +33 (0)3 88602218.
E-mail address: p.romby@ibmc-cnrs.unistra.fr (P. Romby).

http://dx.doi.org/10.1016/j.febslet.2014.05.037
0014-5793/© 2014 Federation of European Biochemical Societies. Published by Elsevier B.V. All rights reserved.

Please cite this article in press as: Fechter, P., et al. Novel aspects of RNA regulation in *Staphylococcus aureus*. FEBS Lett. (2014), http://dx.doi.org/10.1016/j.febslet.2014.05.037

opportunistic pathogen combats the host immune system by producing a battery of virulence factors that are responsible for adhesion, invasion and dissemination in host tissues and for acquisition of nutrients [16,17]. Expression of these factors is temporally regulated by multiple regulators involving two component systems, transcriptional regulatory proteins, and RNAs [18]. Among these systems, R. Novick and coworkers have identified two intracellular effectors of the accessory gene regulator (*agr*) quorum sensing system, the sensor protein AgrA and the regulatory RNAIII (Fig. 1A), which are both pivotal in *S. aureus* virulence [16,17,19]. The *agr* system is composed of two divergent transcripts, RNAII that encodes a quorum sensing cassette (AgrBD) and a two-component system (AgrAC) and RNAIII, a multifunctional RNA (Fig. 1A). The quorum sensing cassette produces an autoinducer peptide (AgrD), which upon a threshold concentration, activates the membrane kinase AgrC and the response regulator AgrA through a cascade of phosphorylation reactions. In turn, AgrA activates the synthesis of its own operon (RNAII) and of RNAIII, but also up-regulates the phenol-soluble-modulin (PSM) cytolysin genes, and down-regulates genes involved in carbohydrate and amino acid metabolism [19]. The bifunctional RNAIII is both a mRNA encoding the PSM δ-hemolysin (*hld*), and a regulator which promotes the switch between the expression of surface proteins and the synthesis of excreted toxins ([17]; Fig. 1A). It is still not known if the translation of *hld* may alter the regulatory activities of RNAIII but the presence of an open reading frame within RNAIII is not found in all *staphylococcal* strains [20]. Intriguingly, the translation of *hld* was delayed by 1 h compared to RNAIII synthesis, and was abolished by the deletion of its 3′UTR [21]. These data suggested the involvement of a trans-acting factor and/or a conformational change to induce *hld* translation. The non-coding parts of RNAIII are the regulatory domains: its 5′UTR binds to the leader region of *hla* mRNA encoding α-hemolysin to facilitate ribosome recruitment while its large 3′UTR is primarily acting as a repressor domain. The 3′UTR is the most highly conserved domain of RNAIII. It is characterized by several C-rich sequence motifs located in unpaired regions, which represent the seed sequences to promote basepairing interactions with target mRNAs (Fig. 1A). Although the topologies of the repressed mRNA–RNAIII complexes vary, binding of RNAIII prevents ribosome binding in all cases, which is usually followed by the rapid degradation of the repressed mRNAs [22–24]. These mRNAs encode virulence factors expressed at the surface of the cell (protein A, coagulase, SA1000), and the transcriptional repressor of toxins, Rot. A recent work has shown that three distant regions of RNAIII including its 5′ and 3′UTRs bind respectively to the coding region and the ribosome binding site of *sbi* mRNA to prevent its translation ([25,26]; Fig. 1A). Although distant domains of RNAIII bind to target mRNAs (Fig. 1A), only the region encompassing H13 and H14 of RNAIII is essential for translation repression while the other domains of RNAIII reinforce the stability of the RNAIII–mRNA complexes [24,25]. In addition to protein A, Sbi protein is another immunoglobulin-binding cell surface protein that protects the bacteria from the host immune system [27]. Hence, RNAIII decreases the production of two major adhesins, proteins A and

