RNA editing in kinetoplastids is the post-transcriptional insertion and deletion of uridylic residues in mitochondrial transcripts, directed by base pairing with guide RNAs. Models for editing propose transsterification or endonuclease plus RNA ligase reactions and may involve a guide RNA-mRNA chimeric intermediate. We have assessed the feasibility of the enzymatic pathway involving chimeras in vitro. Cytochrome b chimeras generated with mitochondrial extract were first found to have junctions primarily at the major endonuclease cleavage sites, supporting the role of endonuclease in chimera formation. Such cytochrome b chimeras are then specifically cleaved by extract endonuclease within the oligo(U) tract at the editing site, and the mRNA cleavage products are then joined by RNA ligase to generate partially edited mRNAs with uridylate residues at the editing site. These in vitro generated partially edited mRNAs mimic partially edited mRNAs generated in vivo. Specific endonuclease cleavage in the editing region of the partially edited RNA demonstrates the potential for further in vitro editing. Finally, sensitivity to various ATP analogs suggests that all editing-like activities reported thus far utilize a mechanism involving RNA ligase.

The term RNA editing describes a variety of processing events that generate RNAs that are different from those predicted by their genes (reviewed in Ref. 1). In trypanosomatids (Trypanosoma, Herpetomonas, Crithidia, and Leishmania) and other related kinetoplastids (Trypanoplasma), RNA editing refers to the specific insertion and deletion of uridylic (U) residues in mitochondrial mRNAs. Since its discovery in kinetoplastids (2), RNA editing has been shown to create translational start and stop codons, correct frameshifts, and extend open reading frames (reviewed in Refs. 3–6). The extent of editing can be small (e.g. the insertion of four U residues into Trypanosoma brucei cytochrome oxidase subunit 2 (COII) mRNA (2)) or extensive (e.g. the creation of >50% of the total transcript length of T. brucei COII mRNA (7)). Because trypanosomatids diverged from one another 200–300 million years ago (8, 9), this RNA editing is at least that old.

The genetic information directing RNA editing resides in short (50–70 nt) mitochondrial transcripts (10). These guide RNAs (gRNAs) contain a 5′ anchor sequence (4–18 nt) that is complementary to the pre-edited mRNA immediately 3′ of the segment to be edited, a guiding region that is complementary (allowing for G:U base pairing) to the fully edited mRNA segment and a nonencoded (−5 to −24 nt) 3′ poly(U) tail (4). Presumably the gRNA base pairs with the pre-edited mRNA and directs editing to progress 5′ from the anchor region, inserting and deleting U residues to yield mRNA complementary to the guiding region (10). The poly(U) tail may further stabilize the duplex of gRNA with the purine-rich mRNA (11) and/or serve as the source of U residues for insertion (12).

Blum et al. (10) proposed that each cycle of U insertion or removal involves an endonuclease to cleave the RNA, a terminal uridyl transferase to insert or an exonuclease to delete U residues, and an RNA ligase to rejoin the 5′ and 3′ half mRNAs. Indeed, these proposed enzymatic activities are present in trypanosomes (13–16). Editing was later proposed to involve sets of transesterification reactions (12, 17). In the most popular of these schemes, the 3′ hydroxyl of the U tail of the gRNA attacks the mRNA at the first gRNA:mRNA mismatch, creating a gRNA-mRNA chimeric molecule. The chimeric is then attacked by the 5′ hydroxyl of the 5′ mRNA fragment again adjacent to the duplex region, within the poly(U) tract, generating a partially edited mRNA and liberating the gRNA. Although the transesterification model has been considered very appealing because of its common mechanism with RNA intron removal (reviewed in Ref. 18) and because of the ancient existence of gRNA-mRNA chimeric molecules in trypanosomes (12), identical chimeric intermediates and partially edited RNAs could alternatively be generated by endonuclease cleavages and RNA ligations (Ref. 19; see Fig. 1).

