ducting slabs, and lithospheric plates should be performed. Carefully designed seismic field projects on the continents and in the oceans are required to achieve this challenging task. The resulting estimates of lateral and vertical mass fluxes in the mantle will provide a firmer basis for geodynamic computer models and should lead to a consistent three-dimensional Earth model.

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11. I thank U. Christensen for stimulating discussions on mantle plumes.

PERSPECTIVES: EVOLUTIONARY BIOLOGY

Predictive Evolution

David M. Hillis

Pick up a random issue of almost any biological journal these days, and you are likely to see one or more phylogenetic trees. One of the reasons that these estimates of evolutionary history have become ubiquitous is because they are needed to make biology predictive. Just as the periodic table of elements allows chemists to make predictions about chemical reactions, so a phylogenetic tree allows biologists to make predictions about behavior, morphology, physiology, biomolecular structure, or any other biological attribute. Usually, the main difference is that chemists make predictions about reactions that have not yet occurred, whereas biologists make predictions about attributes that have already evolved, but have not yet been observed in a particular species. On page 1921 of this issue, Bush and Fitch (*1*) show that phylogenetic analyses of the human influenza A (subtype H3) virus can be used to make predictions about the evolutionary course of future human influenza strains. This information should prove valuable for accurately predicting the correct strains of flu virus to include in the vaccine prepared each year to protect against the upcoming influenza season.

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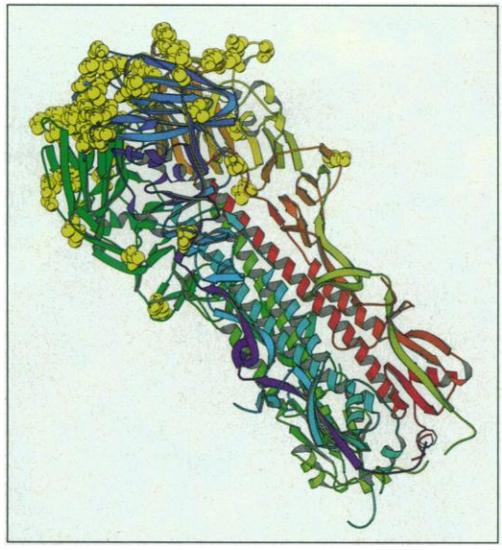
Earlier phylogenetic studies of human influenza A (*2*) have shown that strains of this virus form a rather unusual phylogenetic tree. Phylogenetic trees of most viruses that have been studied to date show a continuously diverging phylogeny. For instance, the tips of the tree of human immunodeficiency virus type 1 (which represent samples of viruses taken at any one time) are more diverse and distant from one another today than they were a few decades ago [for example, (*3*)]. In contrast, although many different strains of influenza A may be circulating at a given time, most lineages do not survive to contribute to future influenza diversity. Instead, one principal (or "trunk") lineage survives and gives rise to future lineages of influenza A, whereas the other lineages quickly become extinct. The unusual shape of the influenza virus phylogenetic tree makes it easy to discern the course of past evolution. One factor influencing that course appears to be positive selection for particular changes in the amino acids in hemagglutinin, one of the two proteins that comprise the large spikes on the surface of the influenza virus (see the figure). If a person develops antibodies against a particular hemagglutinin, then the individual is much more likely to fend off infection by the viral strain carrying that hemagglutinin. However, certain substitutions in the gene encoding hemagglutinin result in changes in the amino acids of this protein's HA1 domain. The altered amino acids result in a reduced immune response in an individual who has been exposed only to the hemagglutinin of an ancestral strain of influenza. Bush and Fitch found that 18 codons of the hemagglutinin gene's HA1 domain are under positive selection for changes in the amino acids that they encode. Furthermore, they established that of the strains of influenza A that are circulating at any one time, those that are most likely to be ancestral to future influenza epidemics (the surviving or trunk lineage of the phylogeny) are the ones that show the greatest number of changes among these 18 amino acids. This allowed the investigators to make predictions about which of the strains circulating today are most likely to give rise to future lineages of influenza A.



Defeating the flu. Molecular model of hemagglutinin, the protein on the surface of the influenza virus that is recognized by the host immune system. The three hemagglutinin chains are shown in blue, green, and red. Substitutions among 18 amino acids in hemagglutinin's HA1 domain (yellow spheres) allow influenza to avoid immune recognition in a naïve host. Consequently, there is positive selection for flu strains that have the greatest number of changes among these 18 amino acids. The model is adapted from Protein Data Bank entry 1HGG (*4*) and was created in MolScript (*5*).

To test the effectiveness of the prediction method, Bush and Fitch examined 11 recent influenza seasons and made retrospective predictions about which of the circulating strains of influenza would be part of the future trunk lineage. The test was successful in 9 of 11 seasons. In the two unsuccessful seasons, the same isolate was chosen three seasons in a row, but only represented the correct trunk lineage in the first season it was selected. A refinement of the test that eliminates previously selected strains from consideration (on the basis that they could no longer continue to produce immune avoidance) might solve this problem. The investigators suggest another possible refinement—simply eliminate extinct lineages from the analysis. Either of these refinements might increase the performance of the method. Nonetheless, the performance of the existing test is impressive: If isolates were chosen at random, then the probability of selecting nine or more of the trunk lineages correctly is only 4.48×10^{-9}.

Bush and Fitch are careful to point out that predicting which current strain of in-

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fluenza will be most closely related to future strains is not necessarily equivalent to predicting the epidemic strain for the subsequent year. Strains may persist for several years, and a strain that is part of the epidemic one year may not represent the future course of the main trunk lineage of the virus. However, their method does predict with reasonable accuracy which current strain will eventually be most closely related to that causing future outbreaks of influenza. Thus, this method can be used in conjunction with standard epidemiological data to select strains of influenza for producing effective vaccines in advance of influenza epidemics. This would greatly help in the production of vaccines that are efficacious.

