

MOLECULAR RECOGNITION IN ENZYMES — PROTEASES AND RESISTANCE / APOBEC3G AND OLIGOMERIZATION

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The interplay between viral and host enzymes and what they recognize is critical to the course of viral infection. We use protein crystallography in combination with other techniques to elucidate these recognition events.

Viral proteases, critical to maturation, are effective targets for antiviral therapy. However, when the virus evolves, resistance quickly emerges. In studying HIV-1 protease, we developed the substrate envelope hypothesis and designed potent inhibitors that are less susceptible to drug resistance by staying within the substrate envelope. Yet, we have recently discovered that changes in HIV Gag also confer PI resistance in a PI specific manner. These results reinforce the complexity that resistance occurs as the balance of substrate recognition/processing and inhibitor binding are perturbed.

As inhibitors are being developed for another viral protease, Hepatitis C NS3/4A, resistance is also emerging quickly. Once again, crystal structures of product complexes verify that most of these mutations are occurring outside of the HCV substrate envelope, suggesting that the substrate envelope constraint should also be applied to development of HCV inhibitors to make them less susceptible to resistance.

The host enzyme APOBEC3G is a DNA cytidine deaminase that has anti-viral activity against HIV-1 and other pathogenic viruses. We solved the crystal structure of the catalytically active C-terminal domain to 2.25 Å. This structure and complementary mutagenesis validate structural features previously observed in NMR studies. Oligomerization is postulated to be critical for the function of APOBEC3G. Intermolecular interfaces observed in this crystal structure, some containing residues critical to both APOBEC3G's DNA deaminase and anti-HIV activity, as well as a unique Zinc binding site, suggest potential models for APOBEC3G oligomerization. The role of this oligomerization in viral infection remains to be elucidated.