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?

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