inviability in any group or Haldane's rule for sterility in female-heterogametic taxa. The dominance theory also provides a natural explanation for two additional phenomena: The repeated finding that the X chromosome appears to contribute disproportionately to hybrid inviability and sterility (the "large X effect") (*11*) and the absence of Haldane's rule for sterility in mammals [see (*9*) for an explanation]. Conversely, faster-male evolution unquestionably plays a role in Haldane's rule for sterility in *Drosophila* and mosquitoes.

What remains to be done? We still know too little about the genes that cause postzygotic isolation. We lack, for instance, direct genetic analyses assessing whether X-linked incompatibilities in hybrids behave recessively, although several lines of evidence suggest that they do (*4*, *9*, *12*, *15*). The demonstrated power of analyzing Haldane's rule in diverse taxa should encourage researchers to look more carefully beyond Diptera. New insights may emerge from dioecious plants, such as *Silene*, with heteromorphic sex chromosomes (*5*). We also need more genetic analyses of Haldane's rule in female-heterogametic species. If the faster-male mechanism is working in these taxa, as suggested by the pervasive phenotypic evidence for sexual selection in birds and butterflies, it should oppose the appearance of Haldane's rule for sterility. In female-heterogametic taxa, therefore, we might expect to see a relative excess of hybrids producing Haldane's rule for inviability rather than sterility. In fact, the most recent data (*3*, *4*) show that 69% of the 84 examples of Haldane's rule in birds and Lepidoptera involve inviability, in contrast to only 19% of 217 examples in Diptera. Birds and Lepidoptera pose an additional challenge because their sex chromosomes are generally much smaller than those of Diptera. In these groups, how can dominance give rise to Haldane's rule when there are so few X-linked loci (*9*)? Although the main causes of Haldane's rule now seem clear, many ancillary questions await further analyses.

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PERSPECTIVES: DEVELOPMENT

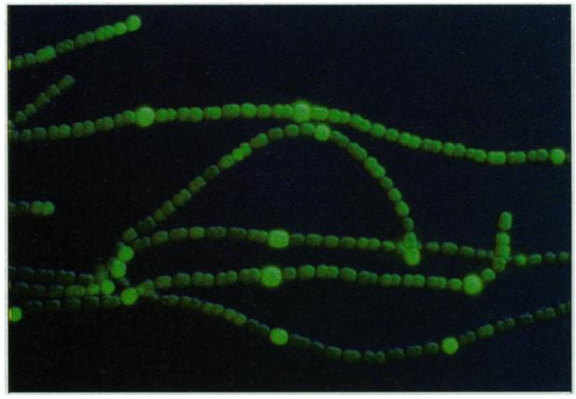
How Cyanobacteria Count to 10

Robert Haselkorn

The cyanobacterium *Anabaena*, although a prokaryote, develops elegantly in a way that more closely resembles eukaryotic development. About every tenth cell in its linearly arranged string of photosynthetic vegetative cells differentiates into an anaerobic, nitrogen-fixing heterocyst, as shown in the figure. This differentiation is provoked by an environmental cue—the absence of a fixed nitrogen source in the growth medium. Genetic analysis of mutants that cannot differentiate properly has led to a complex picture of interacting gene products that control the frequency of differentiating cells along each filament. In this issue on page 935, Yoon and Golden show that the gene *patS*, which encodes a 17–amino acid peptide, contributes to the spacing pattern by preventing the differentiation of cells between two heterocysts (*1*). Heterocyst differentiation can be suppressed completely by the external addition of the carboxyl-terminal five amino acids of the peptide Arg-Gly-Ser-Gly-Arg.

Control of differentiation by a small peptide sounds distinctly eukaryotic. Many other aspects of *Anabaena* heterocyst differentiation also recall or, in some cases, anticipate, signaling processes in eukaryotes. For example, some of *Anabaena*'s genes encoding nitrogenase proteins contain intervening DNA elements that have to be excised during each heterocyst differentiation, in a process reminiscent of the rearrangements of immunoglobulin genes in developing B lymphocytes (*2*). *Anabaena* also houses several serine-threonine–type protein kinases (*3*), a very large number of histidine kinases (*4*), probably a tyrosine kinase, and certainly a phosphotyrosine phosphatase (*5*).

How does a suppressing peptide fit into the current scheme for pattern regulation in *Anabaena*? We already know the identity of a few gene products that are required for heterocysts to differentiate. The protein acting earliest in the process, NtcA, is a DNA-binding factor required for transcription of numerous genes encoding components for nitrogen transport and utilization. NtcA is related by sequence to the cyclic AMP–binding protein of *Escherichia coli* (*6*). Among the genes regulated by NtcA is one called *hetR*, whose product is required for heterocyst differentiation (*7*). The figure shows the distribution of *hetR* transcripts, revealed by a fusion of the *hetR* promoter to the *gfp* gene, which encodes the green fluorescent protein. The filaments were photographed 1 day after nitrogen concentrations were decreased, when mature heterocysts display their characteristic spacing, about one every ten cells. The striking result is that the *hetR* gene is transcribed only in the differentiating cells. Exactly the same result is reported for another gene, *patS*, in the new work by Yoon and Golden (*1*). However, there is a critical difference, established both by the mutant phenotypes and the phenotypes of cells carrying extra copies of either the *hetR* or *patS* genes. That is, cells with mutant HetR do not initiate differentiation, whereas cells with mutant PatS dif-



Signs of differentiation. Superimposed Nomarski and fluorescent images of wild-type *Anabaena* PCC 7120, taken 25 hours after differentiation was initiated by nitrogen withdrawal. Differentiated heterocysts are marked by expression of green fluorescent protein (GFP) from a plasmid containing the *hetR* gene promoter fused to the GFP coding sequences.

