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Journal club

FINDING ORDER IN CHAOS

A recurrent strategy used by the adaptive immune system is to employ a stochastic process to generate a diverse repertoire of molecules, and then overlay stringent biochemical criteria to select for the desired candidates. This juxtaposition of chaos and elegant design aptly applies to the rules of antigen presentation.

The first X-ray crystallographic structure of an MHC molecule (Bjorkman *et al.*, 1987) revealed the presence of a dedicated antigen-binding groove that is formed by the highly polymorphic residues within the α1 and α2 domains of the MHC molecule. The material in the binding groove was unresolved in that study, presumably owing to the heterogeneous nature of bound peptides, but we would learn from the work of Hans-Georg Rammensee and colleagues (Falk *et al.*, 1991) that contained therein was only a small fraction of the universe of available peptides: only those peptides that met the biochemical requirements for MHC class I binding.

> “strict biochemical rules … govern the ability of a peptide … to become a member of the antigenic universe”

In a classic experiment, these authors stripped peptides out of the groove of a particular MHC molecule, H-2K^d, and had the audacity to attempt to sequence what appeared to be a totally random mixture of peptides directly by Edman degradation. This approach could only yield meaningful results if a high proportion of the peptides were of the same length and if certain positions along the peptide had sequence homology. This supposition was borne out by the fact that certain sequencing cycles revealed a much higher than random percentage of a particular amino acid residue. They then went on to sequence peptides from different MHC alleles and found that each was unique with respect to the peptide residues and positions that were favoured. Based on these results, the authors predicted that the favoured residues corresponded to the position and shape of pockets within the peptide-binding cleft of each MHC allele.

These early studies led to the discovery of peptide-binding motifs that are unique to each MHC class I allele. In turn, this has enabled us to predict the sequence of antigenic epitopes in pathogens, autoantigens and tumour antigens. Indeed, what appeared to be a random set of peptides by X-ray crystallography was decidedly not, and we now know that there are strict biochemical rules that govern the ability of a peptide to successfully bind an MHC class I molecule to become a member of the antigenic universe.

Linda Sherman
The Scripps Research Institute, La Jolla, California 92037, USA.
lsherman@scripps.edu

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ORIGINAL ARTICLE Falk, K. *et al.* Allele-specific motifs revealed by sequencing of self-peptides eluted from MHC molecules. *Nature* **351**, 290–296 (1991)
FURTHER READING Bjorkman, P. J. *et al.* Structure of the human class I histocompatibility antigen, HLA-A2. *Nature* **329**, 506–512 (1987)