Retroviruses can cause diseases such as AIDS, leukemia, and tumors, but are also used as vectors for human gene therapy. All retroviruses, except foamy viruses, package two copies of unspliced genomic RNA into their progeny viruses. Understanding the molecular mechanisms of retroviral genome packaging will aid the design of new anti-retroviral drugs targeting the packaging process and improve the efficacy of retroviral vectors. Retroviral genomes have to be specifically recognized by the cognate nucleocapsid domain of the Gag polyprotein from among an excess of cellular and spliced viral mRNA. Extensive virological and structural studies have revealed how retroviral genomic RNA is selectively packaged into the viral particles. The genomic area responsible for the packaging is generally located in the 5′ untranslated region (5′ UTR), and contains dimerization site(s). Recent studies have shown that retroviral genome packaging is modulated by structural changes of RNA at the 5′ UTR accompanied by the dimerization. In this review, we focus on three representative retroviruses, Moloney murine leukemia virus, human immunodeficiency virus type 1 and 2, and describe the molecular mechanism of retroviral genome packaging.

Keywords: retrovirus, genome, RNA, NC, structure, dimerization, packaging

INTRODUCTION

Retroviruses belong to a diverse family of RNA viruses causing various diseases, such as leukemia, tumors, demyelination disease, and AIDS. One unique feature of retroviruses is their integration of reverse transcribed genome into the host chromosome as a provirus. Some retroviruses have been engineered to function as vectors for the delivery of corrective human genes, and vectors derived from the Moloney murine leukemia virus (MoMLV) have been used for the treatment of severe combined immunodeficiency (Nelson et al., 2003). An understanding of the molecular mechanism for retroviral replication is needed for the development of anti-retroviral therapies as well as retroviral vectors.

All retroviruses, except foamy viruses, package two copies of full-length genomic RNA into progeny viruses, the genomic RNA having to be specifically selected from among a large amount of spliced viral and cellular RNA (Figure 1; Berkowitz et al., 1996). Virological and genetic studies have shown that the specific packaging of retroviral genomic RNA is mediated via interaction with the nucleocapsid (NC) domain of the Gag polyprotein (Rein, 1994; Berkowitz et al., 1996; Jewell and Mansky, 2000; Greatorex, 2004; Paillart et al., 2004b; Russell et al., 2004). Retroviral NC domains are generally highly basic and contain one or two zinc knuckle motifs composed of C–C–H–C arrays (Henderson et al., 1981; Summers et al., 1990; Kodera et al., 1998; D’Souza and Summers, 2004; Matsui et al., 2007). The zinc knuckles form a metal-coordinating “reverse turn” stabilized by NH–S hydrogen bonds. Most retroviral zinc knuckles contain a hydrophobic cleft on the surface of the mini globular domain, recognizing specific structures of RNA or DNA. The basic N- and C-terminal tails of NC domains are conformationally labile (Summers et al., 1992).

Retroviral genomes are known to be non-covalently dimerized in progeny virions (Rizvi and Panganiban, 1993). The region responsible for retroviral genome packaging is generally located between the splice donor (SD) site and the gag start codon in the 5′ leader region (Watanabe and Temin, 1982; Mann and Baltimore, 1985; Lever et al., 1989; Mansky et al., 1995; Kaye and Lever, 1999; Browning et al., 2003; Mustafa et al., 2004). Interestingly, the packaging signal generally overlaps with the site of dimerization (Paillart et al., 1996, 2004a; Greatorex, 2004; Hibbert et al., 2004), implying that the packaging event is coupled with genome dimerization (Russell et al., 2004). Inhibition of genome dimerization by deletion or insertion mutations at dimer initiation sites (DIS) causes a drastic reduction in genome packaging (Berkhout, 1996; Paillart et al., 1996; Laughrea et al., 1997; McBride and Panganiban, 1997). Moreover, studies with mutant viruses containing two 5′ untranslated region (UTR) packaged monomeric genome, indicate that genome packaging is achieved by the interaction of two 5′ UTRs (Sakuragi et al., 2001, 2002). Experiments with MoMLV have indicated that the conformational change induced by genome dimerization causes the exposure of NC-binding sites (D’Souza and Summers, 2004). A recent study also indicated that human immunodeficiency virus type 1 (HIV-1) employs a similar strategy for genome packaging (Lu et al., 2011a). In addition, several structures have been determined among complexes of NC and RNA fragments functioning in genome packaging, which provide the molecular mechanism for retroviral genome recognition of NC at the atomic level. In this review, we describe the molecular mechanisms of retroviral genome packaging.
Miyazaki et al. Retroviral genome packaging

