Transcription termination control in bacteria

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Transcription termination is a dynamic process and is subject to control at a number of levels. New information about the molecular mechanisms of transcription elongation and termination, as well as new insights into protein–RNA interactions, are providing a framework for increased understanding of the molecular details of transcription termination control.

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Abbreviation
RNAP RNA polymerase

Introduction

Regulation of gene expression at the level of transcription termination, originally discovered as a key element of the bacteriophage λ developmental program, has emerged as an important mechanism for control of a variety of genetic systems. Two classes of transcription termination signals, both of which are active in the nascent transcript, have been identified in bacteria: intrinsic terminators, composed of a G+C-rich stem-loop followed by a series of U residues, and Rho-dependent terminators, whose activity relies on binding of the Rho protein to a *rut* (Rho utilization) site on the nascent transcript, followed by interaction with RNA polymerase (RNAP). Recent analyses of transcription, using elegant biochemical and structural biological approaches, have yielded new levels of understanding of the mechanisms of transcription elongation and termination (reviewed in [1••,2••]; see Severinov, this issue pp 118–125). This information continues to provide insight into the ways in which these processes can be controlled, through modulation of the activity of RNAP and through alterations in the structure of the nascent RNA. The possibility remains that important differences between *Escherichia coli* RNAP and the transcriptional machinery in other organisms may impact control mechanisms in interesting and unexpected ways. This review focuses on the basic themes of transcription termination control mechanisms found in bacteria (reviewed in [3]) with an emphasis on systems for which new information has recently been described.

Effects on transcriptional processivity

Transcription termination at both intrinsic and Rho-dependent terminators is dependent on pausing of RNAP at a specific site, followed by destabilization of the paused complex. Pausing is directed by sequence and structural elements, and the sensitivity of RNAP to these elements can be modulated in a variety of ways, including interaction of protein factors with RNAP to control pausing or escape from the paused state. Systems of this type were reviewed recently [4••].

Protein-directed effects on RNAP

The classic example of this type of mechanism occurs in phage λ and its relatives. The general pattern, as exemplified for λ N-mediated antitermination, involves binding of N protein to the nascent transcript at a specific site, designated the *nut* (N utilization) site, followed by assembly of a set of additional host-encoded proteins (NusA, NusB, NusG and ribosomal protein S10). These proteins, together with N, associate with elongating RNAP and alter its processivity so that it becomes stably resistant to downstream termination and pause sites [4••,5]. Recent progress in this system has revealed important information about the structure of the N protein and its interactions with both its RNA-binding site in the nascent transcript and its protein targets in the transcriptional machinery. The *nut* site has been characterized in detail [6,7], and the RNA-binding motif of N has been localized to a 22 amino acid arginine-rich motif (ARM) at the amino terminus, which is α-helical in structure [8,9]. Legault *et al.* [10••] have now demonstrated by NMR analysis that the crucial GAAGA bulge region of the *nut* site forms a structure very similar to a standard GAAA tetraloop, with the fourth residue extruded to contact NusA protein. Similar results with the related phage P22 support these conclusions [11•]. Residues 34–47 of N were shown to be crucial for interaction with NusA, while the carboxy-terminal region is involved in interaction with RNAP. These latter regions of N appear to assume an ordered structure only when bound to their targets [12•].

An interesting variation on this type of mechanism is provided by the λ Q system, which controls the transition from delayed early to late transcription. Q protein plays the role of N in directing the conversion of RNAP into a termination-resistant form. The key difference is that Q joins RNAP only when RNAP is directed by the σ^{70} subunit to pause at position +16 of the transcript; region 2.2 of σ^{70}, which is involved in stabilization of the open complex during transcription initiation, is also required for Q-mediated antitermination [13••]. An elegant set of biochemical studies demonstrated that Q acts to prevent destabilization of the elongation complex by an intrinsic terminator hairpin [14••]. In addition, the requirement for Nus factors is less significant for the Q system, although NusA remains an important component.

In the phage systems described above, termination control is mediated by influencing the processivity of RNAP so that downstream pause sites are ineffective. Many of the features identified in these systems, including the

boxA component of the *nut* site and host-encoded factors, have been shown to also play a key role in transcription of ribosomal RNA (*rrn*) operons. Both increased elongation rate and suppression of Rho-dependent termination during *rrn* transcription are dependent on a *cis*-acting *boxA* element. Several of the Nus factors, including NusA, NusB and NusG, have been shown to be essential for normal *rrn* transcription [15,16•]; other cellular factors also appear to be involved. Since control of ribosomal RNA synthesis is crucial to cell viability and growth rate control, the *rrn* system is indicative of the important contribution of transcription termination control to cell physiology, and provides a biological role for the Nus factors in normal growth. Although this system has been analyzed in detail only in *E. coli*, it is likely that the most important features will be uncovered in other organisms as well, given the widespread conservation of Nus factors. However, it appears that there may be important differences. In *Bacillus subtilis* Rho-dependent termination appears to play a much less important role, NusG is not an essential gene and NusA is essential for viability independent of its effect on Rho-dependent termination [17•]; the consequence of these differences for *rrn* transcription remains to be determined.

