model simulations from the Atmospheric Model Intercomparison Project (*11*), in which GCMs were forced only with SST variations, with the observations, Mao and Robock (*12*) showed that although the winter pattern of 1986–1987 was well simulated by an average of the eight best simulations during a period without volcanic aerosols, the 1982–1983 pattern resembles the winter warming found in the volcanic GCM simulations and in observations (*13*) and does not resemble the El Niño pattern (see figure). Kirchner and Graf (*14*) have shown that it is possible to distinguish the signals of SST and volcanic forcings and that both are important in Northern Hemisphere winter climate variations.

We are entering a new period for stratosphere-troposphere exchange (*15*), with enhanced emphasis on the stratosphere by the World Climate Research Programme "Stratospheric Processes and Their Role in Climate" project (*16*). The problems are fascinating, challenging, and complex and involve understanding the simultaneous interactions of atmospheric dynamics, radiative physics, aerosols, and chemistry. Volcanic eruptions also affect ozone concentrations by providing aerosol surfaces for heterogeneous chemical reactions with anthropogenic chlorine compounds. GCMs are just now becoming available with enhanced stratospheric resolution and explicit consideration of the radiative effects of aerosols and the chemical variations induced by changing UV radiation, anthropogenic chemicals, and aerosols. With these new tools and our enhanced awareness of the potentially large impacts of stratospheric variations on the tropospheric climate, we will soon have a much richer understanding of seasonal and interannual climate variations and their causes and improved predictive skill to enhance that already existing from SST variations.

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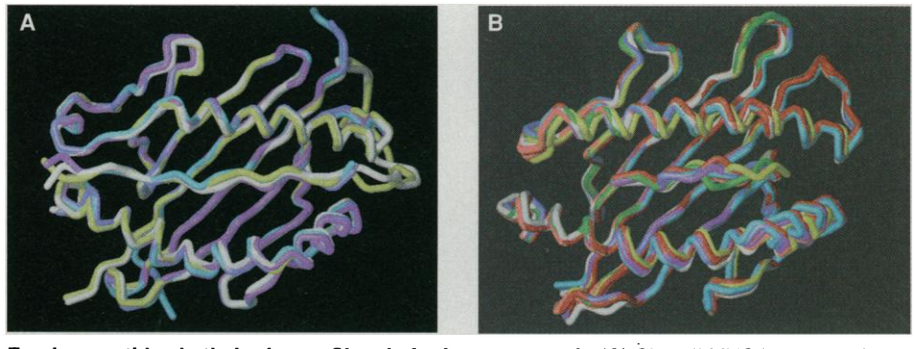
Another Twist to MHC-Peptide Recognition

Ian A. Wilson

The immune system cuts foreign invaders into little pieces, which are then displayed on the surface of cells. There, bound to one of two proteins—major histocompatibility complex (MHC) class I or class II—these foreign peptides trigger the defensive reactions of the host. MHC class I receives its peptide pieces inside the cell, derived from an intruder that has taken up residence there; but class II is filled with molecular bits of invaders from outside the cell. Before being filled with their real cargo, the binding groove of MHC class II molecules is occupied by a "dummy" peptide, CLIP. Inside a vesicle that contains the proteolyzed remains of foreign invaders from outside the cell, the acidic conditions promote dissociation of this place-holding molecule and insertion of a foreign one. A report in this week's issue of *Science* yields clues about how pH may control replacement of CLIP with foreign peptides (*1*).

Structural analyses of single peptides bound to class II molecules from human (*2*, *3*) and mouse (*1*) have allowed us to see exactly what the peptide looks like as it sits in its MHC groove (*4*). In MHC class II molecules, peptide antigens—13 to 25 residues long (*5*)—are embedded in the MHC binding groove but spill out over the ends of the binding site (*1–3*). The central nine residues are forced into a supertwisted ribbon structure that closely resembles a polyproline II–type conformation. On the walls of the groove, the "peptide-like" side chains of four conserved Asp and Gln residues of human (DR) and mouse (I-E) class II molecules hydrogen bond similarly with each peptide antigen backbone in a pseudo–β-sheet–like interaction that causes the peptide to writhe and twist along the groove into the regular, shallow polyproline II spiral. Even though the binding sites are open at either end, this backbone interaction imposes



Foreign peptides in their places: Signals for immune attack. (**A**) Class II MHC human and murine molecules with their bound peptides. Superposition of I-E^k (*3*) (white and yellow), HLA-DR1 (*1*) [1dlh (blue and cyan)], and HLA-DR3 (*2*) (magenta). The I-E^k peptides are covalently linked to the MHC molecule in a construction that allows coexpression (*16*). (**B**) Class I MHC molecules and their bound peptides. The molecules superimposed include five peptide complexes of HLA-A0201 (*17*) [1hhg (red), 1hhh (green), ihhi (blue), 1hhj (cyan), and 1hhk (magenta)], HLA-Aw68 (*18*) [1tmc (yellow)], and three complexes of murine H-2K^b (*19, 20*) [kbo (white), kbs (orange), and kbv (red)]. [Figure by R. Stanfield; coordinates provided by D. Fremont (I-E^k), T. Jardetzky, P. Ghosh, and D. Wiley (HLA-DR1 and HLA-DR3), and the published class I structures (*17–20*)]

The author is in the Department of Molecular Biology, Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, CA 92037, USA. E-mail: wilson@scripps.edu

tight structural constraints upon the class II peptide. Only slight deviations from peptide to peptide occur in the backbone conformation of the central residues (see the figure). This seemingly general conformation for all class II peptides (6) is more restricted in nature than its class I counterpart (7).