FIGURE 1 | Illustration showing retroviral genome packaging events. The retroviral genomic RNA is exported from the nucleus to cytoplasm and used as the mRNA for ribosomal synthesis of the Gag and Gag–Pol polyproteins. (A) The retroviral genomic RNA promotes conversion of the dimeric form of genomic RNA via the NC domain of Gag. (B) The Gag and retroviral genomic RNA complex is transported to the plasma membrane, where further assembly and budding occur, mediated by the myristoylated MA domain of Gag. (C) In contrast, spliced viral RNA or cellular RNA is not bound to the NC domain of Gag or may be bound to a small number of Gag polyproteins insufficient for trafficking to the plasma membrane.

MOLONEY MURINE LEUKEMIA VIRUS

Moloney murine leukemia virus is a simple prototypical retrovirus, with a single splicing event producing a spliced RNA for synthesizing Env during its life cycle. MoMLV is one of the most extensively studied retroviruses. Nucleotides 215–565 of the 5′ UTR have been identified as a responsible site for genome packaging (Ψ-site; Mann et al., 1983). The secondary structure of the 5′ UTR was determined by RNase protection assays using cross-linking reagents combined with computational analyses such as phylogenetic and free-energy calculations (Tounecki et al., 1992; Mougel et al., 1993). The monomeric Ψ-site is composed of a series of RNA stem-loops. Differences in RNase protection patterns were observed for the dimeric Ψ-site (Tounecki et al., 1992; Mougel et al., 1993; D’Souza and Summers, 2005). It was reported that a dimerized RNA fragment containing the entire Ψ-site was bound to a significant number of NCs (Miyazaki et al., 2010a). Meanwhile, a mutant RNA fragment that inhibited dimerization was bound to a few NCs. Thus, dimerization-dependent genome packaging is strongly indicated in MoMLV.

The minimum region sufficient for genome packaging is referred to as the core encapsidation signal (ΨCES), though a virus containing only ΨCES exhibits less efficient packaging than a virus containing the entire Ψ-site (Bender et al., 1987; Adam and Miller, 1988; Murphy and Goff, 1989; Mougel and Barklis, 1997; Yu et al., 2000). ΨCES consists of three RNA stem-loops (DIS-2, SL-C, and SL-D, see Figures 2A,B). DIS-2 harbors a palindromic sequence and is able to convert heterologous extended dimers. The structure of NC in a complex with a mutant RNA of ΨCES mimicking the dimer-like conformation was determined by nuclear magnetic resonance (NMR) spectroscopy (Figures 2C,D; D’Souza and Summers, 2004). UAUCUG residues sequestered by base-pairing in the monomeric conformation are exposed as a linker by dimerization. NC recognizes the UCUG sequence. NC is a highly basic protein, consisting of a zinc knuckle motif and labile tails in both the N- and C-terminus. Biophysical study indicated that NC specifically recognizes RNA fragments including a Py (C or U) – Py-Py-G sequence (Dey et al., 2005). The interface of NC–UCUC is complementary in both shape and charge (D’Souza and Summers, 2004; Dey et al., 2005). The guanosine base attaches to the deep hydrophobic pocket of the zinc knuckle via hydrophobic and hydrogen bonds. The three upstream nucleotides make contact with hydrophobic residues on the surface of the zinc knuckle.

