HIV cDNA integration: molecular biology and inhibitor development

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Introduction

Retroviruses such as HIV are distinguished from other viruses by two steps in the viral life cycle, reverse transcription of viral RNA to make a cDNA copy, and integration of cDNA into one of the host's chromosomes [1,2]. The reverse transcription step has been exploited as a target for antiviral agents. Another viral function, the required proteolytic processing of viral proteins, has also been exploited as an inhibitor target. Inhibitors of these steps, however, have been found to be plagued by viral escape mutants in clinical applications [3], adding interest to the search for new inhibitors of other targets. Here we review recent advances in the study of the second defining step of retroviral replication, integration, and attempts to develop integration inhibitors.

Molecular mechanisms involved in retroviral integration

DNA cutting and joining reactions involved in integration

The DNA cleaving and joining reactions believed to mediate retroviral cDNA integration are presented schematically in Fig. 1a. Early studies incorrectly concluded that a circular form of the viral cDNA (see below) was the substrate for integration [4,5]. Subsequent studies have established that the linear form of the viral cDNA is the immediate precursor [6,7], although unfortunately the former view can still be found in many textbooks.

Prior to integration, the viral cDNA ends are cleaved to remove two nucleotides from each 3' end (Fig. 1a). The recessed 3' ends are then attached to the target DNA (Fig. 1a) [7–9]. The points of joining on each strand are offset by a few base pairs. The exact spacing is characteristic of each retrovirus; for HIV the spacing is 5 base pairs. The resulting gapped intermediate is then processed, either by host DNA repair enzymes or possibly viral enzymes, to yield the integrated provirus (Fig. 1a). The repair of the gaps creates the characteristic short duplication of target sequences at the host–provirus junction. Integration *in vivo* is sequence non-specific with respect to the target DNA [10].

Integrase protein

Early progress in understanding integration came from Grandgenett *et al.* [11], who identified a new viral protein with endonuclease activity encoded in the *pol* gene of avian sarcoma-leukosis virus (ASLV). Genetic studies identified mutants containing changes in this region that were specifically defective in integration [12–15]: mutant viruses were capable of carrying out reverse transcription, but the cDNA did not become integrated and replication was greatly impaired. On the basis of these findings the protein encoded in this region was named 'integrase' for its apparent role in integration.

The development of assays in which purified integrase carried out covalent attachment of model viral DNA to target DNA *in vitro* established that integrase was in fact the recombinase that carried out integration (Fig. 1b) [16–18]. On the basis of the genetic studies alone, it had remained possible that integrase was only a required cofactor for a cellular recombinase.

Initially integration products made *in vitro* by purified integrase were detected using a sensitive genetic assay [17–20]; later methods relied on detecting products made with simple model substrates on gels (Fig. 1b) [16,18,21]. Purified integrase also carries out the removal of two nucleotides from each 3' end of model long terminal repeat (LTR) substrates [16,21–25].

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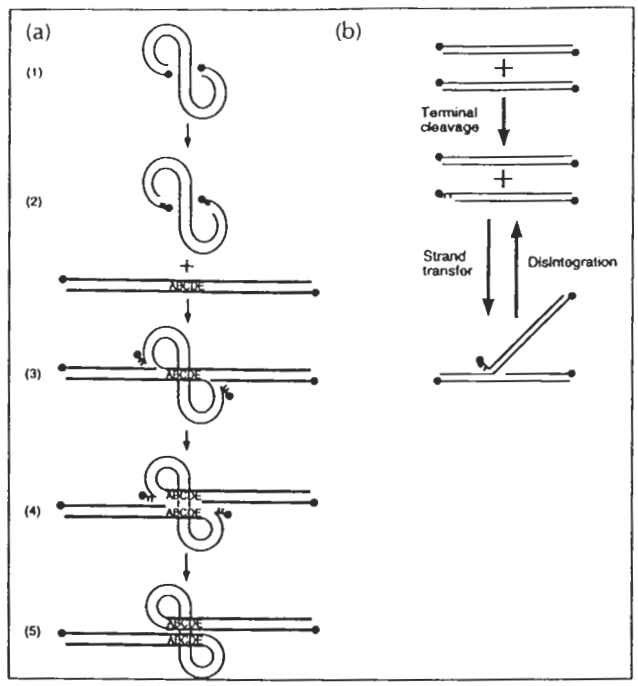

