ABSTRACT
Synthesis of integration-competent, double-stranded DNA from the positive (+) RNA strand genome of retroviruses and long-terminal repeat-containing retrotransposons reflects a multi-step process catalyzed by the virus-coded reverse transcriptase (RT). In conjunction with RNA and DNA-templated DNA synthesis, a hydrolytic activity of the same enzyme (ribonuclease H, or RNase H) is required to remove genomic RNA of the RNA/DNA replication intermediate. Together, these combined synthetic and degradative functions ensure correct selection, extension and removal of the RNA primers of minus (–) and (+) strand DNA synthesis (tRNA and the polypurine tract (PPT), respectively).

For human immunodeficiency virus type 1 (HIV-1) RT, a quarter century of research has not only illuminated the biochemical properties, structure and conformational dynamics of this highly versatile enzyme, but also witnessed drug discovery advances from the first Food and Drug Administration-approved anti-RT drug to recent use of RT inhibitors as potential colorectal microbicides. Salient features of HIV-1 RT and extension of these findings into programs of drug discovery are reviewed here.

HIV-1 DNA Synthesis

The individual steps of HIV-1 DNA synthesis, catalyzed by the multifunctional reverse transcriptase (RT), are summarized schematically in Figure 1. (–) strand DNA synthesis, initiated from a cellular tRNA (tRNA^{Lys,3}) hybridized to the genome-coded primer binding site (PBS), continues to the 5' terminus, creating (–) strong-stop DNA. RNase H-mediated degradation of the resulting RNA/DNA hybrid promotes relocation of nascent (–) DNA to the genome 3' terminus by a strand transfer event that exploits sequence homology between the 5' and 3' termini. RNA-templated DNA synthesis continues, accompanied by RNase H-mediated degradation of the RNA genome, the exception to which are two short, purine-rich segments (the 3' and central polypurine tracts, or PPTs) from which (+) strand DNA-dependent DNA synthesis is initiated. Newly synthesized (–) strand DNA and 18 nucleotides of the covalently-attached tRNA^{Lys,3} primer provide the template for 3' PPT-primed (+) strand DNA synthesis, until the replication complex stalls at a position corresponding to the first modified tRNA base (A57). As a consequence, the C-terminal RNase H domain is positioned at the (–) DNA/tRNA junction and degradation of the tRNA “template” promotes a second, or (+) strand transfer event supported by homology between (–) and (+) strand DNA primer binding sites. Although bidirectional DNA synthesis would be sufficient to complete DNA synthesis, HIV utilizes a second, central PPT (cPPT) primer, thereby producing a (+) strand discontinuity (1) . Following (+) strand transfer, 3'-PPT-mediated DNA synthesis continues, displacing ~100 nucleotides of cPPT-primed (+) DNA, but abruptly ceases at the central termination sequence (CTS), a prominent feature of which is phased A-tracts that induce minor groove compression (1-3), creating the “central flap” (4-7) (Figure 1). While central flap function remains controversial (8,9), its mutation or deletion has been shown to impair virus replication (4,10,11), and it improves transduction efficiency when incorporated into lentiviral vectors (12-16).
Biogenesis and Structural Organization of HIV-1 RT

Although HIV-1 RT is encoded by a single open reading frame of the Gag/Pol precursor polyprotein, the biologically-relevant enzyme is a heterodimer of 66 and 51 kDa polypeptides (p66/p51, Figure 2 (a)) derived via cleavage of p66 by the virus-coded protease between residues Phe440 and Tyr441 (17,18). Both subunits thus contain four similar subdomains, designated fingers, palm, thumb, and connection, while p66 retains the C-terminal RNase domain (19,20) (Figure 2 (a)). Despite identity in primary sequence, the p66 and p51 subdomains adopt significantly different folds, i.e. while the p66 DNA polymerase domain exhibits an open, extended structure with a large active-site cleft, the equivalent region of p51 forms a closed, compact structure incapable of participating in catalysis (19,21). Both the DNA polymerase and RNase H activities are catalyzed by the p66 subunit, while proposed roles for p51 include providing structural support to p66 (19,20,22,23), facilitating p66 loading onto template-primer (24) and stabilizing the appropriate p66 conformation during tRNA-primed initiation of reverse transcription (25,26). In contrast to p66, which undergoes large-scale motions (especially the fingers and thumb subdomains), the p51 subunit is essentially rigid (27). Although the extreme p51 C-terminus has not been resolved crystallographically, its contribution to maintaining RT architecture is supported by observations that reconstituted enzymes with short deletions show increased RNase H inhibitor sensitivity (28) and altered thermal stability (S. Chung and S. Le Grice, unpublished observations).