SL-C and SL-D, which are part of ΨCES, promote genome packaging (Mougel et al., 1996; Mougel and Barklis, 1997; Fisher and Goff, 1998). Both are highly conserved among gammaretroviruses and contain GACG loops (Konings et al., 1992; Kim and Tinoco, 2000; D’Souza et al., 2001). A stem loop RNA fragment containing the GACG tetra-loop has a unique property (Kim and Tinoco, 2000). The C and G (5′) residues of the loop undergo intermolecular base-pairing (kissing interactions). This property of the stem loop containing GACG has led to speculation that SL-C and SL-D function in genome dimerization (Kim and Tinoco, 2000; D’Souza et al., 2001; Hibbert et al., 2004). Interestingly, the RNA fragment of SL-C forms two alternative conformations (one containing the GACG tetra-loop and the other, a CGAGU loop; Miyazaki et al., 2010b). NMR data showed that SL–CD was in a state of equilibrium between kissing and non-kissing interactions even at a high sample concentration and physiological ion-strength. The two alternative conformations of SL-C may regulate genome dimerization though the biological meaning of this is not yet clear.
The tertiary structure of a RNA fragment of a SL–CD mutant locking to form a single conformation containing the GACG tetra-loop was determined by NMR spectroscopy and confirmed by Cryo-electron tomography (Miyazaki et al., 2010b). The structure revealed that SL–CD is dimerized by intermolecular cross-kissing (SL-C to SL-D’ and SL-D to SL-C’). These intermolecular cross-kissing interactions were also proposed based on selective 2’-Hydroxyl acylation analyzed by primer extension (SHAPE; Gherghe and Weeks, 2006; Gherghe et al., 2010). In addition, SL-C and SL-D stack end to end. Consequently, the two residues at the 5’-end of the SL–CD dimer are separated by ~20 Å. There are two UCUG sequences just upstream of SL-C. The intermolecular kissing interactions of SL-C and SL-D induce the proximity of four of the NC-binding sites. The genomic RNA has been suggested to promote the retroviral Gag/Gag interaction (Dawson and Yu, 1998; Burniston et al., 1999; Campbell and Rein, 1999; Cimarelli et al., 2000; Sandefur et al., 2000; Khochid et al., 2002; Huseby et al., 2005). Both the DIS DIS-1 and DIS-2 are followed by two UCUG elements. The abundance and proximity of exposed UCUG and related elements within the dimeric 5’ UTR may facilitate Gag–Gag interactions (Figure 2E).

Of note, a totally different monomeric structure for a portion of the Ψ-site (nucleotides 205–374) was proposed based on SHAPE (Gherghe and Weeks, 2006), where the RNA region spanning nucleotides 231–315 forms a large stem-loop structure, which contains residues corresponding to DIS-2. SL-C also differed from

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**FIGURE 2** (A) Genomic organization of MoMLV. (B) Secondary structure of the core encapsidation signal (ΨCES). Dimerization of DIS-2 induces a frame shift, exposing a UCUG element as a linker. (C) Secondary structure of mutant ΨCES that mimics the dimer-like conformation. (D) The complex of NC and mutant ΨCES. (E) Hypothetical mechanism for the genome packaging of MoMuLV. Upon dimerization, SL–CD exhibits a cross-kissing interaction, promoting the proximity of NC-binding sites. The SL–CD dimer functions as a scaffold that facilitates the Gag–Gag interaction. The ribonucleoprotein complex is transported to the plasma membrane. Reprinted with permission from (A–D): D’Souza and Summers, 2004; (E): Miyazaki et al., 2010b.
Virological studies have indicated the HIV-1 5′ or destabilization of the stem of McBride and Panganiban, 1997). This indicates that the stem-loop Panganiban, 1996, 1997; Clever and Parslow, 1997; Harrison et al., including the entire 5′ of secondary structural models for the 5′ addition, the residues of AUG form base-pairs with the residues (Huthoff and Berkhout, 2001). In this conformation of the 5′ leader RNA, a small number of NCs are capable of binding the 5′ leader RNA. In contrast, the interaction of AUG with US residues promotes genome dimerization via exposure of DIS (center). In this conformation of the 5′ leader RNA, a greater number of NCs are capable of binding the 5′ leader RNA. The different RNA elements in the 5′ leader region are color coded: DIS (red), SD (blue), Ψ (orange), and AUG (green).

