Interferon-α, which is produced by dendritic cells, is the body's natural defence against many viruses. In addition, certain subsets of dendritic cells express TLR7 and TLR9 exclusively out of the ten known TLR family members. The essential role of TLR7 in the response to these viral agents provides compelling evidence for its general involvement in antiviral host defence. This mechanistic understanding that imidazoquinolines stimulate the immune system through TLR7 is welcome news for the future design of antivirals based on TLR7 ligands. This work raises new questions about whether TLR7 interacts directly with viruses on infection. Furthermore, because each Toll receptor recognizes different microbial components, these receptors might be useful as specific antibacterial and antifungal targets.

Melanie Brazil

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DRUG RESISTANCE

Hit where it hurts

Protease inhibitors are a key part of many treatment regimes for AIDS, but rapid evolution of resistance can limit their effectiveness. Using crystal structures of human immunodeficiency virus (HIV) protease and its complexes with inhibitors, in combination with clinical resistance data, Wei Wang and Peter Kollman now suggest a strategy to combat this problem. Analysis of the energetics of binding and variability at each sequence position of HIV protease indicates that designing drugs to interact more strongly with highly conserved residues could limit the development of resistance.

The authors assessed the variability of HIV protease residues using multiple alignments of the sequences of 80 related viral proteases from different species. Low variability indicates that a residue is well conserved, and so might be catalytically or structurally important. Indeed, comparison with known resistance mutants revealed that no single drug-resistance mutations have been observed at residues with variability below a certain threshold; these residues include those known to be crucial for catalysing peptide cleavage.

But what is the molecular basis of resistance? To identify residues crucial for ligand binding, structural data for HIV protease bound to a substrate analogue and to each of the five FDA-approved protease inhibitors were used in molecular-modelling calculations of the binding energetics for each residue. Next, the difference between the contribution of each residue to drug binding and to substrate binding was evaluated. Taking these data together with the residue variability statistics revealed that single drug-resistance mutations often occur at poorly conserved residues that interact more favourably with the drug than with the natural substrate. Wang and Kollman thus suggest the following mechanism for drug resistance: if drug binding depends on an interaction with a poorly conserved residue that is more favourable than the corresponding interaction of the normal substrate with the residue, then mutation of the residue can lead to resistance by significantly reducing drug binding without affecting protease function. So, resistance-evading drugs should be designed to interact strongly with highly conserved residues. On the basis of the interactions of the current protease inhibitors with their target, the authors suggest several alterations that might allow resistance to be overcome, which could be a starting point for a medicinal chemistry programme.

Furthermore, the authors propose an empirical parameter that is defined as the product of a residue's contribution to the binding energy and the variability of that residue, which can be used for the quantitative prediction of mutations that cause drug resistance, as indicated by its 76% success rate with the drugs analysed. The parameter and the approach that the authors use for decomposing binding contributions in terms of individual residues are general, and so could potentially be used to assist the design of resistance-evading drugs for any target.

Peter Kirkpatrick

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