The p66 nucleic acid binding cleft is formed by its fingers, palm and thumb subdomains and co-crystal structures of HIV-1 RT with duplex DNA and an RNA/DNA hybrid have identified numerous contacts with both strands of the template and primer (20,29-31). Interactions are primarily between the sugar-phosphate backbone and highly conserved motifs of the p66 DNA polymerase and RNase H domains. Superimposing X-ray structures of unliganded and nucleic acid-containing enzymes highlights considerable flexibility of the p66 thumb subdomain (32). Both X-ray crystallography and spin-labeling studies of unliganded RT (33) depict the thumb as folded into the nucleic acid binding cleft (34,35), while nucleic acid binding produces large changes in orientation relative to the p66 palm, resulting in a more open conformation. Helix $\alpha$-H of the thumb mediates extensive contacts with the primer strand in the minor groove of the DNA (36-38). Pro227-His235 comprises the $\beta$12-$\beta$13 hairpin, designated the DNA polymerase “primer grip”. This highly-conserved motif (39) has been proposed to maintain the primer 3'-OH in an orientation appropriate for nucleophilic attack on the incoming dNTP (20). Important primer grip contacts involve the main-chain atoms of Met230 and Gly231 with the primer terminal phosphate (29) and mutational studies of these residues induce pleiotropic effects, altering DNA polymerase and RNase H activity, as well as reducing dimer stability (36,37,40-46). Contact with the template strand is mediated by the “template grip”, comprising elements of the p66 palm ($\alpha$B-$\beta$6 loop, $\beta$-strand 9, $\alpha$-helix E and the $\beta$8-$\alpha$E connecting loop) and fingers ($\beta$-strand 4) (20,29). In contrast to original proposals (20), the co-crystal structure of Huang et al. (30) showed the template overhang ahead of the polymerase active site was not co-linear with the duplex, but bent away and contacting the p66 fingers, revealing contacts with nucleobases +1, +2 and +3.

The DNA Polymerase Active Site

The palm subdomain of HIV-1 RT houses the DNA polymerase active site (Figure 2 (b)) characterized by the Asp110, Asp185 and Asp186 catalytic triad, a common feature of nucleic acid polymerizing enzymes (19,20). Among polymerase families, palm subdomain architecture is also highly conserved, comprising a four- to six-stranded $\beta$-sheet flanked on one side by two $\alpha$-helices (47). In nucleic acid-containing crystal structures, catalytic aspartates are close to the 3'-terminus of the primer. Asp185 and Asp186 are part of the conserved -Tyr-Met-Asp-Asp- motif, which adopts an unusual $\beta$-turn conformation ((29,35,48), possibly to promote their positioning for
catalysis), while the Tyr183 phenoxy sidechain is involved in hydrogen bonding with nucleobases at position -2 (29). Comparing crystal structures of DNA-bound RT with unliganded or nonnucleoside RT inhibitor (NNRTI)-bound enzymes reveals significant conformational differences for the -Tyr-Met-Asp-Asp- motif, implicating a high degree of structural flexibility (29).

The incoming dNTP is tightly coordinated by p66 fingers residues Lys65 and Arg72, the main chain NH groups of residues Asp113 and Ala114 and two divalent metal ions, while its ribose is accommodated by a pocket lined by Asp113, Tyr115, Phe116 on one side, and Glu151 and Arg72 on the other. Additional dNTP contacts involve base-pairing and base-stacking with the template-overhang (30). The fidelity of dNTP insertion is critically influenced by interactions of the \(\gamma\)-phosphate with Lys65 (49), while mutagenesis studies have designated Tyr115 the “steric gate”, suggesting it aids in discriminating between deoxy- and ribonucleoside triphosphates (50,51).