In the new work on murine I-E^k MHC, Fremont *et al.* (1) examine why peptide loading is enhanced at the low pH of the endosomal-like compartment where peptide exchange takes place. Foreign peptide substrates are produced by proteolytic degradation of invading microbial pathogens by way of the endocytic pathway. An exchange is required so that the CLIP peptide (derived from the Invariant chain), acquired by MHC en route from the endoplasmic reticulum, is substituted by the foreign peptide antigen (8). A DR3-CLIP peptide structure (2) revealed that this "universal" peptide is bound like other peptides except that the specificity pockets for the central peptide side chains may not be optimally filled. Still, this complex is relatively stable even at low pH (2), so another MHC lookalike, HLA-DM, is required for timely catalysis of this exchange (9, 10).

Fremont *et al.* propose that a pair of conserved acidic residues in the DR1 and I-E MHC molecules at the bottom of the binding groove ensures that loading is favorable only at low pH, conditions under which protonation of these acidic residues is enhanced. However, these acidic residues also participate in a continuous hydrogen bonding network (1) that includes the same Asn and Gln residues that influence the polyproline II peptide conformation. This network could also orient the Asn and Gln side chains to guide proper polarity and orientation of the peptide in the binding site. SRC homology 3 domain (SH3) molecules also bind polyproline II peptide structures, but can do so in both directions (11). Because of their proline-rich nature, their backbone atoms are more restricted in their availability for hydrogen bonding, so they also make use of other interactions with peptide side chains to orient the peptide (11).

Do all class II molecules adopt the same peptide recognition strategy? Other class II families, such as human DQ and murine I-A, have substantially different α chains but retain the same hallmark peptide binding residues that include all of the key Asn's (12). Nonclassical class I molecules, such as H2-M3, which bind formylated hydrophobic peptides, have indeed provided interesting diversity to the class I recognition story (13). What is already clear is that these MHC class I and class II molecules use somewhat different strategies to form stable, high-affinity peptide complexes, but within the context of the same overall MHC fold. So what of CD1, another distantly related MHC class I which binds diverse homolog antigens, such as fatty acids and lipoglycans derived from mycobacterial cell walls (14, 15)? It will be interesting to see how the MHC fold has adapted to binding such disparate ligands.

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Regulating Cell Proliferation: As Easy as APC

Mark Peifer

Animal cells communicate by an array of signals that travel from cell to cell, each activating its attendant signal transduction pathway. These pathways are critical for normal development and physiology; when they malfunction, cancer often results. Two reports in this week's issue (1, 2) describe new partners for the tumor suppressor APC (product of the adenomatous polyposis coli gene APC), which when mutated can cause cancer. One report (1) places APC firmly in the WINGLESS (WG) and WNT signal transduction pathways (of *Drosophila* and mouse, respectively). The other report (2) identifies a new target for APC, another tumor suppressor *Drosophila discs large* (*dlg*).

WG is a cell-to-cell signal in the fruit fly *Drosophila* that triggers many key developmental processes; WNT is the analogous molecule in mice. Many components of their signal transduction pathway were identified in genetic screens of *Drosophila* for gene products that control embryonic pattern formation (3). In addition to *wingless*, these screens yielded mutations in *porcupine*, *dishevelled*, *zeste white 3*, and *armadillo*, all encoding components of the WG pathway. Their order of action in the pathway has been defined by genetic and molecular studies (4): PORCUPINE is required for production and secretion of WG, whereas DISHEVELLED (DSH), ZESTE WHITE 3 (ZW3), and ARMADILLO (ARM) are required sequentially for signal transduction in the receiving cell. Vertebrates also use this pathway (5). In *Xenopus*, homologs of DSH, ZW3 [glycogen synthase kinase 3β (GSK3β)] and ARM (β-catenin) mediate WNT signaling during dorsal-ventral patterning.

Biochemical and cell biological studies supplement the genetic picture (6). WG recruits DSH to the membrane, presumably through an as yet uncharacterized transmembrane WG receptor. DSH negatively regulates the kinase ZW3, which normally promotes instability of ARM protein in the cytoplasm and nucleus. The WG signal thus stabilizes intracellular ARM, which is thought to act with as yet unknown partners to ultimately alter the expression of target genes like *engrailed*. ARM (and its vertebrate homolog β-catenin) are also key components of cell-cell adherens junctions (7), and β-catenin (and likely ARM) are found in a complex containing the tumor suppressor protein APC (8). In the report on APC in this issue, by Rubinfeld *et al.* (1), the role of the APC–β-catenin interaction is clarified.

APC was not initially found as a member of a signal transduction pathway, but rather as a culprit in cancer. Inheritance of one mutant *APC* gene results in predisposition to colon cancer; *APC* mutations also occur in sporadic colon tumors. These mutations result in benign overproliferation of the colon epithelium, forming a polyp, the first step in tumor development. Data from both patients and a mouse model of colon cancer suggest that both *APC* genes are mutated in polyps; one usually encodes a truncated APC protein lacking its COOH-

The author is in the Department of Biology, University of North Carolina, Chapel Hill, NC 27599-3280, USA. E-mail: peifer@unc.edu