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Peer Review

Review of: "Nuclear Basket Proteins Mlp1 and Nup2 Drive Heat Shock–Induced 3D Genome Restructuring"

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This is a well-written and carefully executed study investigating the role of nuclear basket proteins Nup1, Nup145, Mlp1, and Nup2 in 3D genome reorganization during heat shock. The authors demonstrate that Mlp1 and Nup2 are specifically required for intra/inter chromosomal interactions and intragenic interactions, but not for NPC integrity, heat shock factor recruitment, or Hsf1 condensate formation. This finding highlights a distinct role of these nuclear basket proteins in chromatin organization during the heat shock response.

The manuscript presents a compelling set of experiments, but a few aspects require further clarification and additional data to strengthen the conclusions:

1. The first part of the study characterizes Nup1 and Nup145, yet their roles are not fully discussed in the later sections. A comparison of their involvement relative to Mlp1 and Nup2 would improve the manuscript's cohesiveness.
2. The authors stated that Nup1 and Nup145 are responsible for maintaining nuclear pore integrity. It would be interesting to see if the authors conduct a bulk transport experiment with NPS signal cargo to examine how the distribution of cargo substrates changes with heat shock and depletion, particularly by analyzing the cytoplasm-to-nucleus intensity ratio. As the authors stated, simultaneous depletion of Nup1 and Nup145 compromises NPC integrity and alters the localization of Nup2 and Mlp1, which may consequently affect transport activity. doi: 10.1534/genetics.111.127803 may provide insight to frame such an experiment.
3. The observed reduction in intra/inter chromosomal interactions in Mlp1/Nup2-depleted cells (Figure 4F-H) is a significant finding. However, validating these results by assessing the extent of colocalization using fluorescence microscopy would strengthen the conclusions. One point that

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remains unclear is how the authors distinguish between HSP104 and HSP12 in Figure 1B and C, given that both are tagged with GFP—is this differentiation solely based on intensity? Additionally, how do the authors account for the oligomerization of HSP12 upon heat shock, which may increase its intensity?

4. The study examines chromatin interactions at only three time points after heat shock. Extending this analysis to later points could reveal whether chromatin restructuring is sustained or transient in Mlp1/Nup2-depleted cells.

The remaining concerns have already been addressed by the other reviewer, so I will not reiterate them.

Declarations

Potential competing interests: No potential competing interests to declare.