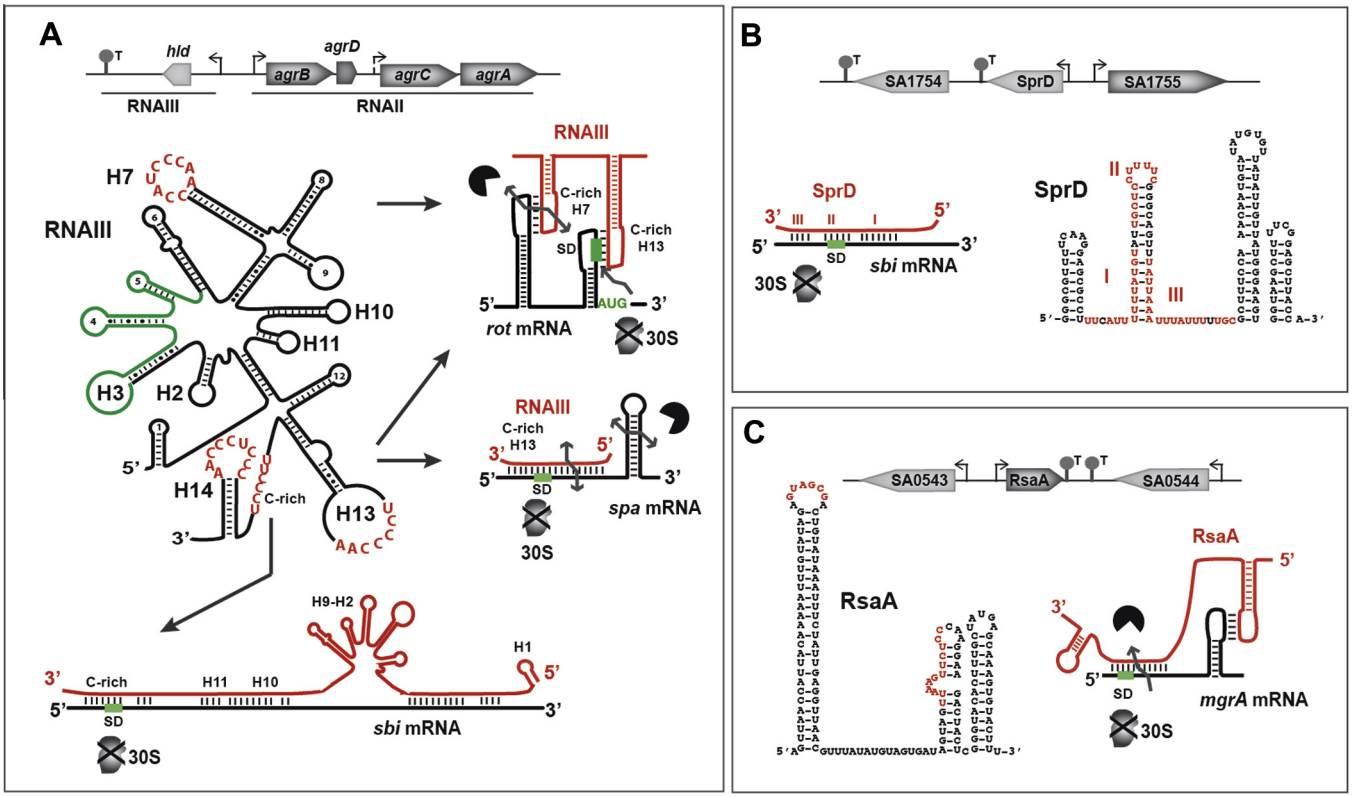

Fig. 1. Examples of regulatory RNAs and their mechanism of action. (A) Genomic organization of the quorum sensing *agr* system and mechanisms of repression by RNAIII on specific target mRNAs. The schematic secondary structure of RNAIII is given. The *hld* gene encoding δ-hemolysin is in green. The various C-rich sequence motifs of RNAIII (in red) represent the seed sequences that bind to the Shine and Dalgarno (SD) sequence of mRNA targets. Various topologies of inhibitory RNAIII-mRNA are given. These topologies prevent binding of the 30S small ribosomal subunit (30S) and for several mRNAs, the duplexes are appropriate to promote specific cleavage by the double strand specific RNase III (grey arrows). The data for *spa*, *rot*, and *sbi* regulations are from Huntzinger et al. [22], Boisset et al. [24] and Chabelskaya et al. [36], respectively. (B) Repression of *sbi* mRNA translation by SprD. Three different regions of SprD form basepairing interactions with the 5′ untranslated region and the beginning of the coding sequence of *sbi* mRNA. The duplex prevents the formation of the initiation ribosomal complex. The data are from Chabelskaya et al. [25]. (C) Repression of *mgrA* mRNA by the small non coding RNA, RsaA. Two regions of RsaA form a duplex with the ribosome loading site stabilized by a loop-loop interaction within the coding region. The two regions are essential to repress translation, which is subsequently followed by the degradation of the mRNA. The data are adapted from Romilly et al. [46]. T is for Rho-independent terminator of transcription.

Please cite this article in press as: Fechter, P., et al. Novel aspects of RNA regulation in *Staphylococcus aureus*. FEBS Lett. (2014), http://dx.doi.org/10.1016/j.febslet.2014.05.037

Download English Version:

https://daneshyari.com/en/article/10870379

Download Persian Version:

https://daneshyari.com/article/10870379

Daneshyari.com