type of hereditary color agnosia cannot be detected by the standard Ishihara color test for color blindness or the Farnsworth-Munsell 100-hue test for color matching (*10*). Tests for "general intelligence" (such as the Stanford-Binet and WAIS tests) do not reflect the function of a broad range of brain regions but mainly recruit a specific system in the frontal lobes (*15*).

Considering all these factors, some common cognitive dysfunctions may still await discovery. In Piaget's model of human cognitive development (genetic epistemology), children learn by assimilation, the fitting of the perception of a new event or object to existing schemes, and by accommodation, the adaptation of cognitive schemes to new percepts. With one or more dysfunctional cognitive skills, cognition may still reach a sufficient functional level, but the cognitive network will become stretched and bent in the process. Therefore, any congenital functional or anatomical differences, as in congenital prosopagnosia or protanopia (red-green color blindness), will cause the neural networks to develop and connect in specifically different ways and lead to typical behavioral changes.

These processes and the underlying functional and anatomical dynamics are an extremely promising field for further research. As well, cognitive tests could evolve in ways such as defining the scope of tests more precisely. The human cognitive system is praised for its enormous adaptability. To help affected persons and to acquire a more comprehensive understanding of the brain, greater attention needs to be directed toward the structures, dynamics, and limits of these adaptive processes.

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MOLECULAR BIOLOGY

Syntheses That Stay Together

The rate of mRNA translation determines the rate of mRNA synthesis in bacteria through direct coupling of the respective molecular machinery.

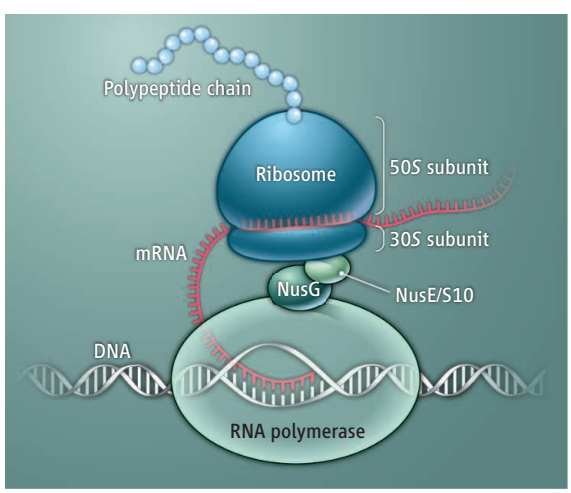
Jeffrey W. Roberts

An old principle of macromolecular biosynthesis in bacteria is that the speed of protein synthesis (translation) matches that of messenger RNA (mRNA) synthesis (transcription), but how this integration occurs has not been clearly defined. An obvious conjecture is that ribosomes move along the emerging mRNA at whatever speed RNA polymerase goes so that translation and transcription remain coordinated, as it is known to do when conditions change (*1*). However, on page 504 (*2*) and 501 (*3*) of this issue, Proshkin *et al*. and Burmann *et al*., respectively, suggest the opposite: Efficient binding and progression of ribosomes along mRNA increase the speed of RNA polymerase, whereas the absence of ribosomes allows the polymerase to slow and wait for ribosomes to catch up.

Proshkin *et al*. measured the rate of RNA polymerase progression along DNA in bacteria when translation was slowed in any of three ways: treatment with an antibiotic, expression of a mutated ribosomal protein, and an increase in the abundance of rare codons in the transcribed DNA. In each case, transcription slowed correspondingly. Furthermore, a ribosomal mutation that increased the rate of translation accelerated transcription.

What connection between RNA polymerase and ribosome underlies this unexpected effect? Proshkin *et al*. suggest that it depends on the polymerase's ability to "backtrack," in which it momentarily stops elongating mRNA and spools backward instead (*4*, *5*). Consequently, the newly synthesized mRNA end is extruded from the "secondary" channel of RNA polymerase and the upstream segment of mRNA is drawn back into the usual exit pore of the enzyme. RNA polymerase moves relatively freely between these isomeric states, although backtracking is favored when the mRNA-DNA hybrid is stronger in the backtracked position than in the forward position. Backtracking also is the response of polymerase to a physical barrier in its path, such as a DNA binding protein, even in the absence of an energetically favorable hybrid. A reasonable proposition is that temporary barriers in the chromosome make backtracking frequent enough to slow the overall rate of transcription. But backtracking is inhibited if another molecule binds to upstream mRNA and prevents its retraction into the enzyme (*6*). Along these lines, Proshkin *et al*. propose that a ribosome closely following RNA polymerase restrains the emerging mRNA. This would inhibit backtracking and favor net forward movement of the polymerase.

How does this mechanism relate to the fundamental regulatory step in which gene expression varies with the rate of ribosome access to its binding site at the beginning of the mRNA (*7*)?



