Research Roundup

The pore–transcription connection

The transcriptional 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.

Reference: Casolari, J., et al. 2004. Cell. 117:427–439.

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 Goverman says the escaping T cells are still worrisome because they are present in the periphery. “If they get activated by some other mechanism,” she says (by viral infection, for example), “then they’ll wake up, see MBP, and attack it. And they see the ligand really well, because they are high affinity.”

Reference: Perchellet, A., et al. 2004. Nat. Immunol. 10.1038/ni1073.