CREDIT: W. J. BUIKEMA

The author is in the Department of Molecular Genetics and Cell Biology, University of Chicago, Chicago, IL 60637, USA. E-mail: r-haselkorn@uchicago.edu

ferentiate precociously (*1*, *7*). Conversely, cells with extra copies of *hetR* differentiate supernumerary heterocysts, whereas cells with extra copies of *patS* cannot differentiate at all. The two proteins, HetR and PatS, therefore represent two sides of the coin, one positively encouraging differentiation and the other suppressing it.

The HetR protein has remarkable properties. If the NtcA control of *hetR* transcription is bypassed, by using the copper-regulated *petE* promoter (also used by Yoon and Golden to drive *patS* expression), the resulting level of HetR can be so high that 30% of the cells differentiate, even in the presence of the usually inhibitory nitrate or ammonia (*8*). HetR can, therefore, drive differentiation even under normally repressing conditions. Second, there is a critical serine residue in HetR (*7*). When a strain carrying a Ser→Asn mutation, which does not differentiate, was forced to revert, five of five revertants had the wild-type serine restored. Third, HetR appears to be a serine protease, capable of digesting itself, inhibited by DFP, and probably phosphorylated on a serine (*9*).

This information suggests a simple hypothesis: A PatS peptide cleavage product is an inhibitor of the HetR protease activity. Because both of the genes are expressed in developing heterocysts (compare figure 4 of Yoon and Golden with the figure above), we need to explain how HetR is able to promote its own synthesis in the presence of PatS, which it is known to do (*8*). One possibility is that PatS is an inactive precursor substrate for the HetR protease and that the active cleaved peptide, Arg-Gly-Ser-Gly-Arg, is released into the periplasm and transported to vegetative cells, where it is indeed active against HetR. All of the elements of this proposal are testable by using recombinant HetR and synthetic peptides. Other models are equally plausible and testable in the same way. For example, HetR could cleave the PatS peptide to yield an inhibitor of PatA, a kinase required for HetR's positive activity (*8*, *10*).

The *hetR* gene has at least four promoters, several of which are activated after nitrogen is decreased. None of these contains the canonical sequence to which NtcA binds, so there must be intermediate signaling molecules (protein kinases?) between NtcA and *hetR* transcription; these could be targets of PatS control. It will of course be interesting to determine where the *patS* transcript starts and what its promoter sequence looks like. HetR, directly or indirectly, promotes its own gene transcription in heterocysts and represses it in vegetative cells. These activities require phosphorylation, because they are affected by mutations in the kinase PatA (*10*). In a *patA* mutant, all but the terminal cells in the majority of filaments fail to activate transcription of the *hetR* gene. In the *hetR* Ser→Asn mutant, however, transcription of *hetR* increases in all the cells after nitrogen has been reduced. We conclude that wild-type HetR has two activities: enhancement of *hetR* transcription in heterocysts and repression of *hetR* transcription in vegetative cells. The first of these requires the PatA kinase, whereas the second does not. These considerations suggest another possible site of action of the PatS peptide: inhibition of the PatA kinase.

No matter what mechanism is found to apply ultimately, the remarkable discovery of peptide control of differentiation in such a simple experimental system should lead to insights applicable to a wide range of more complex problems in eukaryotes.

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NOTA BENE: PHYSICS

Just a Light Squeeze

Quantum mechanics is a rigorous taskmaster, but occasionally it will let you get away with magic. An example has recently been reported by Schmitt *et al.* (*1*) of the University of Erlangen-Nurnberg, who used fiber optics to create unusual pulses — solitons—marked by even more unusual behavior called a "squeezed state."

Solitons are isolated waves on the verge of both creation and destruction. A typical pulse of light propagating in a glass fiber wants to spread out, smearing its energy over broader and broader regions. Yet in a nonlinear material, which glass becomes at very high optical intensity, the energetic pulse modifies the fiber's index of refraction in a way that leads to sharpening and narrowing. If these two tendencies are in balance, the pulse becomes a soliton (solitary wave) and can propagate without loss for very long distances. This has made optical solitons attractive to builders of long-haul communication networks.

Schmitt *et al.* have used soliton pulses of 126 femtoseconds duration to explore the strange phenomenon of quantum mechanical squeezing. Heisenberg's uncertainty principle says that if one knows the position of a particle to high accuracy, then one's knowledge of momentum must suffer. More rigorously, the product of the uncertainties of position and momentum must be greater than or equal to h, the Planck constant. Position and momentum are called "conjugate" variables, wedded as they are in quantum mechanical bliss and blessed by Heisenberg. But there are other conjugate variables, such as energy and time, or the number of photons in an optical pulse and their phase relations. Here is where tricks can be played: If the quantum fluctuations in one variable are allowed to be large, the uncertainty in the conjugate variable can be reduced, or "squeezed." For this reason, squeezed states are of considerable interest to researchers developing ultraprecision measurements.

Squeezed solitons from fibers have been observed before (*2*), but Schmitt *et al.* achieved a direct observation of reduced fluctuations in the photon number, in contrast to the earlier measurements, which measured aggregate optical amplitude. Their apparatus consisted of a Sagnac interferometer, made from a 6.4-meter loop of highly precise optical fiber, a pulsed laser, beam splitters, and photodetectors. The Sagnac loop allows two counterpropagating pulses to interfere with each other and trade off quantum fluctuations, and if the relative amplitude of the two pulses is carefully adjusted, the loop becomes a factory for squeezed solitons. The direct photon number squeezing reflects the quantum behavior of individual frequency components in the pulse, rather than some average, and hence provides a more detailed picture of the squeezing process. Taken together, these results offer a better understanding of the nature of optical quantum processes and the possibility of a ready source of squeezed pulses for measurement and communications.

—DAVID VOSS

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