depth and heat-flow anomalies have come under renewed scrutiny.

Of special interest have been possible anomalies over hotspot swells. The GDH1 model reduced inferred anomalies at swells like Hawaii, implying that reheating of the lithosphere was less than previously thought (*10*). This reduction leads naturally to the consideration of "superswells", such as the Darwin Rise region (see figure), where multiple hotspot tracks may indicate that in the Cretaceous (before 65 million years ago), an unusual outpouring of mantle heat produced a broad upwelling. Depth anomalies relative to different reference models yield quite different maps and hence tectonic inferences (see figure). The entire Darwin Rise is shallow relative to a half-space model (*11*). Relative to PSM, much of the area is also shallow, suggesting a remnant regional thermal signature of the volcanism that formed the swells (*12*). However, because almost all lithosphere of this age is shallower than these models predict, the anomalies need not indicate that the Rise currently differs from lithosphere of this age elsewhere. In contrast, relative to GDH1, swells associated with volcanic chains are shallow, whereas depths between them are within a standard deviation of that predicted. Because of the three models GDH1 best describes average old lithosphere, it indicates that much of the Darwin Rise is not significantly deeper than lithosphere of the same age elsewhere, implying that the region between the swells retains no significant large-scale thermal signature of the Cretaceous events (*10*).

The superswell region near Polynesia, considered a possible present analog to the Darwin Rise, is also receiving new scrutiny. Although the extent of the depth anomaly is under debate (*13*), the region is shallow relative to all three reference models, which make similar predictions because the lithosphere is relatively young. The suggestion that the depth anomaly and weakening of the lithosphere inferred from satellite gravity observations reflected regional thermal thinning of the lithosphere (*14*) now seems precluded by heat-flow data (*10, 15*). Hence, the weakening seems likely to be mechanical, with the plate acting as though it were broken (*10*). The extent and cause of the depth anomaly remains an active research area, because of the challenge of separating any regional shallowing due to large-scale mantle upwelling from the effects of localized volcanism.

The revived interest in depth and heat flow anomalies seems likely to continue. New thermal models are being proposed (*16*), and new analysis techniques are being developed. The growing availability of data on the World Wide Web—including depths from combined shipboard and satellite observations (*17*), sea-floor ages (*18*), sediment thickness (*19*), and heat flow (*5*)—provides useful tools. Geophysicists will thus be inverting data, improving models, reducing misfits, pondering alternative depth anomaly maps, and debating their implications for years to come.

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TRANSCRIPTION

Paths to Activation of Transcription

E. Peter Geiduschek

The activities of genes are frequently regulated "up front", at the initiation step of transcription. The molecular picture of how this occurs is far from completion, but lots of progress is currently being made on many fronts, and work on the relatively simple bacteria continues to provide new insights. Two reports, on page 1658 and page 1655 of this issue (*1*, *2*), describe incisive experiments on the mechanisms that regulate the initiation of transcription in bacteria, with implications for understanding common mechanisms of all transcription.

NtrC (nitrogen regulatory protein C) is a transcriptional regulator that activates transcription. In a process that requires energy in the form of adenosine 5′-triphosphate (ATP) hydrolysis, NtrC converts polymerase-promoter complexes of the σ^{54}-RNA holoenzyme $E\sigma^{54}$ (E designating the core enzyme and σ^{54} the promoter-recognizing and initiation-specific subunit) from a closed state to a transcription-ready open state. NtrC is brought to the region of its target transcription units by binding to enhancers, which characteristically have two binding sites for dimeric NtrC.

Wyman, Rombel, and co-workers have now examined the binding of NtrC to an enhancer by scanning force microscopy (SFM) in coordination with an analysis of transcriptional activation in vitro (*1*). They show, in a visually striking way, that large oligomers, comprising more protein mass than the expected pair of phosphorylated NtrC dimers, accumulate on DNA when the transcriptionally active phosphorylated form of NtrC binds to its enhancer. With the use of SFM, these authors estimated the sizes of these large complexes, which appear as mounds piled up on ribbons of DNA. The mounds comprise protein-protein sandwiches, the functional significance of which has been demonstrated by a striking complementation: NtrC that can still bind DNA but that cannot activate RNA polymerase and NtrC that can activate RNA polymerase but not bind DNA can cooperate to activate transcription. Under these conditions, these molecules also form large protein oligomers on the enhancer.

Other experiments from the Kustu laboratory (*3*), and further work by others (*4*), indicate that the formation of these large phosphorylated NtrC oligomers is required for ATP hydrolysis, which is in turn directly coupled to the opening of the promoter. One might imagine that ATP hydrolysis would directly drive DNA strand separation at the transcriptional start site, but this is not the case (*5*): Until it is subjected to the

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action of NtrC or of one of its other activators, σ^{54} blocks isomerization entirely (6) and prevents proper initiation of transcription, even when the DNA strands surrounding the start site are artificially separated (5). Thus, the indications are that activation involves a reconfiguration of the promoter-bound RNA polymerase (7) that converts the polymerase from a transcriptionally inactive to an initiation-competent state [c1→c2 in the nomenclature of (8)]. The complex of $E\sigma^{54}$ with its promoter is latched in its transcriptionally incompetent (c1) form by an NH_2-terminal segment of σ^{54} (6). The ATP-hydrolyzing phosphorylated NtrC oligomer probably springs this latch open and may also reorient σ^{54} so that it now stabilizes the reconfigured (c2) RNA polymerase structure (6).