In vitro studies on possible mechanisms of RNA editing have identified an editing domain-specific endonuclease in T. brucei that is single strand-specific (20) and cleaves cytochrome b (CYb) pre-edited mRNA predominantly at editing sites (ES) 2 and 3 (14). T. brucei mitochondrial extract was also shown to direct chimera formation, specifically joining a model CYb gRNA to pre-edited mRNA (21), although the precise position of the junction (whether at ES1, ES2, and/or ES3) remained unclear. Investigations of the in vitro activity that forms chimeras have shown it to co-sediment with both RNA ligase (15) and the editing domain specific endonuclease (22), demonstrating the feasibility of chimera formation through the enzymatic pathway (22). Rusch et al. (23) and Sabatini and Hajduk (24) then demonstrated that gRNA-mRNA chimeras are formed in
alized as described (22). Where indicated, cleavage was augmented by the addition of heparin (0.5 mg/ml final). For sizing standards, sub- 

strate RNAs were treated with RNaseT1 (USB) or RNaseU2 (Phar- 

macia Biotech Inc.) for 5–10 min at 50°C.

Generation of Chimeras and Partially Edited mRNAs—The 20-μl chimera-forming reactions contained 1μl-labeled CYb pre-edited mRNA (50–100 pmol), 2μl-labeled CYb gRNA (0.5–2 pmol), and 2 μl of mitochondrial extract in MRB buffer supplemented with 1 mM ATP and were incubated for 30 min at room temperature. CYb chimeras were also formed using MBN and T4 RNA ligase as described (22).

CYb partially edited mRNAs were formed using the 5’ half of CYb pre-edited mRNA (isolated from MBN-digested 5’ end-labeled CYb pre- 
edited mRNA), the 3’ half of CML15-2 RNA (prepared by digestion of pCP C-mRNA with either mitochondrial extract or MBN), and 2 μl of mitochondrial extract or 15U T4 RNA ligase as described for chimera formation. The samples were phenol-chloroform extracted, etha- 

nol precipitated, electrophoresed, and visualized by autoradiography. PCR Amplification, Subcloning, and Sequencing of Junctions—The chimeric and partially edited RNA products were gel isolated from reactions scaled up 6–20-fold and reverse transcribed and PCR ampli- 

fied using the thermostable rTth reverse transcriptase RNA PCR kit (Perkin-Elmer) and a Hybaid Omnigene Thermocycler (Marsh Biomed- 

ical). Both of the reverse transcription reactions (20 μl) contained primer I (CCACCGTCGACAGTACATCCACACTCCAC) and were incubated for 20 min at 70°C and then placed on ice. They were then diluted by 0.75 μl EGTA (to chelate the Mg2+) and 1.5 mM Mg2+ and either primer II (TGCTGGAGCTATGATTAAAAAGAC) or primer III (GAGAATTCGAGCTCGGTACCCG) was added for amplification of chimeric and partially edited cDNAs, respectively. Chimeric cDNA was amplified by incubation at 92 (2 min) and then 95°C (2 min), followed by 40 cycles alternating between 95 (30 s) and 68°C (30 s). Partial- 

ly edited cDNA was amplified by incubation at 90 (1 min) and then 94°C (1 min) followed by 42 cycles alternating between 94 (30 s), 68 (30 s), and 72°C (30 s). The PCR products were digested with MluI (primer I) and either BclI (primer II) or EcoRI (primer III), gel-purified, mixed with MluI/BamHI- or MluI/EcoRI-digested pBluescript vector (Internation- 

al Biotechnologies Inc.), and incubated with T4 DNA ligase for 1 h at 37°C. Reaction mixtures were transformed into E. coli JM109 compe- 

tent cells using the transformation and storage solution procedure (28). Plasmid DNA from 3 ml cell cultures was isolated using the alkaline lysis procedure (29) and suspended in 20 μl of water. Sequencing was carried out with the Sequenase kit (U. S. Biochemical Corp.) using 2 μl of the miniprep plasmid DNA and 1 pmol of universal (–20) sequencing primer.

Secondary Structure Modeling of RNAs—Secondary structure calcu- 

lations were performed with the University of Wisconsin Genetics Com- 

puter Group program FOLD (30) using updated energy values on a VAX model 8530.

Enzyme Assays Using ATP Analogs—Mitochondrial extracts were de- 

pleted of endogenous ATP by incubation with 5 μM glucose and 1 unit of hexokinase (Sigma)20 μl for 30 min at room temperature (23). Chimeras assays (described above) and ligase assays (described in Refs. 22 and 23) were carried out without added nucleotides or in the presence of 1 mM ATP, AMP-CPP (Boehringer Mannheim), AMP-PNP (Boehringer Mannheim), or AMP-PCP (Sigma). Analogous ligase assays were also performed using 3 units of T4 RNA ligase.