Fig. 1. DNA cutting and joining reactions involved in retroviral integration. (a) Initially, a nucleolytic cleavage step removes two nucleotides from the 3′ end of the viral DNA (2). A subsequent DNA strand transfer step joins the resulting recessed 3′ ends of the viral DNA to the 5′ ends of a staggered break made in the target DNA; the 3′ ends of the break in the target DNA remain unjoined at this stage (3). The 5 base-pair spacing shown is characteristic of HIV. The unpaired bases at the 5′ ends of the viral DNA are then removed, and gap repair completes the integration process (4). The viral integrase carries out the nucleolytic cleavage and DNA strand transfer reaction; cellular enzymes are likely to be responsible for trimming the unpaired bases from the 5′ ends of the viral DNA and the gap repair step. Unpaired bases are shown as bars perpendicular to the DNA strand. (b) Diagram of reactions directed by purified integrase. (—), viral DNA; (▬), target DNA; (●) DNA 5′ ends; ABCDE, host–provirus junction.

Subsequent studies revealed that the sequence of only a few nucleotides at each end of the model LTR substrates (approximately 6–9 base pairs) is critical for integration [21,25–32]. Studies *in vivo* have yielded similar conclusions [9,33–38].

Biochemical and genetic studies have begun to reveal important determinants of integrase function. Integrase proteins contain two conserved amino-acid motifs (Fig. 2). Near the amino terminus a sequence $H\text{-}X_{(3-7)}\text{-}H\text{-}X_{(23-32)}\text{-}C\text{-}X_2\text{-}C$ was identified [39] and shown to be important for zinc binding [40,41]. Near the center of the protein another conserved sequence was found, $D\text{-}X_{(39-58)}\text{-}D\text{-}X_{35}\text{-}E$ [42–44]. Interestingly, this second motif was also recognized in certain bacterial transposase proteins. More recently, relatives of this motif have been proposed to exist in many transposase proteins of transposons from higher eukaryotes [45,46]. Mutational studies revealed that the conserved residues are important for function *in vitro* [47–55] and *in vivo* [54,56–66].

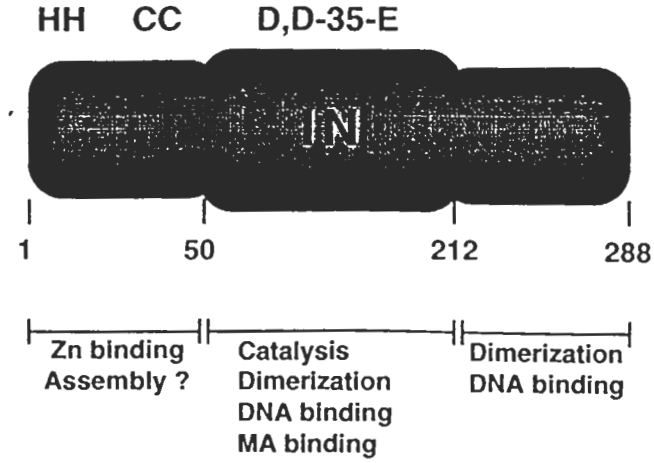

Fig. 2. Organization of the HIV-1 integrase protein (IN). HH CC and D,D-35-E represent the two sequence motifs common to integrase proteins. Numbers represent amino acids (see text for details).

Analysis of the activities of HIV-1 integrase fragments *in vitro* have revealed that the central domain of HIV-1 integrase alone contains the enzyme active site. These studies were made possible by the finding that the back reaction of integration, playfully named 'disintegration' (Fig. 1b) [67], was more permissive than the forward reaction. It was found that a fragment of HIV-1 integrase composed of only amino-acids 50–186 contained detectable disintegration activity [41,68]. Similar findings were later made for integrase proteins from other viruses [69,70]. Studies of complementation among mutants *in vitro*, together with other studies, have indicated that the integrase protein probably acts as a multimer [71–73].

