PERSPECTIVES: BIOCHEMISTRY

# Sense and Sensitivity—Controlling the Ribosome

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One of the stunning advances of the past few years has been the elucidation of the precise structure of the ribosome, the molecular factory of the cell that makes proteins (*1*). Thousands of ribosomes are present in each cell of all organisms from bacteria to humans. These large RNA-protein complexes are responsible for the dynamic and highly regulated process of protein synthesis. Antibiotics and toxins that interfere with ribosome activity cause cell death. Recent work suggests that the ribosome is surprisingly sensitive to the amino acid chain that it is synthesizing. Now, Gong and Yanofsky (*2*) report on page 1864 of this issue that the forming (nascent) polypeptide chain regulates gene expression by stopping the ribosome in its tracks. They show that in the bacterium *Escherichia coli* the nascent regulatory peptide controlling the synthesis of tryptophanase (the enzyme catabolizing tryptophan) is able to halt the ribosome that is making this peptide when tryptophan is delivered to the ribosome's catalytic site. The existence of similar mechanisms for regulating the synthesis of other enzymes suggests that the feedback modulation of ribosome activity by nascent peptides is a widespread regulatory strategy (*3*–*6*).

Proteins are synthesized by translation of their mRNAs, a process carried out by ribosomes. This process can be divided into three stages: initiation of translation, elongation of the nascent peptide, and termination of peptide synthesis. The rate of elongation and termination is determined by the amount of aminoacylated tRNA available to decode the mRNA and by the activities of various translation factors. However, evidence is emerging that the nascent peptide itself—within the ribosome that is making it—can profoundly affect mRNA translation.

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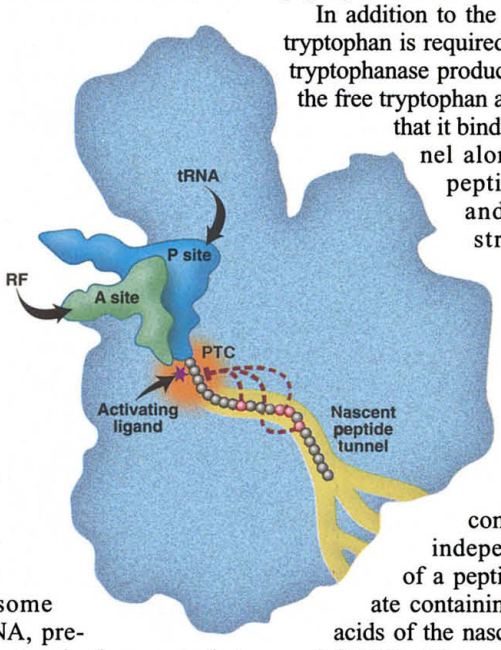
Studies by Yanofsky and co-workers have elucidated a mechanism for the control of tryptophanase gene expression that depends on the synthesis of a short peptide encoded by the *tnaC* gene, located in the leader region of the operon. In the presence of abundant tryptophan, this nascent peptide interferes with the termination of its own synthesis, resulting in persistent linkage of the TnaC peptide to tRNA. As a result, the translating ribosome stalls on the mRNA, preventing transcription termination events that normally preclude expression of the downstream tryptophanase gene. Several other enzymes in bacteria and eukaryotes resemble tryptophanase in that their production depends on peptidyl transferase inhibition and ribosomal stalling mediated by nascent peptides that act in concert with small-molecule cofactors. Among the many intriguing questions raised by these regulatory systems is how the ribosome senses both the nascent peptide and the regulatory cofactors.




**Sensing the nascent peptide.** During the termination of protein synthesis, a release factor (green) enters the A site in the large subunit of the ribosome (blue), triggering the hydrolysis of peptidyl-tRNA at the peptidyl transferase center (PTC, orange). However, residues in the nascent polypeptide chain (red) may interact with components of the tunnel (yellow). When cofactors (purple) are present, these interactions between the nascent peptide chain and the tunnel may block the PTC activity required for peptidyl-tRNA hydrolysis, as appears to be the case for the *E. coli* TnaC peptide. Some nascent peptides with their associated cofactors can interfere with the elongation step catalyzed at the PTC.