**HUMAN IMMUNODEFICIENCY VIRUS TYPE 1**

Virological studies have indicated the HIV-1 5′ leader region including the entire 5′ UTR and a portion of the gag coding region to be involved in genome packaging (Lever et al., 1989; Aldovini and Young, 1990; Clavel and Orenstein, 1990; Poznansky et al., 1991; Buchsacher and Panganiban, 1992; Kim et al., 1994; Luban and Goff, 1994; Parolin et al., 1994; Berkowitz et al., 1995; McBride and Panganiban, 1996, 1997; McBride et al., 1997; Harrison et al., 1998; Helga-Maria et al., 1999; Clever et al., 2002; Russell et al., 2002; Sakuragi et al., 2003, 2007). The 5′ leader RNA consists of a series of RNA stem-loops referred to as the transacting responsive element (TAR), primer-binding site (PBS), polyadenylation signal [poly(A)], DIS, SD, and residues spanning the gag start codon (AUG; Figure 3; Hayashi et al., 1992, 1993; Baudin et al., 1993; Skripkin et al., 1994; Clever et al., 1995; McBride and Panganiban, 1996, 1997; Clever and Parslow, 1997; Harrison et al., 1998; Damaarda et al., 2004; Wilkinson et al., 2008; Watts et al., 2009). It has been suggested that an RNA fragment of the 5′ leader RNA has two alternative conformations, whose secondary structure has been determined by chemical probing assays (Berkhout and van Wamel, 2000). One conformation is referred to as the long distance interaction (LDI) structure, in which the residues of DIS are base-paired with those of poly(A) and SD. The other conformation is referred to as the branched multiple hairpin structure (BMH), in which the residues of DIS, SD, and Ψ form a stem-loop structure as indicated before (Huthoff and Berkhout, 2001). In addition, the residues of AUG form base-pairs with the residues of the unique 5′ region (US). Of note, it has been proposed a lot of secondary structural models for the 5′ leader (Lu et al., 2011b). NC catalyzes LDI to BMH. DIS is exposed as a stem-loop in BMH, which promotes the kissing dimer conformation and following the genome packaging event. However, the BMH structure is mostly observed in HIV-1-infected cells, but the LDI structure fails to be detected (Paillart et al., 2004a). Thus, the biological significance of the BMH/LDI riboswitch model remains to be elucidated.

RNA fragments of DIS, SD, Ψ, and AUG have been studied extensively since the region from DIS to AUG was initially identified as a Ψ-site (Lever et al., 1989; Aldovini and Young, 1990; Clavel and Orenstein, 1990; Poznansky et al., 1991; Harrison and Lever, 1992; Kim et al., 1994; McBride and Panganiban, 1996, 1997; Harrison et al., 1998). The RNA fragments of SD and Ψ are bound to NC with high affinity (Clever et al., 1995; Amarasinghe et al., 2000a,b), whereas the RNA fragments of DIS and AUG are bound to NC with relatively low affinity (Darlix et al., 1990; Amarasinghe et al., 2001; Lawrence et al., 2003). The RNA fragment of Ψ is bound to NC with the highest affinity (Kd = 100 nM) among these four RNA fragments (Amarasinghe et al., 2000b). Deletion or destabilization of the stem of Ψ results in a significant reduction in genome packaging efficiency (Clever and Parslow, 1997; McBride and Panganiban, 1997). This indicates that the stem-loop structure of Ψ is important for genome packaging. Ψ consists of a GGAG tetra-loop and a stem. The structure of the ribonucleoprotein complex NC–Ψ has been determined by NMR spectroscopy. Guanosine residues of the GGAG tetra-loop are inserted into the hydrophobic clefts of both the N- and C-terminal zinc knuckles (De Guzman et al., 1998). The adenosine residue of the loop packs against the N-terminal zinc knuckle and an N-terminal alpha-helix domain binds to the major groove of the RNA stem. Thus, overall, NC residues are involved in binding with Ψ RNA, by which the tight binding of NC–Ψ is achieved. In addition, the intramolecular interaction of two zinc knuckles may help to stabilize the complex of NC and Ψ RNA.