Suppression of Rho-dependent termination by RfaH, a NusG homolog, is also involved in lipopolysaccharide and hemolysin gene expression in *E. coli* and *Salmonella* [18–20]. RfaH function is dependent on a *cis*-acting element, designated *ops*, but the details of the regulatory mechanism and the control of RfaH activity remain to be elucidated.

RNA-directed effects on RNAP

Phage HK022, a λ relative, has dispensed with the *trans*-acting components of the λ N antitermination system and instead utilizes a *cis*-acting RNA element, designated *put* (polymerase utilization), to replace N and Nus protein function [4••,21]. Mutations in a cysteine-rich domain of the β′ subunit of RNAP specifically interfere with *put*-directed antitermination, suggesting that this domain of RNAP may interact directly with the *put* RNA [22]. This phage has replaced N with a different protein, Nun, whose role is to interfere with the λ N system: Nun binds to the λ *nut* site with an RNA-binding motif similar to that of N and appears to also interact with the template DNA [23••]. Nun-dependent transcription termination depends on the Nus factors, but with differences in allele specificity from the λ N system [24,25]. The use of RNA-directed antitermination in the HK022 life cycle has apparently permitted HK022 to use Nun to gain a competitive advantage over λ during coinfection. Just as with the N and Q antitermination systems, analysis of Nun-directed termination provides important information about transcription elongation and potential control points.

Control of nascent transcript structure

A variety of systems have been reported in which transcription termination is controlled by modulation of the structure of the nascent transcript, often by formation of an alternate structure that competes with formation of the stem-loop of an intrinsic terminator located in the leader region of the transcript. Originally described for amino acid biosynthetic operons in *E. coli* and *Salmonella*, where the translation efficiency of a leader peptide coding region affects the relative positions of the ribosome and RNAP, variants of this type of mechanism have been described in which leader RNA structure is modified in many different ways.

Positive-acting proteins

In systems such as *E. coli bgl* and *B. subtilis sac*, the leader region terminator is preceded by a sequence capable of forming a competing antiterminator structure; the antiterminator is stabilized by binding of a regulatory protein, the RNA-binding activity of which is controlled by phosphorylation [26]. The structure of the RNA-binding domain of SacY, one of the regulatory proteins in this family, has been determined [27], and RNA binding by BglG is dependent on dimerization of the regulatory protein using a leucine zipper motif and a second carboxy-terminal region [28•]. In addition to its interaction with the antiterminator region of the nascent RNA, BglG was also shown to interact with the β′ subunit of RNAP [29••], suggesting that interactions with elongating RNAP, in addition to RNA binding, are important for antitermination. The *B. subtilis glp* system may be functionally related to the Bgl/Sac family, in that GlpP activates readthrough of a leader region terminator through binding to a target site with some similarity to those recognized by BglG-type proteins; however, GlpP is unrelated to BglG, and instead is similar to an *E. coli* protein of unknown function [30]. It will be interesting to determine if GlpP defines a new class of antiterminator proteins.

The *Klebsiella* NasR and *Pseudomonas* AmiR proteins also act as RNA-binding antiterminator proteins. NasR binds to a stem-loop target located immediately upstream of the leader region terminator in the *nasF* operon; however, there is no apparent structural competition between the NasR-binding site and the terminator, suggesting that NasR may direct readthrough of the terminator either by interacting with RNAP or by interfering with terminator formation by some other mechanism [31••]. Similarly, the relationship between the AmiR target site and the regulated terminator is not well defined. In addition, AmiR is unique in that its RNA-binding activity is controlled by complex formation with a partner protein, AmiC, which acts as a sensor of the effector acetamide [32•]. Further analysis of these systems should reveal the molecular mechanism of termination control.