A 'core' domain fragment from HIV-1 integrase, amino acids 50–212, has been crystallized and solved at 2.5 Å resolution [74]. The integrase core was found to be a compact globular domain composed of mixed α helices and β strands. Two of the integrase monomers in the crystal lattice shared an extensive set of contacts, consistent with the idea that this region represented a biological dimer interface. The three acidic residues of the D,D-35-E motif were found to be near one another (although one was in a short disordered region), as expected if the three acidic residues participate in catalysis. Puzzlingly, the distance between the active sites in the two monomers in the dimer is not that expected if the points of joining of each end of the viral DNA lie across a DNA major groove from one another, as has been inferred from other studies [75,76]. Possible explanations are (1) that the target DNA might be greatly distorted during integration, (2) that integration takes place at one DNA end first, and the complex isomerizes prior to integration at the other end, or (3) that a multimer different from that seen in the crystal mediates integration *in vivo*.

Recently, the structure of a similar catalytic domain fragment of ASLV integrase was determined and found to closely resemble that of HIV [77].

The structure of a fragment from the carboxy terminal region of integrase has also been reported [78,79]. This part of the protein folds into a five-stranded β barrel, resembling an *src*-homology-3 (SH3) domain. This domain is capable of binding DNA non-specifically [44,68,71,80–83]. The contribution of this domain to the activity of the full protein is unclear.

Interestingly, the structure of a part of a bacterial transposase protein, that of phage Mu, is very similar to that generated by linking the core and carboxy terminal structures of integrase [46]. Both HIV integrase and Mu transposase have been inferred to carry out integration by a single step transesterification mechanism on the basis of studies of the stereochemical course of the reactions [84,85]. Earlier proposals that retroviral integration proceeded through a covalent protein–DNA intermediate are at odds with this data and are likely to be incorrect [86]. These structural and mechanistic similarities highlight the evolutionary conservation of this group of enzymes [87].

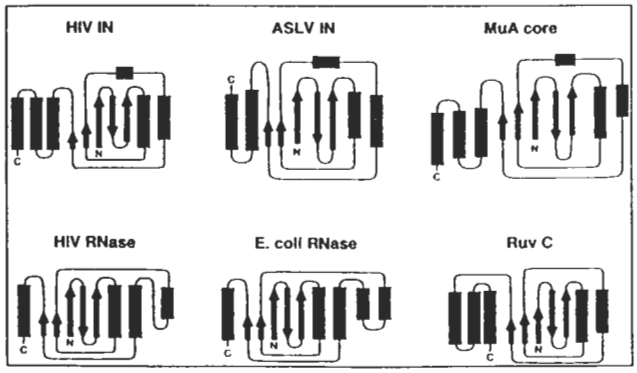

Fig. 3. Secondary structure diagrams of six polynucleotide phosphotransfer domains. Arrows indicate β-sheets; rectangles indicate α helices. IN, Integrase; ASLV, avian sarcoma-leukosis virus.

The structures of the catalytic domains of the integrase proteins and that of MuA are closely related to catalytic domains of three other enzymes, RNAse H of HIV [88], RNAase H from *Escherichia coli* [89,90], and RuvC resolvase from *E. coli* [91]. The type and arrangement of secondary structural elements are highly similar in each (Fig. 3). RNAseH is a nuclease that acts selectively on RNA/DNA hybrids, whereas RuvC is an *E. coli* recombination enzyme involved in resolving Holiday junctions (DNA cruciforms thought to be recombination intermediates). Evidently all these proteins are members of a very ancient family of polynucleotide phosphotransfer enzymes.

Analysis of HIV-1 integrase *in vivo*

For many different retroviruses, certain mutations in the integrase coding region yield viruses that are able to carry out reverse transcription but not integration [56–60]. That is, in infected cells the expected linear and circular forms of the viral DNA accumulate but integration does not take place normally. However, for certain HIV derivatives containing deletion and point mutations, defects in processes including core maturation and reverse transcription have been observed. Such pleiotropic effects may indicate that parts of integrase such as the amino terminal zinc-binding domain are important for assembly or possibly reverse transcription itself [38,59,61,64–66].