RESULTS AND DISCUSSION

Junctions of Extract-generated CYb Chimeras Map to Endo- 

nuclease Cleavage Sites—Although recent data are consistent with the CYb chimera formation in T. brucei mitochondrial extract being catalyzed by the editing site-specific endonuclease of the extract (23), the possibility that these chimeras may have their junctions at ES1 (21) would be inconsistent with this hypothesis, because the site-specific endonuclease cleaves CYb RNA predominantly at ES2 and ES3 (14). We therefore deter- 

mined the mRNA junction site in these CYb chimeras (Fig. 2A). Chimeras formed in extract using CYb pre-edited mRNA and a model CYb gRNA were reverse transcribed using thermostable polymerase (to enable extension through the stable anchor region duplex), PCR amplified, subcloned, and sequenced. In almost all chimera clones, the gRNA was joined to the mRNA either at ES2 or ES3 (Fig. 2B); only in one was it joined at ES1. Using a different, natural input CYb gRNA (g[558]; Ref. 27), we obtained a similar profile of ES junctions, with 19 of the 22
sequence junctions at either ES2 or ES3, two at ES1 and one that is one nucleotide upstream of ES3 (data not shown). Notably, in both cases the location and frequency of the mRNA junctions agree with the previously reported sites of endonuclease cleavage on Cyb pre-edited mRNA - predominantly at ES2 and ES3, with minor cleavages at ES1 and one nucleotide upstream of ES3 (14, 20). Thus, extract-generated Cyb chimeras contain junctions at precisely the positions predicted if these molecules resulted from cleavage of the pre-edited mRNA by the extract endonuclease, followed by ligation to the gRNA. This result, in conjunction with previous data (20, 22-24), provides very strong evidence that extract-generated chimeras are formed via the endonuclease/ligase pathway.

Chimeras can also be generated using MBN and T4 RNA ligase (20). Their junctions should be at the same sites as those generated using mitochondrial extract because MBN also cleaves Cyb pre-edited mRNA at ES2 and ES3 (14). As expected, in all 34 sequenced MBN/T4 RNA ligase-generated Cyb chimeras clones examined, the gRNA is joined to the Cyb mRNA at either ES2 or ES3 (Fig. 2C). Obtaining the same profile of mRNA junction sites in Cyb chimeras generated using either mitochondrial extract or a heterologous single strand-specific endonuclease plus RNA ligase provides additional support that the chimeras generated in the mitochondrial extract are formed by the concerted action of the extract endonuclease and RNA ligase.

Unlike the heterologous enzyme-generated Cyb chimeras (Fig. 2C), most of the extract-generated chimeras did not retain all three U residues from the 3' tail of the gRNA (Fig. 2B). This observation explains the small size difference of the extract-generated and MBN/T4 RNA ligase-generated chimeras (Fig. 2A). Furthermore, chimeras generated in mitochondrial extract using a Cyb gRNA with a 3' tail of 15 U residues retained 0–6 U residues at the gRNA-mRNA junction, and the 3' U tail of the free gRNAs was also observed to decrease in length (data not shown). These results suggest that a 3' endonuclease is active in T. brucei mitochondrial extracts. The observation that this 3'-terminal nucleotide removal appears to stop at the end of the oligo(U) tail (Fig. 2B) suggests that it may be a U-specific endonuclease. An analogous loss of U residues observed in the Leishmania tarentolae NADH dehydrogenase subunit 7 chimer-forming system (31) suggests that a similar endonuclease activity may be active in other kinetoplastids. In vivo, such a U-specific endonuclease activity could function in deleting genomically encoded U residues (10) or in removing excess U residues that were transferred to an editing site.