Biochemical and structural studies provide evidence for a tunnel in the large ribosomal subunit through which the nascent peptide usually exits (*7*–*10*). Because the ribosome can shield about 30 to 40 amino acids of the nascent chain, peptides that are only 20 to 30 amino acids in length such as TnaC are expected to be entirely within the tunnel. Specific amino acids are required at various positions along regulatory nascent peptides if they are to block peptidyl transferase and stall the ribosome. Some of these amino acids—such as prolines at the carboxyl termini of several peptides including TnaC and the product of cytomegalovirus *UL4* upstream open reading frame 2—may act directly within the peptidyl transferase center to impede its activity during translation termination (see the figure). However, others, such as the critical tryptophan residue at position 12 of TnaC, may interact with ribosomal RNA or proteins that constitute the tunnel walls. The requirement for such residues suggests that, rather than simply being a passive "Teflon-coated" conduit, the tunnel may consist of a series of dynamic regulatory gates that inspect the nascent chain as it passes through, in some cases triggering events that shut down the peptidyl transferase center.

In addition to the nascent peptide, free tryptophan is required for the regulation of tryptophanase production. But where does the free tryptophan act? One hypothesis is that it binds in the ribosome tunnel along with the nascent peptide. However, Gong and Yanofsky present strong evidence that tryptophan interacts directly with the peptidyl transferase center. Replacement of the wild-type *tnaC* UGA stop codon with a UGG tryptophan codon causes constitutive tryptophan-independent accumulation of a peptidyl-tRNA intermediate containing the first 24 amino acids of the nascent peptide linked to prolyl-tRNA. The authors propose that after synthesis of the TnaC-prolyl-tRNA, but before addition of tryptophan, the tryptophan-charged tryptophanyl-tRNA binds to the ribosomal A site and interferes with peptidyl transferase action. The requirement for a high concentration of tryptophan with the wild-type template suggests that the binding of the free amino acid is relatively inefficient. When the stop codon is replaced by sense codons other than a tryptophan codon, tryptophan cannot compete successfully with cognate aminoacyl-tRNAs for access to the site. However, when the stop codon is replaced by a tryptophan codon, then the tryptophanyl moiety of tryptophan-charged tryptophanyl-tRNA operates efficiently, presumably because it is delivered directly to its binding site within the peptidyl transferase center by the attached tRNA.

Other small coregulatory molecules act in concert with nascent peptides to control

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ribosome movement along the mRNA. In prokaryotes, the antibiotics chloramphenicol and erythromycin activate the expression of antibiotic-resistance genes. In eukaryotes, arginine and spermidine inhibit the expression of genes in their respective biosynthetic pathways. In all cases, the cofactor and the nascent peptide act together to halt the ribosome. Chloramphenicol presumably acts through its known binding to the peptidyl transferase center, and erythromycin through its interactions with the ribosome tunnel. The sites of action of arginine and spermidine are unknown, but in light of the results of Gong and Yanofsky, it is attractive to consider that these compounds too might act at the peptidyl transferase center.

Important questions still remain to be answered. How do interactions of the nascent peptide with the ribosome tunnel influence events at the peptidyl transferase center, and vice versa? How general are such mechanisms among different organisms? Regulation by nascent peptides with associated cofactors has been observed only for short nascent peptides that would be entirely within the ribosome. Can cofactor- and peptide-dependent regulation affect translation of internal regions of the long reading frames of genes? It will be interesting to determine whether mutations that affect the general structure and function of the ribosome tunnel also affect the activities of these specific nascent peptides and cofactors. From the medical perspective, understanding how nascent peptides regulate ribosome activity in bacteria could provide useful insights for developing new antibiotics. At a minimum, elucidating the interactions responsible for ribosome regulation by nascent peptides should lead to more complete and dynamic models of ribosome action.