A specific defect in integration has been observed for some amino-acid substitutions that have no effect on the enzymatic activities of recombinant integrase (e.g., R199, W235) [62,63]. These mutations may define regions of the protein involved in functions that are not detected in the *in vitro* enzymatic assays. Several highly conserved residues can be mutated without obvious effect on replication in T-cell lines [62,63,65,66]. Perhaps the contribution of these residues to viral replication will be apparent in other cell types, such as primary cells.

Composition and function of the HIV preintegration complex

Brown *et al.* [8] were first to demonstrate that integration-competent subviral complexes could be extracted from cells freshly infected with a retrovirus [in this case Moloney murine leukemia virus (MoMLV)]. When such complexes are presented with a target DNA *in vitro*, the viral cDNA becomes covalently linked to target DNA, yielding the gapped integration intermediate (Fig. 1a) [6,7]. Similar systems have been subsequently developed for HIV and ASLV [92–94].

Gel filtration and sedimentation analyses of MoMLV [95] and HIV-1 [92] preintegration complexes revealed that they were very large — similar in size to ribosomes by these measurements. Complexes were also stable, remaining associated and active during these fractionation steps.

Functional HIV-1 preintegration complexes prepared at high detergent concentrations were found to contain integrase as the only detectable viral protein, indicating that only integrase is essential for the DNA strand joining activity [96]. Fifty to 100 molecules of integrase were associated with each linear viral DNA molecule (unpublished data). Other viral proteins, including reverse transcriptase and matrix protein (one of the products of the Gag polyprotein), were present in fractions partially purified by less stringent means, reflecting a possible looser association of these proteins [97]. The possible roles of cellular proteins are unclear but are under intensive study.

It was recently found that the DNA in active HIV preintegration complexes is not uniformly double stranded, but in fact contains discontinuities in the positive strand [98]. This finding, together with other data, is consistent with the idea that viral DNA synthesis may in fact be completed only after integration. Presumably the gaps in the positive strand are repaired by host DNA repair enzymes, as are the gaps at the host–virus DNA junction generated by the integration mechanism.

Purified HIV-1 integrase can be assembled with an LTR analog to form a stable complex [99,100], and such complexes can form stable higher order complexes with target DNA [101], but assembly of full preintegration complexes remains to be achieved. Evidence for this view comes from the finding that reactions with purified integrase generally resemble those occurring at only one end of the unintegrated viral DNA [17,21,102]. Full integration of the viral cDNA requires spatially coordinated reactions at each end of the DNA (compare Figs 1a and b). Some progress has been made in developing systems based on avian integrase that carry out coupled joining [103–105]. Recently, it has been reported that coupled joining of model HIV DNA is more prominent *in vitro* when virion extracts are used as a source of integration activity [106]. Further studies of this system may allow the determinants of coupled joining to be discovered.

Nuclear import

HIV can replicate in non-dividing cells, requiring the preintegration complex to be actively transported across the nuclear membrane prior to integration.

The viral matrix and Vpr proteins have been proposed to confer the necessary karyophillic properties [107–109]. As mentioned above, matrix protein copurifies with the HIV-1 preintegration complex under some conditions. A specific interaction between the integrase protein and a subset of virion matrix proteins that are tyrosine-phosphorylated has been proposed to link matrix to the preintegration complex [110,111]. The integrase–matrix interaction is unusual in that the matrix phosphotyrosine does not appear to interact with an SH2 domain. The matrix protein contains a prototypical nuclear localization sequence and may link the preintegration complex to the nuclear transport apparatus through this determinant. The mechanism of Vpr function is less clear, although it too may be associated with preintegration complexes.

Autointegration and circularization

The preintegration complex only rarely uses its own DNA as an integration target. This makes evolutionary sense, since such 'autointegration' is probably suicidal for the virus. *In vitro*, HIV-1, MoMLV and ASLV preintegration complexes are able to catalyze autointegration [94,112,113]. Autointegration of HIV-1 or MoMLV can be stimulated to occur when HIV-1 preintegration complexes are incubated in the presence of nucleoside triphosphates [112], or MoMLV complexes are extracted with high salt concentration [113]. These treatments may alter the structure or composition of the complex. In the case of MoMLV, it has been proposed that salt extraction removes a cellular protein that may prevent autointegration [113]. The autointegration reaction is of intrinsic interest as a feature of preintegration complex function, and may also be of practical importance if agents that promote autointegration can be developed as antiviral drugs.