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Coupled syntheses. A model for the coupling of translation and transcription in bacteria is shown. The first ribosome translating a mRNA associates with RNA polymerase through the NusE-NusG-polymerase interaction. This prevents retraction of the emerging mRNA into RNA polymerase, and thus inhibits backtracking-associated pauses that slow RNA polymerase in the absence of the ribosome.

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A strong binding site would allow a ribosome to load immediately onto the mRNA and prevent the advancing RNA polymerase from backtracking. At a weaker binding site, where the ribosome may not engage the mRNA immediately, the polymerase would slow through backtracking until a ribosome advances enough to cover the emerging mRNA, preventing backtracking. This ribosome then could accompany RNA polymerase to the end of the gene.

This model also explains how operons that are weakly translated—and thus have potentially extensive regions of naked mRNA—coexist with a process, mediated by Rho termination factor, which detects untranslated mRNA and terminates transcription. Rho binds 70 to 80 nucleotides of naked mRNA emerging from RNA polymerase, so that infrequent ribosome attachment to mRNA might be expected to provide a target for Rho at high efficiency. However, if RNA polymerase slows to let the first ribosome catch up (a train of ribosomes follows the polymerase in step, forming a "polysome" on the mRNA), the polymerase will be protected from termination, even if there are few ribosomes bound to the mRNA. Rho acts at the (untranslated) ends of operons (*8*), and in addition is the agent of "polarity," the process that aborts transcription when translation stops at a nonsense codon in a gene (*9*–*11*). Because the ribosome that accompanies RNA polymerase (and all following ribosomes) would be removed as soon as the nonsense codon is encountered, emerging mRNA could quickly accumulate to the required length and promote Rho activity.

Further evidence for a direct connection between the ribosome and RNA polymerase is provided by Burmann *et al*., who show through nuclear magnetic resonance (NMR) analysis direct binding between NusE, a ribosomal protein, and NusG, an RNA polymerase–binding protein (*12*)—an interaction also suggested by earlier genetic experiments (*13*) (see the figure). Because the NusG binding surface of NusE is exposed on the outside of the ribosomal 30*S* subunit, the leading ribosome could be tethered to RNA polymerase through NusE-NusG interaction, facilitating the ribosome's access to the emerging transcript and strengthening the inhibition of backtracking. NusG also binds to the Rho termination factor (*14*) and stimulates Rho function. Because Rho and NusG compete for binding to NusE, stimulation of Rho by NusG would be available only in the absence of a ribosome.

What happens to RNA that is not translated, such as ribosomal RNA (rRNA)? In *Escherichia coli* rRNA synthesis, RNA polymerase is modified by an antitermination complex that incorporates the transcription factors NusA, NusB, NusG, and NusE (*15*); this is similar to the well-characterized bacteriophage λ gene *N* antitermination complex (*16*, *17*). The antitermination complex of rRNA operons likely prevents termination of rRNA transcription by Rho. In addition, antitermination factors such as bacteriophage λ N and Q proteins and *E. coli* RfaH protein inhibit pausing and accelerate RNA polymerase (*18*, *19*); if it acts similarly, the rRNA operon antitermination complex may take the role of the leading ribosome in accelerating transcription.

There is also an alternate model to consider for the mechanism by which a ribosome accelerates transcription. The leading ribosome could act by the same pathway as the antitermination factors, which are thought to mediate changes in the active center of the polymerase that inhibit pausing, rather than acting simply to block mRNA movements associated with backtracking. These molecular details of the interconnection between translation and transcription are a fertile subject for future research.

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CLIMATE CHANGE

Toward Understanding and Predicting Monsoon Patterns

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A comprehensive atlas of past monsoon patterns will help scientists understand the causes of monsoon variability.

Much of the world's population lives in monsoon Asia and depends on monsoon rainfall for water and agricultural fertility. The monsoon also affects climate in other parts of the world (*1*). It results from an interplay between the ocean, atmosphere, and land surface (see the figure). Many factors thus affect its strength, including sea surface temperatures (SSTs) in the Indian and Pacific Oceans; variations in solar output; land snow cover and soil moisture over the Asian continent; and the position and strength of prevailing winds (*1*). The links between these factors and the monsoon appear to wax and wane over time, and the observational record is too short to explain this longer-term variability (*2*). This lack of information makes it difficult to forecast and plan for anomalous monsoon activity, and to predict how the Asian monsoon may be affected by global climate change. This situation is now changing: On page 486 of this issue, Cook *et al*. (*3*) report a Monsoon Asia Drought Atlas (MADA) that contains reconstructions of summer dryness and wetness for the region since 1300 C.E., based on tree-ring data.

The MADA offers a more comprehensive perspective on complex regional moisture patterns than that available previously from point source reconstructions (*4*). The new reconstructions cover three key climatic subperiods in the last millennium: the latter part of the Medieval Climatic Anomaly (*5*), the Little Ice Age, and the period of anthropogenic climate forcing. The length of the MADA record opens new possibili-

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