Dynamics of the HIV-1 Reverse Transcription Complex during Initiation of DNA Synthesis*

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Initiation of human immunodeficiency virus-1 (HIV-1) reverse transcription requires formation of a complex containing the viral RNA (vRNA), tRNA\textsubscript{Lys} and reverse transcriptase (RT). The vRNA and the primer tRNA\textsubscript{Lys} form several intermolecular interactions in addition to annealing of the primer 3' end to the primer binding site (PBS). These interactions are crucial for the efficiency and the specificity of the initiation of reverse transcription. However, as they are located upstream of the PBS, they must unwind as DNA synthesis proceeds. Here, the dynamics of the complex during initiation of reverse transcription was followed by enzymatic probing. Our data revealed reciprocal effects of the tertiary structure of the vRNA:tRNA\textsubscript{Lys} complex and reverse transcriptase (RT) at a distance from the polymerization site. The structure of the initiation complex allowed RT to interact with the template strand up to 20 nucleotides upstream from the polymerization site. Conversely, nucleotide addition by RT modified the tertiary structure of the complex at 10–14 nucleotides from the catalytic site. The viral sequences became exposed at the surface of the complex as they dissociated from the tRNA following primer extension. However, the counterpart tRNA sequences became buried inside the complex. Surprisingly, they became exposed when mutations prevented the intermolecular interactions in the initial complex, indicating that the fate of the tRNA depended on the tertiary structure of the initial complex.

Reverse transcription is a key step in the retroviral replication cycle (1, 2), during which the virus-encoded reverse transcriptase (RT),\textsuperscript{1} which possesses RNA- and DNA-dependent DNA polymerase and RNase H activities (3), converts the genomic RNA into double-stranded DNA. In retroviruses, initiation of reverse transcription requires annealing of the 18 3'-terminal nucleotides of a cellular tRNA to the primer binding site (PBS), located near the 5' end of the RNA genome (4–6).

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1 The abbreviations used are: RT, reverse transcriptase; PBS, primer binding site; HIV-1, human immunodeficiency virus; vRNA, viral RNA; d-, deoxy-; dd-, dideoxy-.

In human immunodeficiency virus type 1 (HIV-1), a strong selective pressure maintains tRNA\textsubscript{Lys} as primer. Mutating the PBS to match the 3' end of other tRNAs dramatically reduces viral replication, and rapid reversion to the wild-type PBS is observed (7–9). A similar situation also prevails in avian leukosis viruses (10). In vitro, HIV-1 RT is able to discriminate against non-self-tRNA primers (7, 11). Interestingly, the specificity of the initiation of HIV-1 reverse transcription correlates with virus-specific interactions between the primer tRNA\textsubscript{Lys} and the viral RNA (vRNA). Chemical and enzymatic probing revealed intricate intermolecular interactions between the anticodon loop and stem, part of the variable loop of tRNA\textsubscript{Lys} and sequences upstream of the PBS (12, 13) (Fig. 1). Extended tRNA-vRNA interactions were also identified in avian retroviruses (14, 15) and in yeast retrotransposon Ty1 (16) and proposed in HIV-2 (17).

In HIV-1, the best-characterized specific intermolecular interaction involves the anticodon loop of tRNA\textsubscript{Lys} and an A-rich loop conserved in all viral isolates (helix 6C in Fig. 1). In vitro, this loop-loop interaction prevents extension of the HIV-1 vRNA:tRNA\textsubscript{Lys} complex by heterologous RTs (18, 19), and it is required for efficient transition from the initiation to the elongation of reverse transcription that takes place after the addition of six nucleotides (18, 20). The initiation and elongation phases strongly differ by their polymerization rate and by the dissociation rate of RT from the primer-template complex (20, 21). Interestingly, three-dimensional modeling of the HIV-1 vRNA:tRNA\textsubscript{Lys} and HIV-1 vRNA:tRNA\textsubscript{Met}-RT complexes, based on our probing and footprinting data, indicated that RT does not directly recognize the extended primer-template interactions (22). These interactions favor binding of the homologous RT by preventing steric clashes and ensuring proper orientation of the template domains directly interacting with RT (22).