Extract Cleave within the Oligo(U) Region of Chimeras—The nuclease-ligase model of editing via a chimeric intermediate (Fig. 1) predicts that endonuclease would cleave the chima within its poly(U) region at the gRNA-mRNA junction, transferring one or several U residues to the 5' end of the cleaved 3' mRNA fragment. To continue examining the feasibility of this model, we assessed whether the endonuclease of mitochondrial extract cleaves a Cyb chima with this specificity (Fig. 3A). The chima gRNA CML15-2, which contains 15 U residues (an average size oligo(U) tract for in vivo Cyb chimeras (27)) at the ES2 junction was 3' pCP-labeled to follow the mRNA region. Incubation of CML15-2 RNA with mitochondrial extract indeed resulted in specific cleavage (Fig. 3A, lane 8). Relative to sizing standards (Fig. 3A, lanes 4 and 5), the这件 mRNA portion of the chima (Fig. 3A, lane 8) migrated ~8–11 nt slower than the analogous 3' cleavage product from Cyb pre-edited mRNA (Fig. 3A, lane 2). These ~8–11 extra residues represent a portion of the U\textsubscript{ES} tract that derived from the gRNA tail (see also Fig. 4B). Thus, T. brucei mitochondrial extract specifically cleaves the Cyb chima within the poly(U) region at the gRNA-mRNA junction.

To address whether the structure of the Cyb chima RNA determines its cleavage pattern, pCP-labeled CML15-2 RNA was incubated with MBN, a probe for single-stranded structure. This RNA was also specifically cleaved by MBN (Fig. 3A, lane 9), generating a family of 3' mRNA products containing ~10–13 U residues at their 5' ends. This MBN cleavage within the poly(U) tract of CML15-2 RNA indicates that this region of the chima is single-stranded, a result also predicted by analysis of this RNA using the FOLD algorithm (30) (Fig. 3B).

Such a stem-loop structure may well be a general feature of gRNA-mRNA chimeras, because the duplex involving the anchor region of the gRNA and its complement from the mRNA region presumably remains base paired, whereas the segment between those intervening regions shows only limited self-complementarity. Thus, preferential cleavage by single strand-specific nuclease in the oligo(U) region may be a general feature of chima molecules. The predicted structures for 20 trypanosome pre-edited mRNA sequences also suggested a single strand-specific nuclease sensitivity in the region where editing begins (20). Therefore, a common mitochondrial single strand-specific activity could recognize both the pre-edited mRNA and the gRNA-mRNA chima, based on their secondary structures.

Formation of Cyb Partially Edited Molecules—The nuclease-ligase model for editing next predicts that the 5' half mRNA...
becomes covalently joined to the 3′ half mRNA liberated from the chimeric RNA, thereby transferring U residues to an editing site and resulting in a partially edited mRNA (Fig. 1). To determine whether partially edited mRNA could be generated via this pathway in vitro, the 3′ extract cleavage product (32P-pCP-labeled) from the chimera and the 5′ cleavage product (32P-labeled) from the original CYb pre-edited mRNA cleavage reaction were incubated in mitochondrial extract (Fig. 4A, lane 4). A large product was generated that migrated several nucleotides slower than CYb pre-edited mRNA (Fig. 4A, lane 2), as would be expected from a partially edited mRNA. A similarly sized RNA product was generated by incubation of the 3′ MBN cleavage product (32P-pCP-labeled) of the chimera plus the 5′ cleavage product (32P-labeled) from the original CYb pre-edited mRNA cleavage reaction in the presence of T4 RNA ligase (Fig. 4A, lane 3).

To verify the identity of these putative partially edited mRNAs, both the extract-generated and the T4 RNA ligase-generated products were reverse transcriptase-PCR amplified, subcloned, and sequenced. Partially edited mRNAs were indeed obtained (Fig. 4B). The majority of extract-generated partially edited mRNAs contained 8–9 U residues at ES2, whereas the majority of MBN plus T4 RNA ligase-generated mRNAs contained 10–11 U residues at ES2. These partially edited mRNAs represent products of a complete cycle of in vitro editing, demonstrating that it is indeed possible to transfer U residues from a gRNA tail, through a chimeric intermediate, and to an editing site within pre-edited mRNA. The fact that a full round of U insertion editing can also be mimicked by the structure-specific heterologous enzymes suggests that RNA secondary structural features direct the reaction. These results (Fig. 4B) also confirm the cleavage site data of Fig. 3A.