In addition to the complex circular forms generated by autointegration, additional circular forms of viral DNA can be found in cells infected with retroviruses. A circle containing one LTR and a circle containing two juxtaposed LTR are particularly prominent. *In vitro*, formation of 1-LTR circles has been reported in the ASLV system [94], while formation of both 1-LTR and 2-LTR circles occurs in the HIV-1 system [112]. Analysis of the circularization reactions in the HIV-1 system provides direct evidence that cellular recombination enzymes catalyze the circularization of linear molecules by homologous recombination and end-joining [112].

Target site selection by integration complexes

In vivo the integration target DNA is expected to be coated with proteins. Pryciak, Varmus and coworkers found that DNA wrapped on nucleosomes displayed an altered pattern of integration acceptor sites compared with free DNA [75,114,115]. Sites expected to be exposed on the surface of the nucleosome were favored for integration, and integration efficiency overall was higher in nucleosomal targets. More recent studies have found that integration is greatly increased at two sites in each half of the nucleosome that are known to have widened major grooves (kinks) [76]. These findings together with other studies support a model in which DNA distortion promotes the activity of integrase [25,26,116,117]. Possibly the integrase enzyme distorts its DNA substrates during the course of integration, so that pre-distorting the substrate promotes the reaction.

Consistent with this idea, several further forms of distorted DNA have been found to be preferential integration targets. Complexes containing the *E. coli* proteins, integration host factor (IHF) or catabolite activator protein (CAP), known to contain distorted DNA, are preferential targets [116,118]. DNA containing a static bend induced by periodic poly A is also favored for integration [116,119]. Interestingly, another DNA binding protein, human lymphoid enhancer factor, which bends DNA to the same degree as IHF, did not create a hotspot for integration *in vitro*. These data are probably explained by the radically different conformations of the two complexes (Fig. 4) [118]. Thus not all forms of DNA distortion necessarily promote integration.

Recently, a cellular DNA-binding protein, ini-1, was found to bind HIV-1 integrase, and proposed to influence target site selection [120]. Although the significance of this interaction is at present unclear, the possible inter-

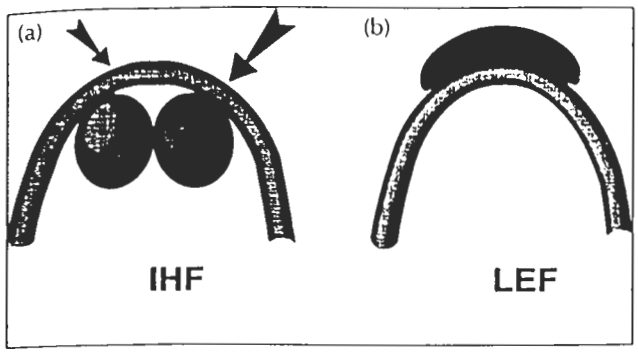

Fig. 4. Complexes containing distorted DNA used as integration targets. (a) Integration host factor (IHF)–DNA complex. (b) Lymphoid enhancer factor (LEF)–DNA complex. Arrows mark the location of integration hotspots created by bound IHF protein; no such hotspots are created by LEF [118].

actions of preintegration complexes with host proteins on target DNA is a fertile area for further study.

Controlling integration site selection?

Although integration normally takes place in non-specific sites in naked DNA, it has recently been shown *in vitro* that target site selection could be controlled by modifying the integrase protein [121]. HIV-1 integrase was fused to the sequence-specific DNA binding domain of phage lambda repressor. The resulting fusion protein was found to be able to direct selective integration into target DNA-containing recognition sites for repressor. A close study of the integration sites used revealed that they lay on the same face of the DNA helix as the repressor sites. This is as expected if the fusion protein bound to lambda repressor sites captured target DNA by looping out the intervening sequences (Fig. 5). Integration on the opposite side of the helix is presumably disfavored due to the torsional rigidity of DNA. It will be of interest to see whether such fusion proteins can be adapted for uses in gene therapy *in vivo* [122].