The second report in this issue, by Miller *et al.* (2), describes another mechanism of transcription activation in the *Escherichia coli* phage N4, which organizes its three-stage transcription program in a strange way: Although its genome encodes two RNA polymerases, these are used for the first two stages of transcription. N4 uses the principal *E. coli* RNA polymerase holoenzyme ($E\sigma^{70}$) only for the final (late) stage of viral gene expression, a strategy that requires N4 late promoters to be intrinsically weak so that they can operate under the control of an activator. The activator is N4's own single-stranded DNA binding protein (SSB), which is also required for DNA replication and recombination and is produced in great abundance during infection.

Miller and co-workers show that the COOH-terminus of N4 SSB is essential for transcriptional activation, but that DNA binding by N4 SSB is not required (2). Incisive affinity chromatography and photochemical cross-linking experiments have established that N4 SSB interacts with a COOH-proximal segment of β′, which lies at the upstream end of the transcriptional initiation complex. That the N4 SSB need not bind to DNA in order to activate transcription is consistent with observations that this activator does not recruit RNA polymerase to late promoters, but functions at a subsequent step of transcriptional initiation.

These two studies differ in regard to biological system and experimental method but yield related insights about the mechanism of action of bacterial RNA polymerase. NtrC and N4 SSB target a step of transcriptional initiation that follows recruitment of polymerase to the promoter. So do two other transcriptional regulators in *E. coli*, the cyclic AMP–dependent activation protein CAP acting at its so-called class II sites (9) and the phage λcI protein (10).

The remarkable thing about these four transcriptional activators is that they bind to diverse sites in the transcription apparatus (see the table): NtrC interacts with σ^{54}, CAP with the NH_2-proximal domain of the RNA polymerase α subunit (α-NTD), N4 SSB with the β′ subunit, and λcI and a gain-of-function mutant of CAP with the σ^{70} initiation protein (9, 11, 12). All these sites of interaction are located far from the transcriptional start site, where DNA strands separate, and at least three of them are located near each other. Indeed, all of these activators may facilitate the same step along the reaction pathway to transcriptional initiation: the c1→c2 reconfiguration of the RNA polymerase–promoter complex.

Current thoughts on mechanisms for ac-

NOTA BENE: IMMUNOLOGY

Tagging T Cells: T_H1 or T_H2?

Like the yin and yang of cellular immunology, T helper 1 (T_H1) and T_H2 cells reflect contrasting responses of an organism to an immunological insult. Each subset secretes a distinctive suite of cytokines: those produced by T_H1 cells promote predominantly cell-mediated immunity (such as the cytotoxic T cell response), whereas T_H2-derived cytokines induce the production of particular classes of immunoglobulin antibodies. These two cellular subsets are mutually antagonistic; one or the other predominates in response to any antigenic challenge. T_H1 responses are associated with immunity to viruses, and T_H2 with allergic reactions. Despite the importance ascribed to this T_H1-T_H2 dichotomy, the only way of discriminating between T_H1 and T_H2 populations has been by painstaking analysis of cytokines secreted by the cells. A cell-surface marker that could tag T_H1 or T_H2 cells would further strengthen the T_H1-T_H2 theory and would be of great practical help, particularly for the development and monitoring of clinical therapies. Just such a marker is described in two papers in the *Journal of Experimental Medicine* (1, 2). Complementary studies in human (1) and mouse (2) demonstrate the differential expression of the β2 chain of the interleukin-12 receptor (IL-12R) in T_H1 and T_H2 cells.

The IL-12R is not present on naïve (unstimulated) T cells, but after stimulation with antigen there is low-level expression of both chains of the receptor. Cells that develop along the T_H1 pathway continue to express both components of the receptor, but in populations destined to become T_H2 cells there is selective loss of β2 chain expression. The findings fit well with previous studies: IL-12 selectively promotes T_H1 responses (3); the β2 chain is the signal-transducing component of IL-12R (4); and IL-12 signaling induces phosphorylation of the transcription factor Stat4 in T_H1, but not T_H2, cells (5).

Continued stimulation with antigen must occur to maintain β2 chain expression; loss of expression, and consequent T_H2 development, is the default pathway. However, even under conditions that promote a predominantly T_H2-type response, IL-12 can cause β2 expression. In addition, interferons (IFNs) can maintain the expression of the β2 chain, and here the two papers yield an enticing species anomaly. In the human system, IFN-α and IFN-β had a stronger effect than IFN-γ, whereas in the mouse system, IFN-γ was most potent. The amount of IFN produced during an immune response may have a determining effect: High quantities of IFNs—induced, for example, by viral infection (IFN-α) or by natural killer cell activation (IFN-γ)—could favor T_H1 responses over T_H2.