Negative-acting proteins

While the proteins described above act positively to promote antitermination, regulatory proteins like TRAP and PyrR function in *B. subtilis* to prevent antitermination [33,34••]. TRAP forms an 11-mer ring which, in the presence of tryptophan, binds to 11 closely spaced triplet

repeats in the leader regions of its target genes. TRAP binding blocks formation of an antiterminator, allowing formation of a competing intrinsic terminator stem-loop. The crystal structure of the TRAP–RNA complex revealed an elegant arrangement in which the RNA is wrapped around the TRAP wheel with each RNA triplet interacting with a binding pocket so that the 11 triplet repeats precisely match the repeat structure of the 11-mer TRAP ring [35••]. A 5′ stem-loop in the leader RNA, upstream of the TRAP-binding site, is required for maximal TRAP-dependent repression of the *trpE* operon, by increasing the affinity of the RNA for TRAP [36•]. The *B. subtilis* PyrR protein operates in a similar manner, in this case by binding to and stabilizing a leader structure that acts as an anti-antiterminator; the PyrR-binding site competes with an antiterminator structure, which in turn competes with the terminator stem-loop [34••]. As with TRAP, binding of PyrR to its RNA target is dependent on the presence of a co-repressor. The crystal structure of PyrR has been determined [37•], and the RNA target site is well defined; it will be of interest to explore the details of the protein–RNA complex.

A set of 11 transcriptional units in *B. subtilis*, most of which are involved in methionine biosynthesis, is regulated by a system which resembles the *pyr* system in that the leader regions of these genes contain conserved sequence and structural elements (designated the S box because of the involvement in sulfur metabolism), which can fit the terminator/antiterminator/anti-antiterminator pattern [38••]. Readthrough is induced by starvation for methionine, and mutational analysis supports the structural predictions and identifies the anti-antiterminator region as a target for negative regulation. The nature of the regulator and the mechanism for sensing methionine availability have not yet been explored. This system is unique in that many transcriptional units are regulated in concert by the same mechanism; genes with similar leader features have also been identified in a number of other Gram-positive species.

RNA-directed effects on nascent transcript structure

A large number of aminoacyl-tRNA synthetase, amino acid biosynthesis, and amino acid transport genes in a variety of Gram-positive species were identified as members of the T box family of genes on the basis of conservation of sequence and structural elements in their leader regions. Expression of these genes is induced by interaction of the cognate uncharged tRNA with the leader RNA; this interaction is proposed to stabilize an antiterminator form of the leader, preventing formation of the alternate terminator form. Genetic analyses have provided support for the model and for the role of uncharged tRNA in several genes in this family in *B. subtilis* and other species [39–43], and data from structural mapping of the *B. subtilis thrS* leader are generally in agreement with models proposed on the basis of sequence conservation [44•]. RNA processing, in addition to transcription antitermination, has been suggested to affect expression for at least some of these genes [45,46]. Although some of the determinants of the specificity of the tRNA-leader RNA interaction have been identified, it is apparent that other features are required [40]. The involvement of additional accessory factors has been suggested [39], but no such factors have yet been described.

New interfaces between transcription termination control and translation

As noted above, control of transcription termination via translation of a leader open reading frame represents a paradigm system for regulating the activity of an intrinsic terminator by controlling leader RNA structure. The *E. coli tna* operon reveals a novel variation on this theme, in which nascent peptide-dependent ribosome pausing blocks access of Rho to a leader region *rut* site, thereby controlling transcription termination and expression of the downstream tryptophanase gene [47]. Growth in the presence of tryptophan is required for antitermination, possibly by affecting the ability of the nascent peptide to act in *cis* to mediate ribosome stalling. Recent studies with leader peptide stop codon variants and release factor mutants suggest that inhibition of ribosome release is crucial for transcription antitermination [48••]. Remaining key questions include the mechanism for sensing of tryptophan as the effector, and the molecular basis for the effect of the leader peptide on ribosome function.

There are also examples where a transcription termination control system has been 'borrowed' for control of translation initiation. The λ N protein, in addition to its role in transcription antitermination, also controls its own translation by binding to the same *nut* site used for antitermination control [49]. Similarly, while TRAP functions to control transcription termination in the *B. subtilis trp* operon, it also represses translation of both *trpE* and the unlinked *trpG* gene [50••]. It seems likely that additional examples of this mechanistic diversity using similar regulatory elements will be uncovered in the future.

Conclusions

A growing number of genetic systems in bacteria are regulated at the level of transcription termination. It is especially notable that analysis of organisms other than *E. coli* and its relatives has revealed novel variations on the paradigm systems. In particular, Gram-positive bacteria seem especially subject to utilization of systems of this type and application of a single mechanism (e.g. the T box or S box systems) to large groups of genes. Further analysis of new groups of organisms is certain to unearth yet more variations on the theme. The growing body of information on the biochemistry of transcription elongation and its control, coupled with the availability of new information about the structures of the proteins and RNAs involved, will also drive a transition from investigations at the genetic level to a more mechanistic understanding of these systems and interfaces with the transcriptional machinery.

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