The extended intermolecular interactions also appeared crucial for the initiation of HIV-1 reverse transcription in cell culture. First, a tRNA\textsubscript{Lys} with a mutated anticodon was incorporated into the HIV-1 particles but did not prime reverse transcription (23). Second, deletion of the A-rich loop resulted in viruses with diminished levels of infectivity and reduced DNA synthesis, and the A-rich loop was progressively restored upon prolonged cell culture (24). Finally, this interaction is a major determinant of primer usage in HIV-1. Indeed, when the PBS was mutated to match the 3' end of other tRNAs than tRNA\textsubscript{Lys}, replication of the virus was dramatically reduced, and reversion to the wild-type PBS was rapidly observed (7–9). However, HIV-1 could stably use tRNA\textsubscript{His} and tRNA\textsubscript{Met} as primers, provided that both the PBS and the A-rich loop were simultaneously mutated to be complementary to these tRNA species (25, 26). When mutated, the other intermolecular interactions (helices 3E and 5D in Fig. 1) were also restored upon prolonged cell culture (27, 28).

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In this report, we used enzymatic probing to study the dynamics of the reverse transcription complex and to follow the fate of the interaction between the anticodon and the A-rich loops during addition of the first six nucleotides to the primer tRNA, i.e. during the initiation phase of reverse transcription.

**MATERIALS AND METHODS**

**Chemicals and Enzymes—**RNase T2 and Neurospora crassa endonuclease were from Amersham Pharmacia Biotech. Heparin was from Sigma. Phage T4 polynucleotide kinase was from U. S. Biochemical Corp. [α-32P]ATP (3000 Ci/mmol) and [5-32P]cytidine 3',5'-bisphosphate (3000 Ci/mmol) were from NEN Life Science Products. Acrylamide and N,N'-methylene bisacrylamide were from Roth.

**RNAs and RTs—**123–217 vRNA, corresponding to nucleotides 123 to 217 of HIV-1 genomic RNA (Mal isolate), was synthesized and 3'-end-labeled as described previously (29). Wild-type and mutant 1–311 vRNA were synthesized as described (18, 30). In the mutant template, the region of the vRNA corresponding to nucleotides 123 to 217 of HIV-1 genomic RNA (Mal isolate), was synthesized and 3'-end-labeled 123–217 vRNA (3000 Ci/mmol) was from NEN Life Science Products. Acrylamide and N,N'-methyl bisacrylamide were from Roth.

**RESULTS**

**Experimental Strategy—**To test the intermolecular interactions between the viral A-rich loop and the anticodon loop of tRNA\textsubscript{Lys} during initiation of reverse transcription and to monitor translocation of RT along the primer-template complex, we first preformed the vRNA:tRNA\textsubscript{Lys}-HIV-1 RT complex. Then we added ddCTP, dTTP + ddGTP, or dTTP + ddGTP. These nucleotide mixtures allowed extension of tRNA\textsubscript{Lys} by 1, 2, 3, and 4 nucleotides, respectively (Fig. 1). Half of the reaction mixtures was used to test the vRNA:tRNA\textsubscript{Lys}-HIV-1 RT complex in these registers.
Heparin was added to the rest of the reaction mixtures to trap RT, thus allowing probing of the primer-template complexes.

Probing HIV-1 RNA Template in Register Zero—To probe HIV-1 RNA in the vRNA

protection of A-200, A-177, and A-164 to A-167 (Fig.

protections of nucleotides 164–167, G-159, and A-157 were due to stabilization of helices 6C and 5D rather than direct contact with RT (22). The increased reactivity at A-155 most probably reflects a slight reorientation of helix 4 upon RT binding.

Finally, we tested the possibility to trap RT dissociating from the primer-template with heparin, since we wanted to use this technique to probe the vRNA in the RNA-RT complex after extension of the primer (Fig. 2A). After the addition of heparin to the RNA-RT complex, the RNase T2 profile was essentially identical to that of the RNA-RT complex before the addition of RT (Fig. 2A). This result not only validates the use of heparin to trap RT but also indicates that RT binding did not induce irreversible conformational changes in the RNA-RT complex.