The RNase H Domain and Catalytic Mechanism

RNase H-mediated hydrolysis is divalent metal-dependent, with a preference for Mg\(^{2+}\). Although models for one- (52) and two-metal assisted catalysis (53) have been proposed, structures of Bacillus halodurans (54,55) and human RNases H (56) bound to an RNA/DNA hybrid have confirmed the original 2-metal hypothesis by Steitz and Steitz (53) (Figure 3). Metal ion coordination is also substrate-dependent, i.e. at physiologically relevant concentrations, productive binding occurs only in the presence of substrate (57). Based on crystallographic studies (54-57), the RNase H catalytic cycle can be summarized in the following steps.

- In a “resting” state, divalent metal ions A and B are separated by ~4 Å, while during catalysis their position and separation varies according to the coordination environment.
- Similar to nucleic acid phosphoryl transfer reactions, hydrolysis proceeds via an SN\(_2\) mechanism, involving a penta-coordinated intermediate and resulting in inversion of configuration at the phosphorus.
- Metal ion A (complexed by conserved carboxylates Asp443 and Asp549) coordinates a water molecule, reducing its pKa and aligning this for in-line nucleophilic attack on the scissile phosphodiester bond.
- In turn Metal ion B, coordinated by Asp443, Glu478 and Asp498, is correctly positioned to stabilize the transition state, facilitating leaving of the 3' oxyanion group.

Since metal ion B undergoes a change from an irregular five-ligand coordination and non-ideal geometry in the substrate and intermediate complexes to a regular octahedral geometry in the enzyme-product complex, this likely lowers the energy barrier for product formation (57). Crystallographic studies have revealed extensive contacts between HIV-1 RT and nucleic acid immediately ahead the RNase H active site (31). This motif, which interacts with the DNA primer 4 to 9 nt upstream of the scissile bond of the RNA/DNA hybrid, is collectively designated the “RNase H primer grip” (31). Amino acids of the RNase H primer grip include p66 residues Gly359, Ala360, His361, Thr473, Asn474, Gln475, Lys475, Tyr501, Ile505, and Lys359 and Glu396 of p51. Through interactions with DNA of the RNA/DNA hybrid, the RNase H primer grip is believed to impose the appropriate trajectory on the RNA strand for catalysis it enters the RNase H active site. RNase H primer grip residues are conserved among retroviral RTs and E. coli RNase HI, and both in vitro and in vivo site-directed mutagenesis studies have demonstrated their importance with respect to cleavage specificity (58,59).

The B.halodurans RNase H-RNA/DNA co-crystal structure (54) has demonstrated that the RNA and DNA strands adopt A- and B-form geometry, respectively. Unfortunately, a structure of HIV-1 RT-associated RNase H with the RNA/DNA hybrid positioned in the active site to promote catalysis remains elusive. Structures of HIV-1 RT containing either duplex DNA (30) or a PPT-derived RNA/DNA hybrid (31) indicate that substrate is positioned for primer extension by the polymerase catalytic center and extents into the RNase H domain, but
does not reach its active site. Modeling studies, based on RNase H-RNA/DNA co-crystals (56) propose the RNA/DNA hybrid cannot be correctly positioned at both active sites simultaneously, necessitating a conformational change to permit “toggling” between catalytic centers. Although a plausible model, Beilhartz et al. have shown that RNase H activity persists in the presence of the pyrophosphate analog foscarnet, which “traps” the nucleic acid substrate in the (31)pre-translocated conformation (60). If indeed there is a mechanism of substrate toggling, it remains to be established whether this is specific to sequences resembling that of the PPT that are refractory to hydrolysis.

