HIV Reverse Transcriptases: Structural Basis for Inhibition and Drug Resistance

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HIV reverse transcriptase (RT) is one of the main target sites for the action of anti-AIDS drugs. Two classes of anti-RT drugs are in clinical use: nucleoside analogues (NRTIs), which bind at the dNTP site and cause DNA chain termination, whilst the non-nucleoside inhibitors (NNRTIs) bind in a pocket distal to the polymerase active site. Extensive crystallographic studies have been used to define the overall architecture of the HIV-1 RT p66/p51 heterodimer, the binding and mode of inhibition for the NNRTIs as well as the binding sites for NRTI drugs. Due to the rapid turnover of HIV and the low fidelity of transcription of RT, drug resistance rapidly emerges which presents a challenge to continued suppression of the virus. Structural studies of many mutant HIV-1 RTs resistant to NNRTIs have shed light on the structural basis for drug resistance and how 'second-generation' compounds are more resilient to the presence of mutations. For RT from the different serotype HIV-2, the crystal structure points to the mechanism of its inherent resistance to NNRTIs. The significant data base of HIV RT structures are being used in structure based design approaches. A number of successful studies have been reported and NNRTIs with greatly improved activity against common drug resistant forms of HIV are now in clinical trials. Thus, although RT was the target for the first anti-HIV drugs, it still has potential for development of new drugs including the targeting of as yet unexploited regions such as the RNaseH active site and tRNA primer binding.

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