Probing HIV-1 RNA during Initiation of Reverse Transcription—To analyze the structural changes in the RNA during initiation of reverse transcription, we used mixtures of dNTPs and ddNTPs, ending extension of tRNA after the addition of 1, 2, 3, and 6 nucleotides. The nucleotide and enzyme concentrations as well as the incubation time of the extension reactions were adjusted to obtain complete extension of the primer (see “Materials and Methods”). The extended RNA-vRNA complexes were then probed with RNase T2 with or without prior incubation with heparin (Fig. 2B and Table I).
The addition of 1 (data not shown) or 2 nucleotides did not significantly change the reactivity profile of vRNA in the absence of heparin, as compared with the unextended ternary complex (compare Fig. 2, A and B). When tRNA<sub>3</sub> was extended by 2 nucleotides, the A-rich loop and the upstream region were still protected against RNase T2 cleavage in the absence of heparin (Fig. 2B and Table I). The addition of heparin restored cleavage at A-157, G-159, and U-161. Protection of the latter nucleotides by RT was most likely due to stabilization of helices 6C and 5D, as was the case in register zero. The reactivity pattern of stem-loop 8 when tRNA<sub>3</sub> was extended by 1 (data not shown) or 2 nucleotides was unchanged, as compared with the ternary complex in register zero (Fig. 2B and Table I). In the absence of heparin, A-200 was protected from cleavage, but it was strongly cut when RT was trapped by heparin. The only significant change taking place upon the addition of the second nucleotide was the disappearance of RNase T2 cleavage at A-177 in the binary complex (Fig. 2B and Table I). Cleavage at C-175 in the absence of heparin was not reproducibly observed in other experiments.

The cleavage pattern of HIV-1 RNA was significantly modified upon the addition of the third nucleotide (Fig. 2B and Table I). In the absence of heparin, A-164, in the A-rich loop, became moderately accessible to RNase T2, whereas cleavage at A-155 strongly decreased, and U-161, G-159, and A-157 remained fully protected. Simultaneously, loop B became significantly cleaved, even in the absence of heparin. Nucleotide A-177, which was now base-paired to the extended tRNA<sub>3</sub>, was totally protected from RNase cleavage. Upon the addition of heparin, cleavage at A-155 was strongly enhanced, as well as cleavages at A-164 and A-165. Comparison of the vRNA−tRNA<sub>3</sub> complexes in registers 2 and 3 is consistent with the unwinding of the distal part relative to the polymerization site of helix 6C upon the addition of the third nucleotide (Figs. 1 and 2B and Table I). In addition, our data indicate that RT interacts with or is close to A-155 in register 3 but not in register 2.

After the addition of the sixth nucleotide and in absence of heparin, all four adenines (A-164 to A-167) that were base-paired with the anticodon loop of tRNA<sub>3</sub> in register 0 became reactive toward RNase T2, as well as A-157, G-159, and U-161 (Fig. 2B and Table I). These cleavages were further increased in the presence of heparin. These data suggest complete unwinding of helix 6C and destabilization of helix 5D at this stage of the initiation of reverse transcription (Fig. 1). Consistent with progression of the polymerase along the template, cleavage of stem-loop 8 in the absence of heparin, which became apparent in register +3, was further enhanced after the addition of the sixth nucleotide (Fig. 2B).