Manipulation of IL-12R β2 expression provides new opportunities for monitoring and, because of its central role in signaling, therapeutic modulation of immune responses in allergy, autoimmunity, cancer, and infectious diseases. The findings also raise new questions about the stability of the T_H1 and T_H2 phenotypes: Can individual cells switch from T_H2 to T_H1, or is such a switch a population phenomenon, with greater or lesser numbers of cells developing along discrete T_H1 and T_H2 pathways?

—**Richard Gallagher**

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Beyond polymerase recruitment: Diverse targets of prokaryotic transcriptional activators

Activator	Target in RNA polymerase†
NtrC	σ^{54}
N4 phage SSB	β'
CAP*	α-NTD
Phage λcI	σ^{70}

* The wild-type protein at class II DNA binding sites (*9*).
† At these targets the activator generates an effect on transcriptional initiation at steps other than polymerase recruitment.

tivating eukaryotic RNA polymerases emphasize polymerase recruitment to the promoter and escape from confinement to the vicinity of the transcriptional start site, but ignore polymerase isomerization an available option (*13*). If it really turns out that eukaryotic transcription cannot be controlled at this isomerization step, a possible reason might be that eukaryotic RNA polymerase II does not require isomerization and is recruited to the promoter in a transcription-ready c2-equivalent configuration. That possibility adds particular interest to the prospect of analyzing the mechanics of transcriptional regulation in the *Archaea*. Archaeal RNA polymerases are eukaryote-like in structure and require two eukaryote-like factors for initiation of transcription (*14*). Are archaeal transcription activators also restricted to polymerase recruitment, or do they, like their bacterial counterparts, exploit a wider repertoire of mechanisms?

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GEOSCIENCE

Earthquakes Cannot Be Predicted

Robert J. Geller, David D. Jackson, Yan Y. Kagan, Francesco Mulargia

Earthquake prediction is usually defined as the specification of the time, location, and magnitude of a future earthquake within stated limits. Prediction would have to be reliable (few false alarms and few failures) and accurate (small ranges of uncertainty in space, time, and magnitude) to justify the cost of response. Previous Perspectives in *Science* may have given a favorable impression of prediction research, and the news media and some optimistic scientists encourage the belief that earthquakes can be predicted (*1*). Recent research suggests to us that this belief is incorrect.

An earthquake results from sudden slip on a geological fault. Such fracture and failure problems are notoriously intractable. The heterogeneous state of the Earth and the inaccessibility of the fault zone to direct measurement impose further difficulties. Except during a brief period in the 1970s (*2*), the leading seismological authorities of each era have generally concluded that earthquake prediction is not feasible (*3*). Richter, developer of the eponymous magnitude scale, commented as follows in 1977: "Journalists and the general public rush to any suggestion of earthquake prediction like hogs toward a full trough... [Prediction] provides a happy hunting ground for amateurs, cranks, and outright publicity-seeking fakers" (*4*). This comment still holds true.

For large earthquakes to be predictable, they would have to be unusual events resulting from specific physical states. However, the consensus of a recent meeting (*5*) was that the Earth is in a state of self-organized criticality where any small earthquake has some probability of cascading into a large event. This view is supported by the observation that the distribution of earthquake size (see figure) is invariant with respect to scale for all but the largest earthquakes. Such scale invariance is ubiquitous in self-organized critical systems (*6*). Whether any particular small earthquake grows into a large earthquake depends on a myriad of fine details of physical conditions throughout a large volume, not just in the immediate vicinity of the fault (*7*). This highly sensitive nonlinear dependence of earthquake rupture on unknown initial conditions severely limits predictability (*8*, *9*). The prediction of individual large earthquakes would require the unlikely capability of knowing all of these details with great accuracy. Furthermore, no quantitative theory for analyzing these data to issue predictions exists at present. Thus, the consensus of the meeting was that individual earthquakes are probably inherently unpredictable.

Empirical earthquake prediction would require the existence of observable and identifiable precursors that would allow alarms to be issued with high reliability and accuracy. There are strong reasons to doubt that such precursors exist (*10*). Thousands of observations of allegedly anomalous phenomena (seismological, geodetic, hydrological, geochemical, electromagnetic, animal behavior, and so forth) have been claimed as earthquake precursors, but in general, the phenomena were claimed as precursors only after the earthquakes occurred. The pattern of alleged precursors tends to vary greatly from one earthquake to the next, and the alleged anomalies are frequently observed at only one point, rather than throughout the epicentral region. There are no objective definitions of "anomalies," no quantitative physical mechanism links the alleged precursors to earthquakes, statistical evidence for a correlation is lacking, and natural or artificial causes un-

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