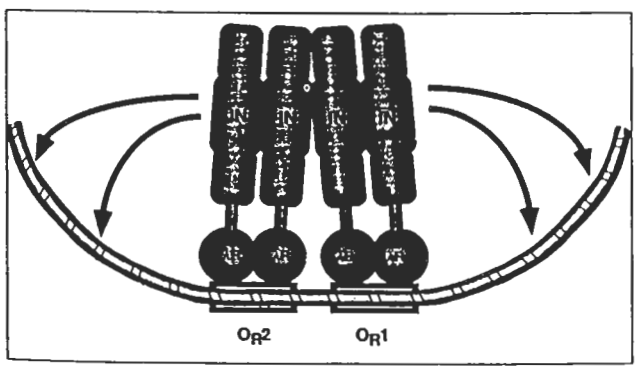

Fig. 5. Selective integration directed by a fusion protein containing HIV-1 integrase linked to the DNA binding domain of lambda repressor (λR). The balls represent the DNA binding domain of repressor; integrase (IN) is represented as in Fig. 2. Arrows mark integration into nearby sequences on the same face of the DNA helix as the repressor binding sites O_R1 and O_R2.

Inhibitors of HIV integrase

Table 1 lists some compounds reported to inhibit the 3'-processing or strand-transfer activities of purified HIV-1 integrase (Fig. 1b) with median inhibitory concentration (IC_{50}) values at or below 100 μM. Integrase inhibitors generally inhibit the end-cleavage and strand-transfer activities in parallel, as expected if both reactions are catalyzed by the same active site [123–125]. We have divided these compounds into four groups for the purposes of discussion.

Table 1. Compounds that inhibit HIV-1 integrase *in vitro* with a median inhibitory concentration ≤ 100 μM.

	Reference
Group I: DNA binders	
DNA intercalators	[123,126,127]
Oxazolopyridocarbazole (OPC)-conjugated oligonucleotides	[128]
Group II: polyanions	
Aurintricarboxylic acid and derivatives	[131]
Cosalane and analogs	[140]
Dextran sulfate	[126]
Suramin	[130]
Group III: nucleotides and analogs	
ATP-2',3'-dialdehyde	[132]
8-Azido-ATP (+ UV light)	[132]
Azidothymidine mono-, di-, and triphosphate	[133]
Pyridoxal 5-phosphate	[132]
Group IV: other compounds	
Bis-catechols	[125]
Caffeic acid phenethyl ester	[123,124]
Chloroquine	[123]
Curcumin	[135]
1,8-Dihydroxynaphthoquinone	[123]
Flavones	[123,124]
NSC 339192	[124]
Peptide inhibitor	[137]
Phenanthroline-cuprous complexes	[136]
Primaquine	[123]

Group I: DNA binders

Screens of topoisomerase inhibitors and DNA intercalators were among the first to identify integrase inhibitors [123,126,127]. All of the topoisomerase inhibitors that inhibit integrase are DNA intercalators, raising the possibility that these compounds act non-specifically by binding the DNA substrates.

Oligonucleotides coupled to the intercalating agent OPC may represent more specific inhibitors of HIV-1 integration [128,129]. These compounds block integrase activity *in vitro* by forming specific DNA triplexes with highly conserved polypurine sequences present at the ends of the viral cDNA. Whether such sequences are accessible *in vivo* is unknown, but could be investigated by testing inhibition by these compounds on purified preintegration complexes.

Group II: polyanions

Polyanionic compounds can bind directly to the integrase protein and interfere with the binding of DNA substrates [130,131]. Inhibition of DNA binding by polyanionic compounds is likely to be non-specific, as other DNA-metabolizing enzymes, including the viral reverse transcriptase and ribonuclease H, have been shown to be sensitive to some of these compounds.

Group III: nucleotides and analogs

Integrase is not known to utilize nucleotides during integration, but integrase can bind free nucleotides and nucleotide analogs *in vitro* [132]. The bound nucleotides and analogs can be crosslinked to integrase, and the crosslinked forms are defective for enzymatic activity [132]. Furthermore, all of the phosphorylated derivatives of azidothymidine inhibit the 3'-processing and strand joining activities of HIV-1 integrase with IC_{50} values in the 100 μM range, and act through the catalytic domain of the protein [133].