Conformational Dynamics of Reverse Transcription

X-ray crystallography has provided incisive insights into structures of the unliganded HIV-1 RT (34) and co-crystals with nucleic acid (20,30) and inhibitors of both DNA polymerase and RNase H function (19,61-64). However, crystallographic analysis does not explain how RT assumes alternative conformations required to catalyze HIV-1 DNA synthesis. We therefore investigated HIV-1 RT-nucleic acid complexes by single molecule spectroscopy (SMS), placing a fluorescent dye on the p66 N- or C-terminus of reconstituted p66/p51 and a second on a surface-immobilized nucleic acid duplex (65) (Figure 4 (a), (b)). While the FRET signal obtained from RT bound to a 50-nt DNA template/19-nt DNA primer confirmed placement of the DNA polymerase catalytic center over the primer 3’ terminus, reversal of the FRET signal in the presence of an RNA primer of identical sequence indicated a binding mode with the C-terminal RNase H domain now over the primer terminus. Substituting chimeric RNA-DNA primers whose RNA component progressively increased from the 5’ terminus indicated that introducing two ribonucleotides (i.e. 2RNA/17DNA) was sufficient to initiate redistribution in enzyme re-orientation, and that the process was virtually complete on a duplex whose primer contained five 5’ ribonucleotides. The structure of HIV-1 RT and a PPT-containing RNA/DNA hybrid (31) shows p66 residues Glu89, Gln91, Ser280 (substituted for Cys280 in (31)) and Arg284 contact the ribose 2’-OH at several positions near the RNA 5’ terminus. Since equivalent contacts are absent with duplex DNA (20,30), additional hydrogen bonding afforded by the RNA strand may stabilize the inverted orientation. Applying SMS to PPT-containing RNA/DNA hybrids indicated that the presence of the incoming dNTP favored a polymerization-competent binding mode, while the NNRTI nevirapine (NVP) increased the frequency with which RT assumed the opposite orientation (Figure 4 (c) - (f)). Since NNRTIs potently and preferentially inhibit initiation of HIV-1 (+) strand DNA synthesis (66), SMS suggests this might be due in part to their ability to induce enzyme binding in a polymerase-incompetent mode. Consistent with the notion that NNRTIs occupy a hydrophobic pocket at the base of the p66 thumb, thereby “loosening” the grip on nucleic acid, SMS also demonstrated increased “sliding” of HIV-1 RT on the template in the presence of nevirapine (67). Although an unresolved feature of this and related studies (68) was the ability of HIV-1 RT to adopt alternate orientations (collectively referred to as “flipping”) without dissociating from its nucleic acid substrate, our work demonstrated the value of single molecule spectroscopy in dissecting the intricate events of reverse transcription.

DNA Polymerase and RNase H Inhibitor Development

Since Food and Drug Administration of azidothymidine (AZT) in 1987, several nucleoside RT inhibitors (NRTIs) have been approved for clinical use, including lamivudine (3TC), emtricitabine (FTC), abacavir (ABC), didanosine (ddI) and stavudine (d4T). NRTIs contain modifications to their sugar moiety, the nucleobase, or both (69). Upon phosphorylation to the triphosphate derivative by cellular kinases, NRTIs function by an equivalent chain-terminating mechanism, but
harbor a phosphonate group, requiring only two phosphorylation steps to their active derivative. In contrast, NNRTIs, e.g. nevirapine and efavirenz, impose allosteric control of DNA synthesis by occupying a site at the base of the p66 thumb that “locks” this subdomain in a configuration incompatible with catalysis (19,70). Subsequent SMS analysis indicate an additional property of NNRTIs of inducing dislocation HIV-1 RT from the polymerization target site and “sliding” on the nucleic acid duplex. Finally, Indolopyridones (INDOPYs) represent a new class of RT inhibitors with a unique mechanism. The prototype compound, INDOPY-1 (which is active against NNRTI-resistant HIV) binds and stabilizes RT-DNA/DNA complexes, trapping this in a post-translocational state. INDOPY-1 binding depends on the chemical nature of the ultimate base pair at the primer 3’ terminus rather than the chemical nature of the templated base engaged in classic base-pairing (71,72). Although the clinical benefits of RT inhibitors in reducing rates of HIV transmission are clear, the rapid emergence of drug resistance continues to pose a challenge (73). On a more positive note, however, the availability of a wealth of high-resolution co-crystal structures has spawned the development of second generation NNRTIs that interact with highly-conserved residues immediately adjacent to the allosteric binding pocket. A more comprehensive synopsis of current anti-RT drugs, and their use in combination antiretroviral therapy is provided in (69).

