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Reviewer # 02254242

The review manuscript "The multifunctional facets of retrovirus integrase" (Manuscript 20150512231259), submitted by Grandgenett, et al., presents a strong summary of retroviral and lentiviral integrase (IN) function. Overall, the review is well written and the organization is easy to follow. The authors have written a review that is accessible to a wide audience and provides much information about the roles of integrase during the retrovirus life cycle. The authors should consider the following minor points:

1. The review focuses on the multifaceted roles of IN in the retrovirus life cycle, so the places where IN is implicated should appear in Figure 1 to emphasize those roles.

In the introduction section, we now describe specific details for IN in Figure 1 (first paragraph of page 4). We now clearly identify which steps (with corresponding number in Fig. 1) that IN has a role in the retrovirus life cycle.

In the manuscript, all changes have been highlighted in yellow.

2. Figure 2. The last sentence states that, "The exact MLV domain sizes are not structurally known". The authors should indicate why the domain sizes are not well defined.

We changed the sentence to read "The exact MLV domain sizes have not been determined experimentally except for the CTD[99] ". A reference has also been added to credit this very recent work.

3. The section "Structures of IN" is better titled as "IN Domains" or "IN Domain Organization", because actual three dimensional structures are discussed later in the review.

The section was modified to "IN Domain Organization"

4. Page 5 bottom paragraph (now top of page 6). The description of "specific mutations" does not say what or where the mutations are located in the HIV IN. For example, are those naturally observed mutations or site specific mutations?

We changed the sentence to read "Site-directed"….

5. Page 6 (now page 7, 2nd paragraph), more correctly, "Whole genomic sequencing…demonstrates…"

Corrected as requested.

6. Page 7, "…highly suggested…" either suggested or indicated.

Corrected as requested.

7. Page 9 (top of page 10), "…is bended…" could be "…is bent…".

Corrected as requested.

8. Page 10 and references. Reference 68 is not on a separate line, but is found in the paragraph for Reference 67.

Corrected

Reviewer #02615858

The authors briefly reviewed the multifaceted biological roles of retrovirus integrase (IN), summarizing the structure/function evidences of this family protein with special emphasis on its use as a target for human therapy. Relevant information is appropriately evaluated and the conclusions are convincingly supported by data presentation and analysis. Minor concerns and suggestions are provided below.

1. Abstract, line 3. "CA sequence" is suggested for better understanding.

Corrected as requested.

2. The title of the section "Structures of IN" (Page 4) should be modified to avoid misleading interpretations; this section refers only to the domain organization of IN proteins.

The section title was changed to "IN Domain Organization"

3. Page 5, 3rd paragraph, first two lines. The sentence is not correct. The Gag-Pol precursor polyprotein (or any polyprotein or even a protein) does not have a 3′ end.

We changed 3′ end to "C-terminal end"

4. Page 5, 3rd paragraph, lines 2-3. "The processing of…" is (not are) "different between…".

Corrected as requested.

5. Page 6, last paragraph. Please define MA and Vpr, and quote reference/s for PIC composition and sedimentation coefficient.

We defined MA and Vpr in the text (now page 7). The references to the PIC composition were references 22 to 27. We removed the sedimentation coefficient (S260) from the text.

6. Page 7, 3rd paragraph, lines 3-5. For HIV infection? It is not clear what it is meant.

We changes "important determinant for HIV infection" to "important for HIV integration site selection" . This will clarify the statement (now top of page 7).

7. Section "Solution properties of IN" (Page 8). The significance of the oligomeric state of IN for its function should be stressed.

We added a single sentence as a separate paragraph at the end of the section to stress the significance of the oligomeric state of IN (now top of page 9). The sentence is-

"In summary, the oligomeric state of retrovirus IN play key roles in virus maturation upon release of the virus particle, stabilization of the cytoplasmic PIC and enzymatic activities for 3' OH processing and concerted integration of viral DNA".

8. Page 10 (now page 11, second paragraph), second to last line. Please define ODN.

We inserted "oligonucleotide" for clarification of ODN.

9. Legend to Figure 4. Please indicate which viral and cellular proteins are represented in this figure.

Only IN (labeled), RT (blue circles) and LEDGF/p75 (gray cylinder) are identified in the figure.

10. Legend to Figures 6 and 8. The program used to redraw the PFV intasome and the active site structures, respectively, should be indicated.

We now indicated what program was used in both Figures 6 and 8.