The RNA fragment of SD is also bound to NC with high affinity though the binding is slightly weaker than that of Ψ (Amarasinghe et al., 2000a). SD RNA contains a GGUUG tetra-loop and a stem containing a characteristic AUA triple base-pairing structure. All guanosine residues of the loop inserted into the hydrophobic clefts of zinc knuckles as observed in the complex of NC and Ψ RNA. A major structural difference between the NC and SD RNA complex and the NC and Ψ RNA complex is the orientation of the N-terminal alpha-helix domain of NC. The domain does not stick into SD RNA and is exposed outside of SD RNA. The N-terminal zinc knuckle interacts with an AUA triple base-pairing motif in the minor groove of the SD RNA stem. A mutant virus with a disrupted lower stem structure of SD exhibited a 20% reduction in genome packaging compared with the wild-type virus, despite the robust binding of Ψ RNA and NC (McBride and Panganiban,
Further study will be needed to clarify the link between the tight binding of SD RNA with NC and its biological relevance.

Dimer initiation site contains a GC-rich palindromic sequence and an inner bulge (G-AGG) in the middle of the stem. This inner bulge is recognized by NC. As described above, guanosine residues not in base-pairs possibly play an important role in the binding to NC (Mihailescu and Marino, 2004). However, the binding affinity of NC–DIS is relatively weak (approximately five times weaker than that of NC–SD/Ψ; Lawrence et al., 2003). NC catalyzes the conversion of DIS from a kissing dimer to a more stable extended duplex conformation (Darlix et al., 1990; Feng et al., 1996). Virological studies have suggested that interaction between the two 5′ UTR is required for genome packaging (Sakuragi et al., 2001, 2002). A very recent study indicated that genome dimerization is controlled by a unique strategy (Figure 3B). RNA containing the entire 5′ UTR and the first 21 residues of the gag coding region forms two alternative conformations (Lu et al., 2011a). In one conformation, DIS is sequestered via a long range interaction with U5, which inhibits genome dimerization. In the other conformation, DIS is exposed by release from the interaction with U5, which promotes genome dimerization.

AUG was believed to form a stem-loop structure, consisting of a GAGA tetra-loop and an unstable short stem containing two wobble G–U base-pairs (Amarasinghe et al., 2001). The GAGA tetra-loop is a type of GNRA (N is A, C, G, or U; R is A or G) tetra-loop, which is frequently observed in ribosomal RNA. GNRA tetra-loop helps fold stem-loops, and one Watson–Crick base-pair is enough to close off the RNA fragment. However, it has been suggested that AUG does not form a stem-loop structure and a portion of the residues of AUG may have a long range interaction with the residues of U5 as indicated in the BMH structure (Abbink et al., 2008). In one conformation, DIS is sequestered via a long range interaction with U5, which inhibits genome dimerization. In the other conformation, DIS is exposed by release from the interaction with U5, which promotes genome dimerization.

Ψ forms two alternative conformations. One is a stem-loop conformation as initially suggested. The other is a globular structure than HIV-1 NC. These structural differences of NCS between HIV-1 and HIV-2 may affect RNA recognition.