### Table I

| Register | 0 | 1 | 2 | 3 | 6 |
|----------|---|---|---|---|---|
| Hx 4<sup>a</sup> | A155 | + | + | + | + | + | + |
| J 4/5D | A157 | + | + | + | + | + | + |
| Jx 5D | G159 | + | + | + | + | + | + |
| J 5D/6C | U161 | + | + | + | + | + | + |
| Jx 6C | A164 | + | + | + | + | + | + |
| J 6/5' | A165 | + | + | + | + | + | + |
| J 5D | A166 | + | + | + | + | + | + |
| J 5'6C | A167 | + | + | + | + | + | + |
| Loop 8 | A177 | + | + | + | + | + | + |
| Loop B | G19, D20 | +++ | +++ | +++ | +++ | +++ | +++ |
| J 5'6C | G30 | +++ | +++ | +++ | +++ | +++ | +++ |
| Hx 6C | U35 | + | + | + | + | + | + |

<sup>a</sup> Numbering of the structural elements is according to Fig. 1; Hx, helix; J, junction.

*Enzymatic Probing of Primer tRNA<sub>3</sub> in Register Zero*—To monitor the conformation of the anticodon loop of tRNA<sub>3</sub> in binary and ternary complexes, we used the single strand-specific endonuclease from *N. crassa* (Fig. 3 and Table I). In agreement with our previous studies (12, 31), the only cleavages induced by this nuclease on free tRNA<sub>3</sub> were located in the anticodon loop. Formation of the primer-template complex strongly decreased cleavage of the anticodon loop, whereas G-30 and G-19 and D-20 in the D loop became susceptible to cleavage, in agreement with the secondary structure model of the vRNA−tRNA<sub>3</sub> complex (Fig. 1) (12, 31). The same cleavage pattern was observed when heparin was added to the vRNA−tRNA<sub>3</sub>−HIV-1 RT complex.

When the ternary complex was probed in the absence of heparin, cleavages by *N. crassa* endonuclease were observed at the same positions, but their intensities were reduced, especially for U-35 and G-30 (Fig. 3 and Table I). Protection of the anticodon loop by HIV-1 RT was due to stabilization of helix 6C rather than direct contact with the polymerase (22). Likewise, protection of G-30 was due to steric hindrance rather than direct interaction with RT (22).

*Enzymatic Probing of tRNA<sub>3</sub> during Initiation of Reverse Transcription*—Little changes were observed after the addition of the first nucleotide, except that U-35 and G-30 were slightly more protected than in register zero. This difference was observed in the presence as well as in the absence of heparin (Fig. 3 and Table I). Upon the addition of the second nucleotide, cleavages by *N. crassa* endonuclease in the anticodon loop at G-30 and G-19 and D-20 all significantly increased, especially in the absence of heparin. Unlike in registers 0 and 1, the anticodon loop of tRNA<sub>3</sub> became more susceptible to cleavage than G-30 in the absence of heparin. Adding this trap has only limited effects, mainly affecting reactivity of G-30.

The addition of the third and sixth nucleotides resulted in the progressive protection of G-30, which became almost unreactive, both in the presence and absence of heparin (Fig. 3 and Table I). At the same time, cleavages in the anticodon loop of tRNA<sub>3</sub> also progressively decreased. Protection of G-30 remained RT-dependent in register 3 but became RT-independent after the addition of the sixth nucleotide, as judged by the absence of heparin-mediated effects in this register. At the opposite, cleavage in the anticodon loop was independent of heparin addition in both registers.

Since, when probing tRNA<sub>3</sub>, the binary complex was formed in the presence of excess vRNA, we performed a control experiment in which the uncomplexed vRNA was removed by chromatography before formation of the ternary complex. Prob-
ing data obtained with this material in registers zero and six, with and without heparin, were identical to those obtained with the unpurified vRNA:tRNA\textsubscript{3'z} complex (data not shown).

**Enzymatic Probing of tRNA\textsubscript{3'z} Annealed to a Mutated vRNA**—To verify that the complex probing pattern of tRNA\textsubscript{3'z} during initiation of reverse transcription actually reflected alterations of the primer-template interactions, we used a vRNA mutated in the conserved A-rich loop. We previously showed that substituting 5'-CUAUG-3' for 162GUAAAA\textsuperscript{167} in the vRNA prevents interaction with the anticodon loop of tRNA\textsubscript{3'z} (13, 18). We also showed that this mutation introduces a defect at the level of the transition between initiation and elongation of reverse transcription (13, 18). Here, we annealed this mutated template to tRNA\textsubscript{3'z} and tested the primer with the *N. crassa* endonuclease in registers 0, +3, and +6 in the absence and presence of heparin (Fig. 4).

