Post-transcriptional regulation of gene expression in bacterial pathogens by toxin-antitoxin systems

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Toxin-antitoxin (TA) systems are small genetic elements ubiquitous in prokaryotic genomes that encode toxic proteins targeting various vital cellular functions. Typically, toxin activity is controlled by adjacent encoded protein or RNA antitoxins and unleashed as a consequence of genetic fluctuations or stressful conditions. Whereas some TA systems interfere with replication or cell wall synthesis, most of them influence transcriptional and post-transcriptional gene regulation. Antitoxins often act as DNA binding transcriptional regulators and many TA toxins exhibit endoribonuclease activity to selectively degrade different RNA species and thus alter gene expression patterns. Some TA RNases cleave tRNA, tmRNAs or rRNAs, whereas most commonly mRNAs either in association with the ribosome or as free transcripts, are targeted. Examples are provided on how TA toxins differentially shape gene expression in bacterial pathogens by creating specialized ribosomes or by altering the transcriptome and how this may be tied in the control of pathogenicity factors.

Keywords: toxin-antitoxin system, TA system, RNase, gene regulation, translation inhibition, pathogenicity, review
on post-transcriptional regulation via TA toxin RNase activity (summarized in Figure 1).

**VapC HOMOLOGS TARGET A MULTITUDE OF SUBSTRATES IN DIFFERENT BACTERIA**

Type II TA systems of the VapBC type are highly abundant in prokaryotes and frequently, multiple paralogs of them are found in bacterial genomes (Pandey and Gerdes, 2005; Jørgensen et al., 2009). In Mycobacteria, the number of identified VapBC type TA systems ranges between one in *M. smegmatis* to more than 40 in the pathogen *M. tuberculosis* (Pandey and Gerdes, 2005). A hallmark of the VapC toxins is the PIN domain, which is typically associated with Mg$^{2+}$ dependent ribonuclease activity (Arcus et al., 2004). Sharp et al. (2012) determined the ACGC or AC[AU]GC motifs of mRNAs as targets of the VapC-mt4 protein of *M. tuberculosis* and reported inhibition of translation mostly by binding to ssRNA instead of cleaving it. Experiments with the VapC20 (Rv2549c) homolog of *M. tuberculosis* in vitro and in *E. coli* have shown cleavage of the 23S ribosomal RNA between G and A in a prominent loop region (Winther et al., 2013). By contrast, purified VapC of *M. smegmatis* exhibits RNase activity preferentially at AUAU and AUAA sites (McKenzie et al., 2012). Microarray studies demonstrated differential expression of almost 3% of the *M. smegmatis* genome upon overexpression of the toxin with a striking downregulation of carbohydrate metabolism genes. The identification of VapC as a post-transcriptional regulator of glycerol consumption in mycobacteria highlights the influence of TA systems in bacterial metabolism. In addition, Winther and Gerdes (2009) were able to link induction of *vapC* expression in *Salmonella enterica* serovar Typhimurium to the stringent response. In contrast to analyzed homologs from Mycobacteria, this VapC protein and the one encoded on the *Shigella flexneri* 2a virulence plasmid pMYSH6000 exclusively target tRNA$^{Met}$ by cleaving within the anticodon stem-loop. Together with the RelE-type toxin YoeB (see below), the concomitant stimulation of translation initiation at elongator codons in lieu of canonical start codons may globally affect the cellular translation program (Winther and Gerdes, 2011).

**THE HicAB TA HOMOLOGS**

Features like induction by the stringent response and cleavage of tmRNA, required to rescue stalled ribosomes (Keiler et al., 1996), are shared by the *E. coli* hicAB TA system, which can also be activated during carbon starvation by a Lon protease dependent process. The HicA toxin furthermore cleaves selected mRNAs such as transcripts of *dksA*, and *rpoD* encoding regulators or subunits of the RNA polymerase or *ompA*, an outer membrane protein (Jørgensen et al., 2009). An orthologous system from the opportunistic pathogen *Acinetobacter baumannii* also targets tmRNA and a set of mRNAs when expressed in *E. coli* (Jurénaitė et al., 2013). To date, it is unclear if and how the hicAB...