These data suggest a nucleotide binding site is present in HIV-1 integrase. Interestingly, the secondary structural elements present in the integrase core domain are related to nucleotide-binding domains of several ATPases [74,134]. Perhaps nucleotide binding by HIV-1 integrase is the result of an evolutionary relationship between proteins catalyzing polynucleotidyl transfer and phosphoryl transfer from nucleotide substrates.

Group IV: other compounds

Inhibition by the compounds in group IV may result from binding directly to the integrase protein. Some of these compounds have been observed to act on the catalytic core domain alone [124,135–137]. Within this group, only the bis-catechol beta-conidendrol has demonstrated some specificity for integrase inhibition *in vitro*; however, this compound fails to demonstrate antiviral activity in cell culture [125].

Structure–activity analyses of inhibition by the flavones and bis-catechols suggest that inhibitory potential is determined by the number and arrangement of hydroxyl groups on planar ring structures [124,125,138]. Fesen *et al.* [124] have suggested that the planar ring structure may interfere with integrase activity by binding to enzyme–DNA complexes through stacking interactions with adenine or guanine bases in the DNA at the active site of the protein, or by competing with purine moieties for binding to sites on the enzyme. Similarities to purine nucleotide structure suggest that these compounds may bind to the same sites on the enzyme as the nucleotide inhibitors. It will be interesting to see whether these design principles can be extended to develop clinically useful integrase inhibitors.

Also included in group IV is a hexameric peptide isolated from a large library of hexamers [137]. This inhibitory peptide is not itself likely to be useful as an antiretroviral agent, but this study does demonstrate that it is possible to isolate integrase inhibitors from a large pool of synthetically generated molecules. Similarly, randomly generated RNA molecules have been selected for high-affinity binding to integrase [139]. Strategies based on such 'combinatorial chemistry' are among the most promising new routes to inhibitor development.

In recent studies from our group, we have found that data on the potency of inhibitors against purified integrase does not reliably predict the potency of inhibitors against preintegration complexes (unpublished data). Furthermore, many compounds that are relatively potent inhibitors of purified integrase are altogether inactive against preintegration complexes. It may be useful in the future to incorporate assays of preintegration complexes in future screens for integrase inhibitors.

Perspectives

Each insight into the function of the retroviral integration system leads to new questions. The integrase protein has been identified as a key component of the viral integration system, but the importance of other players is still being assessed. In particular, the role of host proteins in the preintegration complex is a fertile area for further investigation. Much has been learned about the function of integrase protein, including the structure of two independent domains, but how these domains assemble and act together is unknown. The nature of the active multimer is unknown, as is the arrangement of the DNA substrates in the active multimer. The covalent chemistry of integration is mediated by a single step transesterification, but the mechanism of catalysis is largely unstudied. Further structural and kinetic studies may offer a route to investigate this issue. Ultimately, studies of preintegration complexes and studies of purified components may converge to provide a picture of preintegration complex function at atomic resolution.

Further questions focus on target site selection. What exactly is the nature of the DNA distortion that promotes integration? What chromosomal features favor or disfavor integration *in vivo*? Can integration site selection be controlled *in vivo* using integrase fusions to carry out more advanced forms of gene therapy?

Other questions surround the development of integration inhibitors. Most of the known inhibitors are not adequately specific, and none of the inhibitors reported to date are highly active against HIV in cell culture. It remains to be seen whether any of the known inhibitors will be useful as lead compounds in developing effective drugs. The structure of the catalytic domain may help in structure-based design, although unfortunately a key part of the active site is disordered in the available structure. This region is ordered in the RSV structure, possibly allowing the organization of the HIV active site to be inferred. In the search for integration inhibitors effective *in vivo*, it may be useful to make increased use of assays based on preintegration complexes rather than purified integrase, since assays of the two yield different results.

Given the pace of basic research on HIV DNA integration, it seems likely that effective integrase inhibitors will ultimately be identified.

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