When the primer was hybridized with the mutated vRNA, cleavage of the anticodon loop in register 0 was very pronounced (Fig. 4), in agreement with the lack of interaction with the A-rich loop (compare with Fig. 3). Indeed, cleavage in the anticodon loop was almost as pronounced as that in the D loop (Fig. 4). Interestingly, the cleavage pattern was not affected by heparin, indicating that HIV-1 RT does not interact with the anticodon loop of tRNA\textsubscript{3'z} annealed to the mutated vRNA. Furthermore, the relative cleavage intensities at G-30 and in the anticodon and D loops are similar in registers 0, 3, and 6, both without and with heparin. Thus, with the mutant vRNA, the structure of the primer-template did not change during initiation of reverse transcription.

**DISCUSSION**

The efficiency and specificity of HIV-1 reverse transcription relies on intricate interactions between the viral RNA and primer tRNA\textsubscript{3'z} (12, 13, 18, 19, 21, 22, 25–28, 35). Quasi surprisingly, in HIV-1 the virus-specific intermolecular interactions (i.e. helices 6C, 5D, and 3E) involve viral sequences located upstream of the PBS (12, 13). Thus, they could potentially hinder reverse transcription and have to unwind as DNA synthesis proceeds (18, 19, 35). The present study shed light into the structural changes occurring within the reverse transcription complex during the initiation of DNA synthesis.

Interestingly, even though the interaction between the anticodon loop of tRNA\textsubscript{3'z} and the A-rich loop is located 12–17 nucleotides upstream of the PBS, our probing of the vRNA revealed that this interaction progressively unwinds during the addition of the third to the sixth nucleotide to tRNA\textsubscript{3'z}. Furthermore, detailed analysis indicates that the distal part of helix 6C, relative to the polymerization site, was cleaved before the proximal part; whereas A-164 and A-165 were cleaved in registers 3 and 6, A-166 and A-167 were only cleaved in the latter register. Thus, opening of helix 6C was unlikely due to an unwinding activity associated with RT. Such an activity was proposed on the basis of nuclease footprinting data, indicating that HIV-1 RT may interact with the template up to seven nucleotides upstream from the polymerization site (36). However, detailed kinetics studies suggest that disruption of the template secondary structure during reverse transcription is a passive process (37).

We propose that unwinding of helix 6C at a distance from the polymerization site is a consequence of the tertiary structure of the initiation complex (22). As the first three nucleotides are added to tRNA\textsubscript{3'z}, the flexible single-stranded junction between helices 2 and 7F is copied by RT and, thus, is transformed into a rigid double-stranded RNA-DNA hybrid (Fig. 1). This flexible region is a crucial hinge that allows proper three-dimensional folding of the vRNA:tRNA\textsubscript{3'z} complex (22). Its stiffening introduces topological stress in the initiation complex that might induce unfolding of helix 6C.

The progressive unwinding of helix 6C during the addition of the third to the sixth nucleotides might shed a new light on the finding that most annealed tRNA\textsubscript{3'z} in extracellular viral par-
ticles is extended by two nucleotides (11, 38). This observation was difficult to explain on the basis of in vitro kinetics experiments, which showed a strong pausing site after the addition of the third nucleotide (18–20). Our results suggest that the intermolecular interactions might be stabilized in the viral particles and might block reverse transcription when low concentrations of nucleotides are available.

Translocation of RT on the PBS helix during initiation of reverse transcription was visualized by increased accessibility of helix 8 downstream of the PBS as DNA synthesis proceeded. In addition, changes in the RT footprint pattern were observed far upstream of the polymerization site. The most remarkable change was observed at A-155, which became protected by RT in registers 3 and 6. This results suggests that RT can interact with the template strand up to 20 nucleotides upstream of the polymerization site. This observation contrasts with earlier chemical (39) and enzymatic (36, 40) footprinting studies on model primer-template complexes, showing limited interactions between RT and the template upstream of the polymerization site. The difference between our and previous results undoubtedly originates from the complex tertiary structure of the initiation complex, which was absent from the model substrates.