Despite documentation that loss of virus infectivity following selective inhibition of RNase H function (74) identified this activity as a potential therapeutic target, RNase H inhibitors have failed to advance towards clinical trials. The retroviral enzyme belongs to a superfamily of nucleotidyl transferases, raising concerns of toxicity due to lack of specificity. In particular, inactivating the eukaryotic RNase H counterpart is associated with a lethal embryonic defect in mice due to failure to accumulate mitochondrial DNA (75). These issues notwithstanding, a considerable body of biochemical and structural data for small molecule RNase H inhibitors has accumulated. As might be predicted, chelating the divalent metal essential for catalysis is a shared feature of these inhibitors. For example, the pharmacophore of the N-hydroxyimides described by Klumpp and co-workers (76) contains a 3-oxygen motif, and was originally developed as an inhibitor of influenza virus endonuclease, which shares the two-metal ion mechanism of catalysis (77,78). A second class includes the natural product hydroxytropolones β-thujaplicinol and manicol, the former of which specifically inhibited HIV-1 RNase H with ~30 and ~250-fold enhanced specificity with respect to human and bacterial RNases H, respectively (79). Originally developed as metal-dependent inhibitors of HIV-1 integrase (80,81), compounds containing a diketo acid moiety are moderately effective RNase H inhibitors, among which RDS1643 inhibited RNase H activity inhibited HIV replication in cell culture with an EC$_{50}$ of 14 µM (82).

Based on structural information on pyrimidinol carboxylic RNase H inhibitors, Lansdon et al. (83) have suggested that the relatively open inhibitor binding site is unfavorable and provides a major obstacle to compound optimization. In light of the potential drawbacks of active site inhibitors, targeting a region outside the active site might offer the possibility of allosteric inhibition of RNase H activity, akin to NNRTI-mediated restriction of thumb movement, should be further explored. Compounds fulfilling this requirement include N-acylhydrazones, such as (E)-3,4-dihydroxy-N’-(2-methoxynaphthalen-1-yl)methylene)-benzohydrazide (DHBNH). Surprisingly, while demonstrating selectivity for RNase H function, X-ray crystallography has shown DHBNH binds ~50 Å from the active site, interacting with Trp229 of the primer grip and Asp186 of the DNA polymerase active site. (61). Thienopyrimidinones represent a second class of allosteric inhibitor, demonstrated by both protein footprinting and site-directed mutagenesis to bind at the interface between the p51 thumb subdomain and p66 RNase H domain (84-86). Since interactions of p51 thumb residues Cys280 - Thr290 and p66 RNase H residues Pro537 - Glu546 constitute ~33% of the buried surface at the dimer interface (87), thienopyrimidinones are unlikely to interact with active site residues but rather induce a change in active site geometry that is inconsistent with catalysis. A more
thorough summary of HV-1 RNase H inhibitors can be found in (88).

The Final Chapter? RT Inhibitors as Microbicides

Although considerable structural and biochemical data are now available for HIV-1 RT, it is essential to recognize this in the context of developing new and improved antiretroviral agents to reduce viral burden and rates of HIV transmission. Antiretroviral agents targeting specific enzyme functions of the HIV replication cycle, and in particular RT, have recently emerged as promising vaginal and rectal microbicides (89). Prominent among these is the NtRTI TFV, which functions through a chain-terminating mechanism. In clinical trials, TFV was demonstrated to be safe and well-tolerated in a study on HIV-negative women with a vaginal gel applied during 24 weeks. Repeated application of TFV intravaginal gel was well-tolerated, produced low plasma levels and, importantly, did not select for resistance-conferring mutations. NNRTIs such as Dapirivine (DPV), have also displayed promising virucidal properties. When applied intravaginally, DPV is absorbed by the outer mucosal layers, while plasma concentrations reportedly remained low. Long-term constant release of DPV has been obtained from a variety of intravaginal rings. Although encouraging, HIV microbicide development (reviewed in (89)) still faces considerable formidable challenges, including conclusive demonstration of efficacy in nonhuman primates, selection of drug-resistant virus in clinical settings, cultural acceptability and affordability. These issues notwithstanding, advances in HIV RT research over that last 25 years, which have ranged from expressing active recombinant enzyme for high-throughput screening to the potential of introducing vaginal and rectal microbicides in resource-limited settings, should be considered a bench-to-bedside success and a model for development of future antiviral agents.