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**FIGURE 1 | Regulation of transcription and translation by TA systems.**

TA systems can regulate gene expression on a transcriptional and post-transcriptional level, as follows (examples in parentheses): (1) Canonical transcriptional gene regulation by DNA binding (MqsR). (2) Cleavage of free mRNA transcripts (MazF, ChpBK, PemK, HicAI). (3) Inhibition of ribosome association (RatA, MazF). (4) Cleavage of rRNAs (MazF, VapC). (5) Cleavage of ribosome associated mRNAs (RelE, YoeB). (6) Cleavage of tRNAs (VapC). (7) Cleavage of tmRNAs (HicA, RelE). (8) Inhibition of tRNA synthetase (HipA). (9) Phosphorylation of EF-Tu (Doc). Further information on the mechanisms is available in the respective sections.
locus regulates differential gene expression in the host-cell, but it is likely that some genes are post-transcriptionally influenced by HicA-dependent cleavage.

**MazEF, A JACK-OF-ALL-Trades System**

*mazeF* belongs to the best characterized TA systems and encodes a MazF toxin and a MazE antitoxin protein. MazF homologs have been identified in a large number of bacteria (Mittenhuber, 1999) and archaea, with the *E. coli* system representing the far most extensively studied one (Aizenman et al., 1996). *E. coli* MazF is an ACA sequence specific endoribonuclease, which upon induction cleaves the bulk of all cellular mRNAs (Zhang et al., 2003). Accordingly, as much as 90% of the encoded proteins are no longer produced, leading to growth impediment (Yamaguchi and Inouye, 2009). While it had previously been assumed that ribosomal RNAs and tRNAs are protected from MazF cleavage by ribosomal proteins and secondary structures (Zhang et al., 2005a), Vesper et al. (2011) demonstrated that 16S rRNAs are processed by *E. coli* MazF, presumably in response to stressful conditions. Thereby the anti-Shine-Dalgarno (anti-SD) sequence of the 16S RNA is removed, yielding so-called “stress ribosomes”. These are capable of translating a set of leaderless mRNAs with clipped SD sequences as another result of sequence specific MazF activity. This orthogonal translation system produces about 50 proteins which are associated with population heterogeneity in *E. coli* cultures that leaves only few survivors behind (Amitai et al., 2009). The controversial role of the *mazeF* system is reflected by two opposite camps. One suggests an involvement in programmed cell death (Aizenman et al., 1996; Amitai et al., 2004; Engelberg-Kulka et al., 2006), whereas the other provides evidence for the modulation of physiological activities for a defined time-frame only (Pedersen et al., 2002; Gerdes and Maisonneuve, 2012). The proficiency of *E. coli* MazF and a homologous TA toxin ChpBK, which exhibits less stringent ACA specificity (Zhang et al., 2005b), appear to be enhanced by a pen-tapetide called extracellular death factor (EDF) (Kolodkin-Gal et al., 2007; Belitsky et al., 2011). Functional analogs thereof are also produced by *P. aeruginosa* and *B. subtilis* (Kumar et al., 2013). *Mycobacterium tuberculosis* bears at least seven *mazeF* operons, four of which were validated to encode functional mRNA interferases, targeting different three- or five-base consensus sequences (Zhu et al., 2006, 2008). These MazF proteins were proposed to alter gene expression through selective RNA degradation by each paralog addressing different targets. These also include RNA species beyond mRNA, as in case of MazF-mt6. It cleaves 23S rRNA of *M. tuberculosis* in a bulge region that is part of an association interface between the 3OS and the 5OS subunits. This leads to an mRNA independent global shut-down of translation activity (Schifano et al., 2013). Interestingly, MazF-mt7 (Rv1495) can physically interact with the *M. tuberculosis* DNA topoisomerase I (MtTopA), which inhibits nucleic acid cleavage activity of both enzymes. This interaction exemplifies an additional regulatory function of a TA interferase beyond ribonuclease activity (Huang and He, 2010). Heterologous expression of MazF-mt7 in *M. smegmatis* causes growth cessation, which, together with findings on the MazF-mt6 system, provides further indications for the involvement of TA systems in mycobacterial long-term dormancy. Among the Gram positive pathogens, *mazEF* systems were also identified in *Clostridium difficile*, *Streptococcus mutans*, and *Staphylococcus aureus* (Fu et al., 2009; Zhu et al., 2009; Syed et al., 2011; Rothenbacher et al., 2012). Relative abundances of target sites may serve as gene specific indicators for cleavage sensitivity, direct evidence is mostly lacking and secondary structures and RNA associated factors can influence accessibility. This has striking implications for post-transcriptional regulation of factors associated with host-pathogen interactions. Recently, a *pemIK* system generally related to *mazeF* (Zhang et al., 2004), was identified on two staphylococcal plasmids and in the chromosomes of other *Staphylococcus* species (Bukowski et al., 2013). Whereas PemIKSs fulfills the classical TA systems’ role of ensuring plasmid propagation, its toxin component PemKSa, an UAUU specific endoribonuclease, has also been speculated to post-transcriptionally control chromosomally located *S. aureus* genes. Transcripts biased for a low number of UAUU stretches include ORFs of various virulence factors, whereas numerous transporter genes harbor more target sequences than statistically predicted. The finding that the transcript encoding the PemKSa antitoxin is resistant to PemKSa cleavage led the authors to propose a mechanism for reinstating TA homeostasis after stressful conditions (Bukowski et al., 2013).