The second partner of the complex, tRNA^Lys^, also undergoes complex structural rearrangements during initiation of reverse transcription. Whereas cleavage of the anticodon loop gradually increased during the addition of the second and third nucleotide, in keeping with unwinding of helix 6C, its accessibility decreased in register 6. In any case, cleavage of the anticodon loop in register 6 was not affected by heparin, indicating that the protection observed in this register was not due to interaction with RT. The most likely explanation for the progressive protection of the anticodon loop as initiation of reverse transcription proceeded is that this loop became buried inside the vRNA:tRNA^Lys^ tertiary structure. Indeed, the only alternative candidate for a direct interaction with the anticodon loop is the A-rich sequence in loop 8 (Fig. 1). However, our probing data indicate that the accessibility of this stem-loop progressively increased during initiation of reverse transcription, indicating that it did not interact with tRNA^Lys^.

We previously showed that mutations in the A-rich loop that prevented formation of helix 6C decreased the efficiency of the transition between initiation of reverse transcription (20). However, this transition takes place between addition of the sixth and seventh nucleotides (20, 21), and our probing data indicate that helix 6C does not exist anymore in register 6. Therefore, the effect of these mutations is quite unexpected. Probing of tRNA^Lys^ annealed to the mutated vRNA in registers 0, 1, 2, 3, and 6 brought clues to solve this apparent paradox. In contrast to the situation observed in the presence of wild type vRNA, the anticodon loop of the primer remained accessible at all stages of the initiation of reverse transcription. In register 6, the conformation of tRNA^Lys^ bound to the mutant template significantly differed from that of the primer bound to the wild type HIV-1 RNA. In other words, the conformation of the wild type initiation complex in register 6 depends on intermolecular interactions that were present in register 0 but do not exist in register 6 anymore. This particular conformation might be required for efficient transition from initiation to elongation of reverse transcription. Indeed, detailed studies showed that the specific intermolecular interactions of the initiation complex enhance formation of the vRNA:tRNA^Lys^-RT complex rather than the polymerization rate by the ternary complex (20, 21). Since nucleotide addition is distributive during initiation of reverse transcription (20, 21), the structural rearrangements of the wild type complex are probably crucial for efficient rebind-

The inability of RT to interact with the anticodon loop of tRNA^Lys^ bound to the mutant vRNA at any stages of the initiation of reverse transcription was rather unexpected. Indeed, HIV-1 RT is able to form a binary complex with its primer by interacting with the anticodon loop of tRNA^Lys^ (35–37). Thus, our present data indicate that the role of the interaction between the anticodon and A-rich loops is not to prevent binding of RT to the anticodon stem of tRNA^Lys^. As suggested by our recent footprinting and modeling study (23), its function is most likely to ensure proper folding of the primer-template tertiary structure and, hence, to maximize specific interactions with RT while preventing steric clashes.

In summary, our probing data brought several unexpected results. First, they revealed an interplay between the tertiary structure of the vRNA:tRNA^Lys^ complex and RT at a distance from the polymerization site. The structure of the initiation complex allows RT to interact with the template strand up to 20 nucleotides upstream from the polymerization site. Conversely, nucleotide addition by RT modifies the tertiary structure of the vRNA:tRNA^Lys^ complex at 10–14 nucleotides from the catalytic site. Second, the fate of the anticodon loop and of the A-rich loop as they dissociate is different. Whereas the viral A-rich loop is exposed at the surface of the complex, the anticodon loop of tRNA^Lys^ becomes buried inside it. Finally, our data showed that correct base pairing of the A-rich loop with the anticodon loop in the initial complex is essential for the rearrangement of the complex during initiation of DNA synthesis. This structural rearrangement might be an attractive target for anti-HIV-1 molecules designed against the initiation complex of HIV-1 reverse transcription.

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