The pore–transcription connection

The transcripational state of a gene is connected to its association with the nuclear pore, according to Jason Casolari, Pamela Silver, and colleagues (Harvard Medical School, Boston, MA). Although the silencing of certain loci was known to rely on their localization to the nuclear periphery, where the pores lie, the new results suggest that yeast pores prefer transcriptionally active genes. “You get more bang for your buck if highly active genes are at the pore,” says Casolari, because it may expedite export of the transcripts.

The nuclear pore is, however, important for all sorts of genes—active and inactive, and the boundaries between them. The group shows that pore proteins are fond of both active and inactive genes with binding sites for the Rap1 transcription factor. Rap1 has boundary activity—it shields intervening sequences from the transcriptional state of the outlying DNA. Some nuclear transport proteins also have boundary activity. Association with the nuclear pore might thus prevent the unwanted spreading of either activation or silencing into nearby regions.

Only one nuclear transport protein examined, the Prp20 RanGTP exchange factor, strongly favored inactive genes. As Prp20 helps to release cargo from their import carriers, the authors speculate that it might lie near inactive genes so that it is ready to release any imported transcription factors for fast gene activation.

Prp20 was found at silent GAL genes but was replaced by other pore proteins when the genes were activated. These proteins included both structural and shuttling components of the nuclear pore, which were most often found at strongly transcribed genes. Some of the favorite targets of the pore proteins were genes involved in protein biosynthesis, whose export should be even more efficient as the genes are coexpressed and found in clusters.

The active GAL genes preferred the nuclear periphery, but it is not clear whether transcription precedes the change in localization. How the DNA reaches the periphery is also unknown, but may be a consequence of protein–protein interactions between the transcriptional machinery and pore proteins, perhaps via hnRNPs.


Immune to autoimmunity

New results from Antoine Perchellet, Joan Goverman, and colleagues (University of Washington, Seattle, WA) show that T cells that bind self-peptides most avidly can survive and engulf self-peptides without initiating an autoimmune response. Although appearing innocent, these cells might be potential disease instigators.

Most self-recognizing T cells whose receptors interact too strongly with self-peptides are either killed or made unreactive (by receptor rearrangement) in the thymus. If they somehow escape to the bloodstream, they can also be killed or silenced there. To study how these processes eliminate T cell responses to myelin basic protein (MBP), a target of T cells during multiple sclerosis, the authors created two mice lines that express different MBP-specific T cell receptors.

One receptor, which had a lower affinity for MBP, worked as expected—T cells with this receptor were removed from the thymus or later from the periphery. T cells with the higher affinity receptor somehow persisted, however. Yet the mice did not develop autoimmunity, revealing a third route for preventing autoimmune reactions.

The mice remained healthy because the T cells were ineffective even with their high affinity receptor. The T cells did not proliferate in response to MBP presented by dendritic cells because they did not make interleukin-2 (IL-2). The reason for this failure remains unclear, but it seems to lie downstream of MBP recognition. If MBP-presenting dendritic cells were preincubated with high affinity T cells, the dendritic cells could no longer elicit proliferation of low affinity T cells, probably because they had been stripped of MBP.

The mice were problem free, but

Crystal structures may fit all the data, but a report from Mark DePristo and colleagues (University of Cambridge, UK) warns that, for any given structure in the Protein Data Bank (PDB), there will be many other overlooked structures that are equally consistent with the data.

Crystallographers fit their data to models that pass quality controls, but they usually report only one such model. The Cambridge group generated alternate models that fit the data for several proteins. “We found a reasonable number of structures that are surprisingly different in their finer details,” says DePristo. And as the diffraction resolution decreased, the differences increased.

Most variability was found at the protein surface rather than its core, suggesting that a good idea of protein fold can be gleaned even at low resolution. But detailed conclusions that depend on precise atomic location, such as catalytic mechanism, may be misinterpretations. “We need a change in thinking of structures as less of a static, perfect model, but rather as models that have uncertainties,” says Tom Terwilliger (Los Alamos National Laboratory, Los Alamos, NM). “Crystallographers need to develop a means for communicating the uncertainty in their atomic model.”


### Uncertainty in structures

#### Pollen spares all but self

Many plants encourage genetic diversity by preventing self-pollination. Two groups now show that this system works by protecting only an RNase that destroys self. This RNase stops the growth of genetically identical pollen tubes, but RNases that would destroy nonidentical pollen tubes are themselves degraded.

The RNases are made by a part of the S-locus, a huge, intractable stretch of DNA. Although the female-specific product of the S-locus has long been known to be the S-RNase, the male-specific product (made by the pollen tube) has eluded scientists for a decade. It is now identified as a regulator of ubiquitination that seems to sentence all but self S-RNases to degradation.

Through a brute force sequencing approach, Paja Sijacic, Teh-hui Kao (Penn State University), and colleagues found that the petunia pollen S-component is the SLF F-box protein. Normally, a haploid pollen grain expresses only one S-allele. But forced expression of two different S-alleles alters pollen rejection. The group now shows that two different SLFs can likewise alter pollen rejection, thus confirming that SLF is the male incompatibility protein.

An extra SLF allele makes pollen that would normally not grow survive.

Hong Qiao, Yonghiao Xue, and colleagues (Chinese Academy of Sciences, Beijing, China) found that SLFs from snapdragon bind to both self and non-self S-RNases. But only the non-self enzymes were ubiquitinated and thus degraded.

How SLF prevents degradation of its own S-RNase is not clear. Kao guesses they may have matching interaction domains that either block the ubiquitination site or alter the F-box so that it cannot interact with other SCF components.


### Cells step back in time

Many of us would like to be young again. Results from Maria Sequeira López, Ariel Gomez (University of Virginia, Charlottesville, VA), and colleagues show that a return to youthful activities is possible for at least some mature cell types.

These do-over cells are progeny of renin-secreting cells. The renin–angiotensin system controls body fluid and electrolyte levels. Although many cells make renin during development, those that hold this job in the adult are restricted to a small region of the kidney. During stresses such as dehydration, this population may be unable to make enough renin. To remedy the situation, a population may revert to their renin-secreting ways. In the adult, marked cells included more cells in and near the kidney begin to produce renin.

The authors permanently marked any cell in a mouse that ever expressed renin. In the adult, marked cells included nonrenin-producing vascular smooth muscle, epithelial, and mesangial kidney cells. When fluid homeostasis was threatened, it was these marked cells that dedifferentiated and reverted to their renin-secreting ways.

Cells that had never made renin did not contribute. “At least for this system,” says Ariel, “the change in cell identity is determined by the lineage of the cell. Not all cells can do anything.”