**RIBOSOME DEPENDENT RNases of the RelE FAMILY**

The RelE toxins of the relBE TA family interact with the ribosome and cleave mRNAs at the ribosomal A-site (Pedersen et al., 2003). *E. coli* RelE preferentially targets the trimeric RNA motifs UAG, UCG, and CAG. Interestingly, tmRNA can also be a substrate of RelE, which suggests a role in stress regulation (Christensen and Gerdes, 2003). YafQ toxins, which are structurally similar to RelE family RNases, associate with the 50S ribosomal subunit and specifically restrict selected mRNAs at AAA[AG] consensus sequences. Since the AAA lysin codon is particularly overrepresented at codon +2 in secretory proteins (Zalucki et al., 2007), RelE activity may arrest their translation (Prysak et al., 2009). More recently, also in vivo cleavage of the transcripts lpp (lipoprotein), acpP (acyl carrier protein) and hns (DNA condensing and supercoiling protein) at AAG, GAA, and ACA was demonstrated (Armalyte et al., 2012). Likewise, the *E. coli* YoeB toxin binds to the 50S ribosomal subunit and cleaves the lpp and ompP (porin) mRNA in vivo, three nucleotides downstream of the start codon (Zhang and Inouye, 2009). The YefM-YoeB system promotes colonization of the bladder by uropathogenic *E. coli* (Norton and Mulvey, 2012) and is also found in the chromosome of Gram positive pathogens such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis* (Cherny and Gazit, 2004; Nieto et al., 2007; Yoshizumi et al., 2009). A homologous TA system, termed *axe-txe*, has been identified on *Enterococcus* plasmids before (Grady and Hayes, 2003; Halvorsen et al., 2011) and *Txe* was shown to cleave lpp mRNA at the first base after an AUG start codon when expressed in *E. coli*. Apart from a number of *in vivo* and *in vitro* assays which demonstrate the ribosome dependency for these TA toxins, a holistic picture of which genes are affected under specific conditions is yet to be painted for most of these systems. An
exception is the RelE family toxin HigB from the higBA TA system, which also cleaves RNA in association with the ribosome (Hurley and Woychik, 2009). Schuessler et al. (2013) analyzed an M. tuberculosis strain overexpressing higB by comparative RNAseq in order to define the entire set of RNAs targeted by the toxin. The relative abundances of tmRNA and of 32 different tRNAs (Castro-Roa et al., 2013).

MqsRA MODulates E. coli S TRESS RESPONSE
Whereas many TA systems have been solely characterized in vitro or by heterologous expression in vivo, a distinct physiological role of the type II TA system MqsRA (Yamaguchi et al., 2009) and the modulation of the E. coli stress response has been established (Wang et al., 2011). Apart from MsqA functioning as a transcriptional stress regulator, the MqsR toxin acts as a sequence-specific RNA-interase. In vivo primer extensions revealed cleavage of three different native E. coli transcripts at the GCU triplet upon artificial induction of MqsR. All of the GCU sequences in ompF mRNA were cleaved without exception although mRNAs form secondary and tertiary structures and can associate with proteins. It was speculated that the MqsRA system could also have important implications for uropathogenic strains switching from a motile non-adhesive state in the urine to a recalcitrant biofilm or other types of non-motile bacterial communities (Hadjifrangiskou et al., 2011).