Partially Edited Molecules Are Susceptible to Endonuclease Cleavage—If the partially edited RNAs generated in vitro are intermediates in an RNA editing pathway (Fig. 1), they should be substrates for re-editing, beginning with a specific endonuclease cleavage within the editing domain. This was tested using a CYb partially edited mRNA (PE5-2) containing 5 U residues at ES2 and otherwise identical to CYb pre-edited mRNA. Incubation of PE5-2 mRNA (pCP-labeled) in mitochondrial extract indeed resulted in specific cleavage (Fig. 5A, lane 6), and this cleavage is adjacent to ES2, mapped relative to sizing markers (Fig. 5A, lanes 3, 8, and 9). Higher resolution mapping of the 3′ and 5′ cleavage products (Fig. 5B, left and right) demonstrates a major cleavage at the 3′ end of the 3′ U tract and minor cleavages after each U residue. The complementary cleavage profiles observed using 3′ and 5′ end-labeled mRNA (Fig. 5B) indicate that the minor bands represent initial cleavages in the extract and not secondary degradation products. Thus, extract endonuclease specifically cleaves partially edited CYb mRNA at the incompletely edited site, demonstrating that CYb partially edited mRNA is a potential substrate for re-editing via an enzymatic pathway. MBN also cleaves PE5-2 mRNA at each site within the oligo(U) region but not preferentially at the oligo(U)/ES2 junction (Fig. 5A, lane 7; data not shown). This suggests that the U residues are single-stranded, an outcome also predicted by application of the FOLD algorithm (30) on PE5-2 mRNA (Fig. 5C).

It is notable that this PE5-2 RNA as well as CML15–2 RNA and CYb pre-edited mRNA is cleaved by the extract endonuclease specifically cleaves CYb gRNA-mRNA chimeras. A, endonuclease cleavage reactions contained 0.2 pmol of pCP-labeled CYb pre-edited mRNA (lanes 1–5) or 0.2 pmol of pCP-labeled CML15–2 RNA (lanes 7–9). (CML15–2 is chimeric RNA transcribed in vitro from a reverse transcriptase-PCR amplified and cloned CYb chimera that was generated by MBN and RNA ligase using a CYb gRNA with a 3′ tail of 15 U residues.) The reactions were incubated without additions (lanes 1 and 7) or with 2 μl of mitochondrial extract (lanes 2 and 8), 25 units of MBN (lanes 3 and 9), RNase T1 (lane 4), or RNase U2 (lane 5). The reactions of lanes 2 and 8 also contained 50 mg/ml of heparin. The bracket denotes the 15 U residues of CML15–2 RNA that originally derived from the gRNA tail. B, the predicted secondary structure for CML15–2 mRNA (ΔG = −40.5 kcal/mol) was determined by the FOLD algorithm (30). The major cleavage sites for mitochondrial endonuclease (solid arrows) and for MBN (open arrows) are within the gRNA-derived U tract (bold line). The first 29 nt and last 18 nt of this RNA are vector sequences.
decrease predominantly ~2 nt from the 3' end of the loop, whereas they are cleaved by MBN predominantly at the central positions of the single-stranded loop. A cleavage preference of mitochondrial endonuclease for a site a fixed distance from the 3' end of a single-stranded loop might be predicted for an endonuclease involved in editing.

Comparison of in Vitro and in Vivo Partially Edited mRNAs—Is the CYb partial editing that we observe in vitro reflective of in vivo editing-like activities? Sequence analysis of in vitro generated partially edited RNAs from L. tarentolae and of in vivo generated chimeric RNAs have implicated a model in which editing begins at the 3' most editing site (ES1), so the relevance of editing-like activities that start predominantly at ES2 or ES3 (Fig. 2B) leaving ES1 unaltered must be questioned. Interestingly, sequence analysis of in vitro generated partially edited CYb mRNAs from T. brucei (32) revealed that almost all the molecules were aberrantly edited and many of these molecules have patterns consistent with the in vitro editing reported above. Specifically, over one-third of the steady state T. brucei CYb mRNAs that are partially edited in vivo are unedited at ES1 and instead have partial editing starting at ES2 or ES3 (Fig. 6). This would be expected to occur if their editing modifications were initiated by the editing site-specific endonuclease that initiates in vitro editing at ES2 and ES3. Also like the in vitro generated partially edited molecules (Fig. 4B), the in vivo generated partially edited molecules contain more U residues at the initiating editing site than are present in the correctly edited mRNA (Fig. 6). Thus, the CYb in vivo generated partially edited RNAs may have initiated their editing by events much like those we observe in vitro. Whether these partially edited molecules can be subsequently re-edited to generate the canonical mature mRNA sequence remains to be determined, although their in vitro endonuclease sensitivity suggests that this could be the case (20).

