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REVERSE TRANSCRIPTION

Do the flip

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The reverse transcriptase (RT) of HIV is a remarkable protein. It can synthesize a complementary strand of DNA from viral RNA, it can bind to DNA–RNA hybrids and degrade RNA, and it can synthesize a complementary strand of DNA from DNA. Through these processes, viral RNA is converted into double-stranded DNA that can be inserted into the host genome. RT uses two different activities — either DNA polymerase activity or RNase H activity — to achieve these different feats, but how does it control which activity it uses? Reporting in *Nature*, Xiaowei Zhuang and colleagues show that RT binds its substrates in two different orientations and by flipping its orientation can flip its activity.

Zhuang and colleagues investigated the dual activity of HIV RT using fluorescence resonance energy transfer (FRET). By differentially labelling the different ends of RT, the authors found that RT tends to bind DNA–DNA primer–template hybrids in a different orientation than it binds RNA–DNA primer–template hybrids. Whereas RT bound to DNA–DNA hybrids has its DNA polymerase domain adjacent to the 3′ end of the primer and its RNase H domain adjacent to the 5′ end of the primer, RT bound to RNA–DNA hybrids takes the reverse orientation. Moreover, binding orientation affects RT activity: the polymerase activity of RT correlates quantitatively with how much time the enzyme spends in one of the two orientations. Thus, the activity of RT is determined by how it binds its substrates.

Curiously, one specific set of 15-nucleotide RNA purine primers, known as PPTs, are not cleaved by RT and instead initiate DNA synthesis. FRET analysis revealed that RT binds PPTs in both orientations, providing further insight into the specificity of HIV RT. Unexpectedly, the authors also observed that RT can spontaneously switch between orientations. Furthermore, addition of dNTP stabilized RT, whereas addition of nevirapine, an RT inhibitor and an anti-HIV drug, increased the rate of flipping.

Thus, the activity of RT is determined by its orientation: RT can flip spontaneously between orientations and small molecule ligands can control the ability of RT to flip. These findings, in line with previous proposals, suggest that certain steps during reverse transcription may be particularly susceptible to disruption by antiviral treatments.

ORIGINAL RESEARCH PAPER Abbondanzieri, E. A. *et al.* Direct binding orientations direct activity of HIV reverse transcriptase. *Nature* **453**, 184–189 (2008)
FURTHER READING Arnold, E. & Sarafianos, S. G. An HIV secret uncovered. *Nature* **453**, 169–170 (2008)