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PERSPECTIVES: QUANTUM OPTICS

# Quantum Logic with Light, Glass, and Mirrors

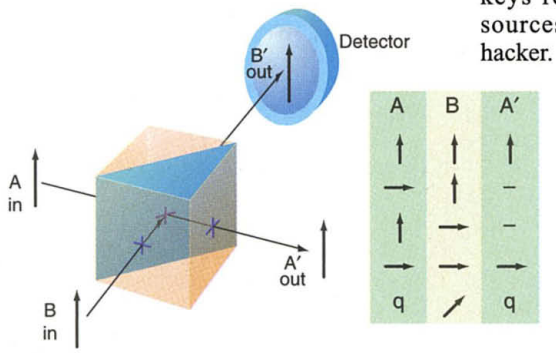
**Andrew Shields**

Recent progress in quantum optics suggests that quantum computers may one day be built based on single photons routed through a circuit of simple optical elements: mirrors and small bits of glass. Such circuitry would revolutionize information technology, allowing fast solution of some of the most difficult computational problems and enhancing ultrasecure communication systems.

Today's computers process information in binary format, as a sequence of **0**'s and **1**'s. With single quanta, information can be encoded not only in pure **0**'s and **1**'s, but also in states that are a mixture of **0** and **1**. These superposition states have some probability of being **0** and some of being **1**. Furthermore, the superposition increases with the number of qubits, so that a system with $n$ qubits can be in $2^n$ states simultaneously.

Quantum computers perform each operation on all $2^n$ at the same time. The resulting massive parallelism can speed up the solution of otherwise intractable problems. Although only a handful of quantum algorithms have been discovered so far, they include important mathematical problems, such as finding the prime factors of large numbers, the Achilles heel of classical cryptography (*1*, *2*).

Proposals for quantum logic hardware are based on single different quantum systems: single electron charges, electron spins, electrons in atoms or ions, photons, magnetic flux, and nuclear spins in solids and molecules (*1*, *2*). Photons have the advantage in that they interact only weakly with their environment, allowing many operations on a single photon before scattering scrambles its quantum information. This inertness also makes photons the natural choice for transmitting quantum information between processors.




**The quantum parity check gate.** This gate transfers the input qubit A to the output qubit A′ if its value is the same as that of input qubit B. If both inputs are **1** (vertically polarized photons), both will be reflected at the beam-splitter. If both are **0** (horizontally polarized), both will be transmitted. In either case, a single count in the detector means that the gate has transferred the value of A to A′. If the two input polarizations differ, either both or neither of the photons is registered in the detector, and the gate fails. The gate also works when the inputs are in superposition states (*6*).

Single-photon communication is the basis for quantum cryptography, a technique for achieving authentication and confidentiality on fiber and free space optical links (*1*, *2*). Unlike every other known method, quantum cryptography can guarantee the secrecy of encryption keys regardless of the computing resources, fancy gadgetry, or guile of a hacker. Quantum cryptography may soon secure optical links between different sites of banks or large corporations across a metropolitan area. Thus the first applications for quantum logic are very likely to be in such photonic systems.

Any measurable property of the photon can store quantum information. Many experiments choose the linear polarization (or spin) of the photon, which corresponds to the direction of its electric-field vector. For example, we could associate a horizontally polarized photon with **0** and a vertically polarized one with **1**. Because the polarization can point in any direction in the horizontal or vertical plane, a polarized photon can encode any superposition of **0** and **1**. We can measure the linear polarization of a photon with a polarizing beam-splitter cube (*3*), which reflects all vertically polarized photons and transmits horizontal ones.

Manipulating the quantum information of a single photon is also straightforward; a thin quartz plate can rotate the photon polarization by any arbitrary angle. However, causing two photons to interact—a vital ingredient for quantum logic—is more difficult to achieve. Few materials are sufficiently nonlinear to allow re-

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