It has been suggested that Ψ-3 can be bound to NC (Tsukahara et al., 1996; Damgaard et al., 1998). A study using RNase protection assays suggested that the NC–Ψ-3 ribonucleoprotein exhibited strong protection at the loop of Ψ-3. This was supported by NMR experiments. The guanosine residue of the UUAGAC loop is inserted into the hydrophobic cleft of the C-terminal zinc knuckle (Matsui et al., 2009). The N-terminal domain of HIV-1 NC forms an alpha-helix, whereas that of HIV-2 NC is too short to do so. Another difference is the intra-molecular interaction of two zinc knuckles of HIV-2 NC, by which HIV-2 NC forms a more globular structure than HIV-1 NC. These structural differences of NCS between HIV-1 and HIV-2 may affect RNA recognition.

It is suggested that the HIV-1 genome's dimerization and packaging are controlled by dynamic changes of the 5′ leader's conformation as indicated in MoMLV (D’Souza and Summers, 2004; Miyazaki et al., 2010a; Lu et al., 2011a). Ψ is indicated to be important for genome packaging, however, it is not clear how Ψ works in the model suggested by Lu et al. (2011a). This will be the next question to answer for a better understanding of the molecular mechanism of HIV-1 genome packaging.
FIGURE 4 | (A) Genomic organization of HIV-2. (B) Representative secondary structures predicted for the 5′ UTR of HIV-2. Variations among recent predictions for AUG (green) are shown. The residues of AUG have been suggested to form a stem-loop structure and show long range interaction with the residues of U5. It has been suggested that HIV-2 genome's dimerization is employed the same mechanism as HIV-1. However, it remains to be clear whether NC preferentially binds the 5′ leader RNA containing the U5–AUG interaction.

studies, however, indicated that HIV-2 genome packaging is primarily mediated by trans packaging mechanism (Ni et al., 2011). TAR contains a palindromic sequence and has been suggested to form a dimer (Berkhout et al., 1993; Andersen et al., 2004). The dimerization of TAR may also function for efficient genome packaging. Further study will be needed to determine how the RNA elements located upstream of SD are involved in genome packaging.

Despite significant differences in the recognition of NC by the 5′ leader RNA, HIV-1, and HIV-2 may employ similar mechanisms for genome packaging. Dirac et al. (2002) observed that the RNA fragment of the 5′ leader region forms two alternative conformations as observed for the HIV-1 RNA fragments of the 5′ leader region. The long range interaction of U5–AUG is observed for the BMH conformation though it is not clear whether the LD1/BMH riboswitch mechanism is utilized for genome packaging in vivo. Recent study also indicated the U5–AUG interaction by SHAPE analysis (Purzycka et al., 2011). Of note, it is suggested that the U5–AUG interaction regulates the HIV-2 genome dimerization as indicated in HIV-1 (Baig et al., 2008). Lu et al. (2011a) suggest that the 5′ leader RNA containing the U5–AUG interaction of HIV-1 is preferentially bound to the cognate NC. A major question is whether the U5–AUG interaction of HIV-2 also promotes the NC-binding to the 5′ leader RNA (Figure 4B).

Phylogenetic and computational analyses suggested that the U5–AUG long range interaction is widely conserved among retroviruses (Damgaard et al., 2004). The long range interaction of U5–AUG may be important for retroviral genome dimerization and genome packaging.

PERSPECTIVES

It has been indicated that the MoMLV NC domain of Gag binds predominantly to dimeric genomes (D’Souza and Summers, 2004; Miyazaki et al., 2010a). HIV-1 was indicated to have a similar system (Lu et al., 2011a). MoMLV showed proximal NC-binding motifs in ΨCES, implying that Gag–Gag multimerization is initiated by genomic RNA (Miyazaki et al., 2010b). A major question is whether the proximity of NC-binding motifs is observed for other retroviruses such as HIV-1 and HIV-2. In addition, is the proximity of NC-binding motifs essential for retroviral genome packaging? Further study for these questions will lead to a better understanding for the molecular mechanism underlying retroviral genome packaging.

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