# Images of charge density waves

THE uses of scanning tunnelling microscopes (STMs) are many: both the manipulation of single molecules and the study of surface topography have been discussed recently in News and Views. R.V. Coleman and co-workers now report (*Phys. Rev. B37*, 2741; 1988) the use of one to study charge density waves (CDWs) on the surface of a metal cooled to 4.2 K. The periodic distribution of conduction electrons is determined primarily by the ions in the metal; but below a critical temperature, interactions mediated by lattice vibrations (phonons) between the electrons (the same interactions lie at the heart of superconductivity) can give rise to additional charge modulation — the charge density waves. Coleman and co-workers report the observation of CDWs in $NbSe_2$ which consists of layers of niobium sandwiched between layers of selenium ions. At low magnification (top left, 94×94 Å^2), the STM reveals the lattice of selenium ions at the surface, observed by the increased tunnelling current detected by the scanning tip as it passes over the ions. (In practice, the tip height is varied to maintain a constant current.) The CDWs, however, become evident only at higher magnification (top right, 55×55 Å^2): there is an additional modulation of the charge density with a period of three times the lattice spacing. The lower micrographs show the charge distribution at the crest (right) and minimum (left) of the CDWs; the central selenium atom on the crest appears to be 'higher' than the surrounding atoms. The distortion of the charge distribution ('leaning' to the right) arises because the CDWs are centred on the offset niobium atoms in the second layer of the crystal and not on the surface selenium ions.
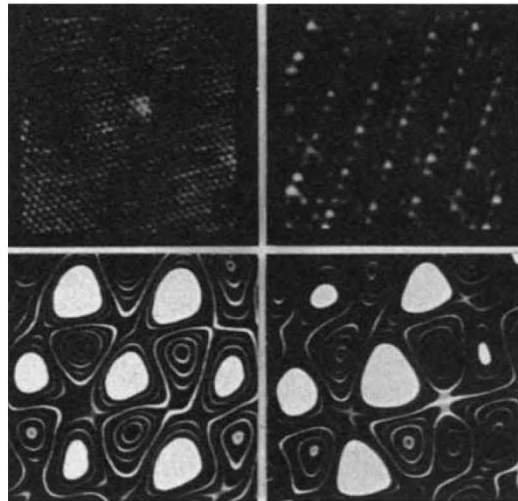
R.V. Coleman

the responding lymphocyte, and the Mls^a–MHC complex on the target cells.

Anatomy of recognition

The inferential nature of the scheme is imposed partly by the absence of direct structural information about the MHC molecules that engage in Mls reactions. There are two classes of MHC recognition responses, broadly corresponding to the two major functional classes of T lymphocyte. Cytotoxic cells generally recognize antigens bound to MHC class I molecules, while helper T cells generally recognize antigens bound to class II MHC molecules. In both cases it is known that the antigen bound to the MHC molecule is a short peptide derived by intracellular degradation from the complete protein antigen, but only for the class I molecule has the crystal structure been solved[8,9]. Because the responses stimulated by Mls^a are helper-cell responses directed against class II molecules, it has been necessary to infer the structural basis of antigen presentation in Mls^a reactions on the basis of structural homologies between class I and class II that suggest that they bind antigen in the same way.

The crystal structure of the class I molecule has revealed that the antigenic peptide is bound in a pocket on the external surface of the molecule, the sides of the pocket being formed by polymorphic residues implicated in interactions with the T-cell receptor[8,9]. Thus the complex of MHC and antigen presented to the T cell consists of one surface of the antigenic peptide flanked by polymorphic residues of the MHC molecule.

Thus, as receptor binding normally depends upon the sum of the contacts made by the MHC molecule and the peptide antigen, the implication is that Mls binds so strongly to the antigen-binding residues of the T-cell receptor that the effect of specific contacts between receptor and MHC is negligible. Hence the violation of MHC restriction. The final link in the chain of inference leads to the question of how this may bear on the expansion of the self-restricted T-cell repertoire in the thymus.

Thymic maturation

According to a current model of T-lymphocyte ontogeny (lucidly summarized in ref. 10), maturation in the thymus occurs in two stages. In the first, functionally immature thymocytes expressing $\alpha\beta$ receptors are positively selected on thymic epithelial cells for weak binding to self MHC molecules, giving rise to self-MHC restriction; in the second, they are negatively selected in the thymic medulla for strong binding to self-MHC molecules, so that potentially self-reactive cells are eliminated and self tolerance is assured.

The nature of the selective mechanism is unknown: it is assumed that thymic epithelial cells induce proliferation in immature lymphocytes binding weakly to MHC molecules on their surface, while bone-marrow derived cells in the medulla kill those cells that bind strongly to their MHC molecules. But whereas it is easy to imagine a mechanism for reliably selecting strongly binding cells, it is more difficult to imagine how cells could be selected for a binding affinity so weak as to be ineffectual in the absence of antigen.

It is this difficulty that Kappler et al. attempt to address by invoking the Mls phenomenon. If the antigen-binding pocket of MHC molecules on thymic epithelial cells is normally occupied by a peptide or peptides with an affinity for the T-cell receptor strong enough to ensure binding in the presence of weak receptor–MHC interactions, then the consequence would be positive selection for weak binding to self MHC.

That the antigen-binding pocket of thymic epithelial cell MHC molecules should be permanently occupied by peptides specific to thymic epithelium is not as gratuitous a supposition as it may seem. There is evidence of various kinds suggesting that the antigen-binding pockets of MHC molecules are unlikely ever to be empty, and thus may normally be occupied by peptides derived from self proteins: the human class I molecule crystallized by Bjorkman et al.[8,9] turned out to contain bound peptide, or peptides, despite extensive purification.

What Kappler et al. propose is that Mls^a has properties that adventitiously mimic the properties of a thymic epithelial cell protein that has evolved to bind with high affinity both to MHC and to the T-cell receptor antigen-binding site, the latter perhaps through conserved residues in this otherwise hypervariable region.

Under this supposition, Mls^a in mice might represent either the aberrant expression of such a thymic peptide in non-thymic cells; or a mutation in some normal cell protein that confers upon it the properties of such a peptide. In any case, it is plain that isolation of the Mls product and analysis of antigenic peptides derived from it is likely to become a significant goal of molecular immunology. □

1. Kappler, J.W., Staerz, U., White, J. & Marrack, P. *Nature* **332**, 35–39 (1988).
2. Macdonald, H.R. et al. *Nature* **332**, 40–45 (1988).
3. Kappler, J.W., Roehm, N. & Marrack, P. *Cell* **49**, 273–280 (1987).
4. Festenstein, H. *Transplant. Rev.* **15**, 62–88 (1973).
5. Janeway, C. et al. *Immun. Today* (in the press).
6. Katz, M.E. & Janeway, C.A. *J. Immun.* **134**, 2064–2070 (1985).
7. Jones, B. & Janeway, C.A. *Immunogenetics* **16**, 243–255 (1982).
8. Bjorkman, P. et al. *Nature* **329**, 506–512 (1987).
9. Bjorkman, P. et al. *Nature* **329**, 512–518 (1987).
10. Marrack, P. & Kappler, J. *Science* **238**, 1073–1079 (1987).

Miranda Robertson is Biology Editor of Nature.