

Dear Editor,

Enclosed please find our response to the reviewers' comments. We find these comments to be insightful and constructive. Below please find our point-to-point response to the reviewer's comments.

Reviewer 00698952

1) *"To explain briefly but clearly the genome-wide chromosomal-capture methodologies: 3C, 4C, 5C and Hi-C. The reference in the main text to Fig. 2 has not illuminated the matter"*.

- a. **We have generated a new Figure 2 to illustrate the key steps of the five different chromosomal-capture protocols, which include 3C, 4C, 5C, Hi-C and ChIA-PET. The legend for Figure 2 has also been expanded to describe these key steps.**

2) *"Annotation of the figures requires further work.*

"Fig. 1: What do the green and orange boxes mean? Why the chromatin tethered to the nuclear envelope has a different colour from the rest?"

- a. **The meaning of green and orange boxes has been indicated in the revised legend. The color of chromatin fiber has also been changed so that they are identical.**

"Fig. 2: How does the figure encompass 2 protocols?"

- a. **We have generated a new Figure 2 to illustrate the key steps of the five different chromosomal-capture protocols, which include 3C, 4C, 5C, Hi-C and ChIA-PET. The legend for Figure 2 has also been expanded to describe these key steps.**

"Fig. 3B: What is Antp? What are 'FD' and 'F1/5'?"

- a. **The meanings of these acronyms have been added to the legend of Figure 3.**

3) *"The English is excellent for the most part of the article, but surprisingly not towards the end. A colon, for example, should not be used to truncate a sentence like '...function of genomic architecture are: ...' Is 'with' necessary between 'correlating' and 'them'? Is a preposition missing in 'could go a long way elucidating'?"*

- a. **The ending portion of the manuscript has been significantly revised to address reviewers' comments. The errors have been corrected.**

4) *"There are sporadic misspellings and errors in subject-verb agreement."*

- a. **We have checked the entire document to eliminate these errors.**

“For concern:

1) Fig. 2 is essentially identical to Fig. 1 of the paper by Stadhouders, et al., published in Nat Protoc. 2013 Mar;8(3):509-24. Is the similarity a problem in copyright?”

- a. **The revised Figure 2 now bears little overlap in scientific content to the Stadhouders et. al., 2013 figure except in elements of graphics. Nonetheless, we acknowledge Stadhouders et. al. to be the source of this adaptation.**

2) Fig. 3B is identical to Fig. 7D of the corresponding author’s paper in Mol Cell Biol. 2015 Dec; 35(23):4018-29. Have the authors obtained permission from the journal? Should the fact that the figure has been previously published be mentioned in the manuscript?”

- a. **We have obtained permission (purchased copyrights) for reusing parts of the figures in our previous Mol Cell Biol. paper in this WJBC mini review (see copyright statement in Figure 3 and enclosed copyright document). In addition, we now acknowledge this adaptation in the Figure 3 legend.**

Reviewer 02608938

“...minor comments.

1. The concept of development should appear in the abstract since the title, topic and data are relevant.”

- a. **We have added a sentence in the abstract to specify the temporal regulation of the SF1-tethered chromatin loops. The emphasis on development was also indicated at the end in the statement that chromatin architecture can “remodel the genomic environment to facilitate gene regulation during development.”**

2. What are mammalian genes relevant to these found in Drosophila described in this review? It is better to list these, at least some. 3. One additional editing seems necessary. For example, "deliver" in the abstract should be "delivering".

- a. **The only characterized dedicated architecture protein in the mammals is CTCF, which we discussed after the Introduction section. Similarly, we also reviewed the role of cohesin and condensin complexes in organizing chromatin loops. Drosophila is unique in its diversity of architectural proteins beyond dCTCF, cohesin and condensin.**

Reviewer 00467115

“...should work on the last part of their manuscript and provide not only a list of knowledge gaps, but also some critical views and testable hypotheses”

- a. In response, we have expanded this section to further elaborate the current gaps and potential future directions of study.**

“The author contributions are missing.”

- a. We have added an author contribution section.**

“Fig. 3 lacks a title. This figure is straight taken out of reference 27, without acknowledging this fact.”

- a. We have added a title to Figure 3. We have now obtained permission (purchased copyrights) for reusing parts of the figures in our previous Mol Cell Biol. Paper (Ref. 27) for this WJBC mini review (see copyright statement in Figure 3 and enclosed copyright document).**

Reviewer 00467115

This reviewer does not have comment for revision.

Dear Editor,

Sorry about the delay due to conferences and other commitments. Enclosed please find the doc file of the revised manuscript. According to the suggestions made by the Journal Editor-in-Chief, we have now added more critical views and testable hypothesis on the main paper discussed in the review (see page 8-9 of enclosed file). Together with the three major gaps of knowledge we pointed out in the previous submissions, the mini-review strongly emphasizes the deficiencies of the current studies in chromatin architecture field and provides both general and specific suggestion for future improvement. Given the limitation of the format, we feel it had provided a succinct and balanced summary of this sub-area of study. Thanks for considering this contribution.

Best regards,

Haini Cai