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FOOTNOTE

The abbreviations used are: ABC, {(1S,4R)-4-[2-amino-6-(cyclopropylamino)purin-9-yl]cyclopent-2-en-1-yl}methanol; AZT, 1-[(2R,4S,5S)-4-azido-5-(hydroxymethyl)oxolan-2-yl]-5-methylpyrimidine-2,4-dione; CTS, central termination sequence; ddl, 9-[(2R,5S)-5-(hydroxymethyl)tetrahydrofuran-2-yl]-3H-purin-6(9H)-one; d4T, 1-[(2R,5S)-5-(hydroxymethyl)-2,5-dihydrofuran-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione; DHBNH, (E)-3,4-dihydroxy-N’-[2-(methoxynaphthalen-1-yl)methyl]benzohydrazide; DPV, 4-([4-(2,4,6-trimethylphenyl)amino]pyrimidin-2-yl]amino)benzonitrile; FTC, 4-amino-5-fluoro-1-[(2S,5R)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one; HIV, human immunodeficiency virus; NRTI, nucleoside RT inhibitor; NNRTI, nonnucleoside RT inhibitor; RNase H, ribonuclease H; RT, reverse transcriptase; 3TC, 2’,3’-dideoxy-3’-thiacytidine; SMS, single molecule spectroscopy; TFV, [(2R)-1-(6-aminopurin-9-yl)propan-2-yl]oxymethylphosphonic acid.

FIGURE LEGENDS

Figure 1. Synthesis of double-strand, integration-competent HIV-1 DNA from the (+) strand RNA retroviral genome. See text for details. DNA and RNA are indicated in red and yellow, respectively.

Figure 2. (a), Structure of the p66/p51 HIV-1 RT heterodimer. For both subunits, the fingers, palm, thumb and connection subdomains have been color-coded blue, red, green and yellow, respectively, while the lighter shading has been used for the p51 subdomains. The p66 RNase H domain has been colored in gold. (b), DNA polymerase active site of HIV-1 RT. Template and primer strands are colored light and dark green, respectively, and dTTP in gold. Mg$^{2+}$ ions are represented as yellow spheres, and assigned hydrogen bonds and metal ligand interactions as dashed lines. Adapted from (30), with permission.

Figure 3. Superposition of active site residues from the substrate complexes of B.halodurans RNase H1 (magenta) and Human-RNase H1 (orange) and the complex of HIV-1 RNase H containing the natural product hydroxypurinolone, β-thujaplicinol (blue) (90). Metal ions (Mg$^{2+}$ for B. halodurans RNase H1, Ca$^{2+}$ for Human-RNase H1 and Mn$^{2+}$ for HIV-1 RNase H) are depicted as spheres. RNA strand from the B. halodurans RNase H1-substrate complex is shown in pink. The inhibitor from the HIV-1 RNase H co-crystal structure has been omitted for clarity.

Figure 4. Examining HIV-1 RT dynamics by single molecule spectroscopy. (a) HIV-1 RT is site-specifically labeled with Cy3 at either the N-terminal, fingers subdomain or C-terminal, RNase H domain. (b), Cy3-labeled RT interacts with surface-immobilized DNA containing the FRET acceptor Cy5 and fluorescence of individual substrates is followed by total-internal-reflection fluorescence (TIRF) microscopy. (c) – (f) HIV-1 RT adopts alternative orientations on the PPT. (c), Ternary complex formation promotes binding to the primer terminus in a polymerization orientation. FRET Histogram of RT bound to the PPT (filled, grey) in the presence of 10 µM (purple) and 1 mM dTTP (cyan). (d), FRET time trace of HIV-1 RT bound to a chain-terminated PPT substrate in the presence of dNTPs, establishing a stable ternary complex. (e), NNRTI binding promotes RT binding to the PPT 3’ terminus in an RNase H orientation. Histograms of RT bound in the absence (filled grey trace) presence of 10 µM (red trace) and...
100 μM nevirapine (orange trace). (f), FRET time trace of HIV-1 RT bound to the PPT substrate in the presence of nevirapine (NVP), indicating multiple transitions, or “flipping” between high and low FRET states. Adapted from (65).
Figure 1

[Diagram of HIV RT processes: tRNA-Primed (-) DNA Synthesis, (-) Strand Transfer, PPT-Primed (+) DNA Synthesis, (+) Strand Transfer, Bidirectional DNA Synthesis]
Figure 2
Figure 3
Figure 4
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