There are other examples in the literature of in vivo edited RNAs in which the editing also begins at ES2 rather than ES1. These include half of the reported Crithidia fasciculata MURF2 partially edited RNAs (33) and an additional T. brucei CYb RNA (27). The literature also contains numerous examples of cDNAs containing an unedited site or sites at a later otherwise correctly edited region (e.g. CYb of Trypanosoma brucei (34), NADH dehydrogenase subunit 7 of T. brucei (35), and G6 (36), CYb, and COII of L. tarentolae (37)), suggesting that editing in vivo may also permit a more relaxed versus a strict 3'-5' propagation.

Chimera Formation, U Insertion, and U Deletion Activities May All Involve RNA Ligase—There are two previously published examples of complete cycles of editing in vitro: a specific gRNA-directed deletion of U residues from ES1 of A6 pre-edited mRNA in T. brucei extracts (25) and an insertion of multiple U residues at sites within the editing domain of CYb pre-edited mRNA in L. tarentolae extracts (26). Might endonuclease and RNA ligase also mediate these reactions, as they do the full round of editing reported here? The potential role of extract endonuclease can be addressed by examining whether the sites of U insertion or deletion also correlate with the sites of endonuclease cleavage. Indeed, the T. brucei extract and gRNAs that direct specific U deletion from ES1 of A6 mRNA also direct cleavage of this RNA at ES1.2-3 Further, the L. tarentolae extract that inserts U residues into CYb pre-edited mRNA, the insertions are at sites within the editing domain and upstream of ES1 (26), and although they are not yet precisely mapped they could well be at the sites of preferential cleavage by the extract endonuclease (16). Thus, endonuclease may be important for all the reported editing-like activities.

Available data also imply that RNA ligase is critical for the T. brucei A6 U deletion (25) and the L. tarentolae CYb U insertion (26), as it is for the T. brucei CYb chimera formation (23, 24) and the U insertion examined here. All of these activities are ATP-dependent, and all are unable to utilize AMP-CPP (an ATP analog with a nonhydrolyzable $\beta-\gamma$ linkage) (23-26), like RNA ligases in general (38). Although the report that the U deletion activity does not utilize AMP-PCP (an ATP analog with a nonhydrolyzable $\beta-\gamma$ linkage) suggested that U

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2 S. Seichert and K. Stuart, personal communication.

3 J. Cruz-Reyes and B. Soliner-Webb, unpublished results.
deletion may also require β-γ bond hydrolysis (25), AMP-PCP also does not efficiently support L. tarentolae CYb U insertion (26), T. brucei chimera-forming action (Fig. 7B), T. brucei RNA ligase activity (Fig. 7B), or even T4 RNA ligase activity (Fig. 7B). However, the L. tarentolae U insertion, T. brucei chimera formation, and T. brucei RNA ligase activities all function with AMP-PNP (another ATP analog with a nonhydrolyzable β-γ linkage) (Refs. 23 and 26 and Fig. 7), and therefore none of these reactions require β-γ bond hydrolysis. (This difference in analog utilization presumably reflects the known structural differences between ATP or AMP-PNP and AMP-PCP (39).) S. Seiwert has kindly assayed the T. brucei U deletion activity in the presence of AMP-PNP and also found it to be active,4

4 S. Seiwert, personal communication.
with U residues transferred to an editing site (Fig. 4), and (v) continue the cycle with another round of specific cleavage (Fig. 5). These reactions are all mimicked by the single strand-specific MBN and T4 RNA ligase, indicating that RNA secondary structure is an important determinant. The observation that many T. brucei in vivo generated partially edited mRNAs (32) show editing patterns that are similar to the in vitro generated partially edited Cyb mRNAs with editing beginning at ES2 or ES3 and not at ES1 (compare Figs. 2 and 4 with Fig. 6) suggests that these in vivo RNAs may also arise from a similar endonuclease-dependent route. Furthermore, it appears that extract endonuclease and RNA ligase are also the catalytic basis of previously reported in vitro systems that support T. brucei A6 U deletion (25) and L. tarentolae Cyb U insertion (26).

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Trypanosoma brucei RNA Editing: A FULL ROUND OF URIDYLATED INSERTIONAL EDITING IN VITRO MEDIATED BY ENDONUCLEASE AND RNA LIGASE

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