of peptides bound to a typical class II molecule includes only small amounts of CLIP. Most of the peptides are a sampling of the proteins present within the endocytic pathway of APCs. How is this CLIP-to-antigenic-peptide switch accomplished?

Evidence that other proteins were necessary for antigenic peptide loading came in 1992: Class II molecules from certain mutant APCs contain only CLIP in the binding groove and not the normal diverse array of antigenic peptides (*3*). The basis for this defect turned out to be the absence of a functional DM protein in these cells (*4*). These results indicated that DM either prevented CLIP binding to class II molecules, prevented CLIP generation, or removed CLIP from class II molecules.

Late in 1995, three groups independently found that DM could remove CLIP from class II molecules and that this removal greatly enhanced antigenic peptide binding to class II molecules (*5*). What was puzzling, however, was that DM was able to facilitate the dissociation of CLIP from class II but did not have the same action on other, non-CLIP peptides from class II molecules. Despite the remarkable similarity between the structure of class II–CLIP and class II–antigenic peptide complexes, DM could tell the difference. It appeared as though DM was seeing something that we could not, perhaps the subtle differences between the two types of class II–peptide complexes.

The new paper of Weber *et al.* (*1*) exploits their observation that the ability of DM to facilitate CLIP removal depends on the presence of certain CLIP amino acid residues that associate with pockets in the class II peptide binding groove. When one of these residues of CLIP is replaced with a corresponding residue of a non-CLIP peptide, DM can no longer catalyze the dissociation of the modified CLIP peptide from class II. By measuring the ability of DM to catalyze the removal of the mutated CLIPs from class II molecules, the authors found that the ability of a given class II–CLIP complex to dissociate in the presence of DM is directly proportional to the intrinsic rate of dissociation of that peptide from class II. They determined that if a given peptide analog dissociates from class II very slowly, it is not a good substrate for DM-induced dissociation, whereas those peptides that dissociate from class II rapidly (like wild-type CLIP) are very good substrates for DM.

So how does DM catalyze peptide dissociation from class II molecules? Weber *et al.* propose that DM functions by stabilizing a transition state of the class II–peptide complex in which hydrogen bonds between the class II molecule and bound peptide are transiently disrupted. The majority of the hydrogen bonds between class II molecules and antigenic peptides (or CLIP) are between class II and the peptide main-chain atoms. (Perhaps this is why CLIP associates with essentially all class II alleles.) Because all peptides are thought to bind to class II molecules similarly, the class II–peptide main-chain bond energy is also similar. It is this phenomenon that allows DM to exert its effects in a manner that is directly proportional to the intrinsic rate of dissociation of a given peptide: Because the class II–peptide bond energy is lowered by DM by a constant amount, peptides that have additional stabilizing forces are resistant to the effects of DM, whereas those that do not have such forces readily dissociate. One can imagine a model of DM function in which DM binds to the class II molecule to transiently pry open the peptide-binding groove by a certain amount. The net effect of this is to disrupt the normal hydrogen bonds between the class II molecule and the bound peptide, so that only those peptides with additional stabilizing forces remain associated with the class II molecule. For example, if a particular peptide has very strong anchor residues, this transient disruption by DM will not destabilize the peptide enough to lead to its dissociation. This model also predicts that there are few additional stabilizing forces in the class II–CLIP complex, and so the complex readily dissociates in the presence of DM.

The exact physical mechanism by which DM exerts this effect remains unknown, although DM seems to bind directly to class II molecules (*6*), a finding that supports the proposed model. Regardless of the mechanism, however, it is clear that in the cell DM prevents peptides with fast intrinsic dissociation rates from remaining bound to class II molecules, independent of the overall affinity of the peptide for class II. Antigenic peptides that have fast dissociation rates are removed by DM in vivo so that they do not appear in the normal array of peptides eluted from class II molecules. In this sense, DM is acting as a true peptide editor, ensuring that only stable peptides remain bound to class II.

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Nota Bene: QUANTUM OPTICS

One plus one is not two

The strangeness of quantum mechanics can be told in the story of photon interference. Light passing through two slits forms a rippled interference pattern. Reduce the intensity to one photon at a time, and the pattern remains. The particle-like photon is at the same time behaving as a wave. In a modern variant of the two-slit experiment, a nonlinear optical photon splitter creates two photons from one input photon. With such a device, Pittman *et al.* (*1*) report a further quantum peculiarity: Two-photon interference is not necessarily the interference of two photons.

In one version of two-photon interference (*2*), the two photons are sent down separate paths and then allowed to meet again. If a small delay is introduced in one path, the expected interference pattern is observed. Because of this, one might conclude that the interference occurs only when the photon wave packets overlap. In fact, Pittman *et al.* (*1*) show that this is not the case: Interference can arise even if the two photons arrive at very different times.

They achieve this by a kind of "quantum eraser" (*3*). A large delay is introduced in one arm of the interferometer; the interference pattern disappears, one would assume, because the photons no longer overlap. But if a catch-up delay is introduced downstream of where the photons would meet, the interference then reappears. The photons have arrived at their intended rendezvous point at widely different times, yet they interfere. The quantum eraser has removed the possibility of distinguishing which path the photon takes, so the interference pattern reemerges. This experiment also erases another intuitive but false notion of how quantum mechanical objects interact.

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