As shown recently, MqsRA also controls another TA system, termed ghoST (Wang et al., 2013). The small GhoT toxin protein inserts into the membrane resulting in lysed ("ghosts") or drug tolerant persister cells (Cheng et al., 2013). Notably, ghoT mRNA lacks the primary MqsR target site GCU (Yamaguchi et al., 2009), but instead is specifically cleaved by the GhoS antitoxin. GhoS in turn targets another 20 mRNAs involved in nucleotide precursor anabolism (Wang et al., 2012). Cleavage of toxin mRNA has so far exclusively been described for GhoST, which represents a type V TA system member with extraordinary activities of self-control.

ADDITIONAL MODES OF POST-TRANSCRIPTIONAL REGULATION
Apart from gene regulation based upon RNA degradation, a number of TA systems exert post-transcriptional regulation by targeting downstream processes. Like mycobacterial MazF-mt6 (see above), the RatA toxin, encoded by the ratAB locus from E. coli, inhibits the association of the ribosomal subunits. Although already assembled ribosomes are unaffected, synthesis of new proteins is impeded (Zhang and Inouye, 2011).

The PhD/Doc system blocks general translation by binding to the 30S ribosome subunit and thus inhibiting translation elongation (Liu et al., 2008). As found recently, the toxicity of the Doc-type protein Fic is mediated by phosphorylation of the elongation factor EF-Tu, which in turn prevents binding to aminoacylated tRNAs (Castro-Roa et al., 2013).

The prominent E. coli hipAB TA system, which is involved in a high persister phenotype, was thought to phosphorylate EF-Tu to nonspecifically inhibit overall translation (Schumacher et al., 2009). Newest results, however, indicate that translation inhibition is caused by impeding the glutamyl-tRNA synthetase, thus leading to an accumulation of uncharged tRNAs and therefore translation arrest (Germain et al., 2013). Although these systems are presumably non-selective regulators due to the unspecific shutdown of translation in general, they may regulate translation of total transcriptomes in stress related situations.

CLOSING REMARKS
Gone are the days when TA systems were considered to solely act as plasmid stabilizers. Instead, a multitude of roles for these genetic elements in the modulation of bacterial physiology has emerged. It became evident that TA systems target numerous intracellular structures and processes in prokaryotes among which the modulation of translational cessation seems to be of prime importance. First approaches have been taken to decipher the entirety of transcripts (including small regulatory RNAs) affected by TA RNases throughout different bacteria (Kim et al., 2010; Schuessler et al., 2013). In this regard, secondary structures of RNA molecules, factors interacting with RNAs such as Hfq or other RNA chaperones (Vogel and Luisi, 2011), as well as activity modulators of TA system RNases, including peptides (Kolodkin-Gal et al., 2007; Kumar et al., 2013) or hierarchically organization of TA systems may need to be considered in greater detail (Winther and Gerdes, 2009; Wang et al., 2012). Most importantly, to elucidate regulatory networks, TA systems must be studied in their cellular and environmental context, as heterologous expression in E. coli and activities observed in vitro most likely reflect only part of the extent of regulation. Numerous clinical isolates of S. aureus and P. aeruginosa have been demonstrated to harbor and express TA systems (Williams et al., 2011), which permits refined in vivo analyses without the need for spurious noise due to artificial induction. Another recently discovered antitoxin-like protein in an enterohaemorrhagic E. coli phase can directly undermine the native TA systems and thus nicely underlines the importance of homologous in vivo experiments (Otsuka and Yonesaki, 2012).

Insights into extended roles of type II antitoxins are emerging. Besides controlling toxin activity by protein-protein interaction and transcriptional autoregulation, some antitoxins have been proven to additionally act as transcription factors controlling other regulons (Kim et al., 2010; Lin et al., 2013). Recent findings underscore the hypothesis that pathogenic bacteria contain higher numbers of TA systems than non-pathogenic relatives (Georgiades and Raoult, 2011). A recent publication furthermore showed a direct effect of a newly discovered Salmonella TA system (sehAB) and virulence in a mouse model (De la Cruz et al., 2013). Taken together, TA systems provide interesting targets for antibacterial strategies (Williams and Hergenrother, 2012), which clearly merits further research in this dynamic field.

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