The ability to make predictions about the future evolutionary course of influenza is the latest example of the many practical applications of evolutionary biology. Evolution isn't just something that happened in the past; evolution can be observed in the present, and in some cases, used to predict the future. In the medical sciences, topics such as in vitro evolution of pharmaceuticals, drug resistance, emerging diseases, and epidemiological studies of pathogens all require a thorough understanding of evolutionary biology. More broadly within biology, an evolutionary perspective is needed to derive general principles from the huge amount of work that is conducted on model organisms, or to interpret any work that compares data across genes, individuals, populations, or species. School boards and science educators need to understand this simple fact: If students don't learn about evolution, they can't possibly understand modern biology or medicine.

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PERSPECTIVES: PROTEIN STRUCTURE

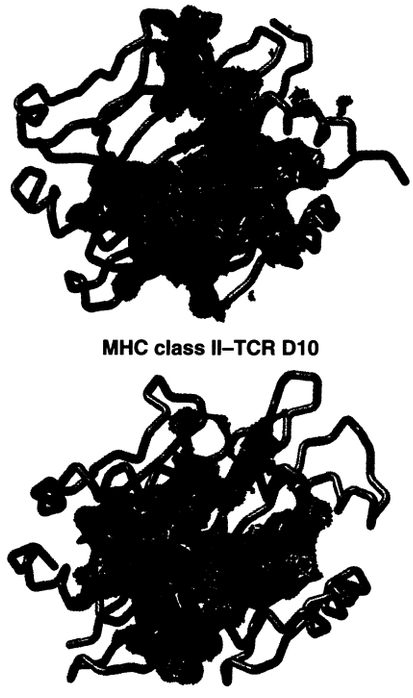
Class-Conscious TCR?

Ian A. Wilson

The T cell receptor (TCR) recognizes peptides of processed antigen bound to class I or class II MHC (major histocompatibility complex) molecules on antigen presenting cells. Structural studies show that the TCR makes a diagonal footprint (buried imprint) on the surface of the peptide–MHC class I complex (*1*–*6*). This diagonal footprint (see figure, this page) enables the TCR both to interact with conserved MHC molecules and to discriminate between different antigenic peptides. The structure of the TCR bound to the peptide–MHC class I complex reveals that the genetically more diverse regions of the TCR (the central hypervariable loops, CDR 3α and 3β) interact most closely with peptide, whereas the less-variable CDR 1 and 2 regions interact with the α helices of MHC class I. The CDR 3α and 3β regions could interact with peptide in any number of orientations but to maintain the specificity of immune recognition, the number of orientations needs to be restricted. This could be accomplished by the interaction of the TCR–peptide MHC complex with coreceptors CD4 or CD8 on the T cell or through steric constraints imposed by extensive glycosylation of both the TCR and MHC (*7*). Now, Reinherz *et al.* report on page 1913 (*8*) the crystal structure at 3.2 Å of the variable region of the TCR D10 interacting with mouse MHC class II (I-A^k) bound to peptide antigen. The investigators propose that the orthogonal orientation of the TCR–class II interaction is more conserved than the diagonal orientation of the TCR–class I interaction. Differing specificities of TCR for MHC class II versus class I would then direct differentiation of T lymphocytes into either $CD4^+$ (helper) or $CD8^+$ (cytotoxic) cells, respectively.

Comparison of the new structure with the three previous TCR–peptide MHC class I structures—mouse 2C (*1*, *3*), human A6 (*2*) and B7 (*4*)—reveals both similarities and differences. Even within this rather small structural database, the range of TCR orientations extends from diagonal to almost orthogonal (see figure, next page). There are several ways in which the TCR variable region of the β chain (Vβ)—composed of CDR 1β, 2β, and 3β—has been seen to interact with the peptide-MHC complex. For example, Vβ of the mouse TCR 2C makes only a few interatomic contacts with either the peptide or MHC. In the human TCR A6 there is almost no contact between CDR 1β and 2β and the peptide-MHC, but, because of its larger size, CDR 3β dominates the Vβ interaction. Similarly, in the complex of TCR with B7, the Vβ region makes minimal contacts with the MHC, whereas CDR 3β makes extensive contacts with the peptide. For the interaction of TCR D10 with MHC class II, the size of the buried surface area by itself does not tell the whole story. CDR 2β and 3β dominate the interactions with the MHC helices, but have extraordinarily little contact with peptide. Thus, even though the surface area of Vβ buried in the MHC-peptide complex (338 A^2) is in the middle of those observed for the class I TCRs (260 to 430 A^2), the complementarity of the interface (0.70 versus 0.45 to 0.64) is much better than for other TCR–peptide MHC pairs (*8*).

So, how can the different interactions of TCRs with peptide-MHC complexes be consistent with a standard overall orientation? The variable loops of TCR's α chain (Vα) maintain a relatively constant and significant van der Waals interaction with both peptide and MHC in all four complexes. It appears that Vα dictates the overall orientation and that the position of Vβ is additionally modulated by the pair-



Footprints in the sand. Comparison of the footprint of a class II TCR D10 (*8*) and a class I TCR B7 (*4*) on their respective MHC molecules. The surface of the CDR variable loops are shown in dark blue (1α), dark purple (2α), dark green (3α), orange (4α), light blue (1β), light purple (2β), and light green (3β). The 27α and 51α residues are in yellowish-green, the amino-terminus of the α chain in B7 is in black, and the peptides in red. Figure calculated with MS (*11*) and rendered with MIDAS (*12*).

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