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Pluripotency vs. Self-Renewal of ES Cells: Two Sides of The Same Coin or More?

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To The Editor

The study by Katano et al [1] reports the effect of Nanog and Esrrb in rescuing the loss-of-pluripotency phenotype of nucleostemin (NS)-depleted embryonic stem cells (ESC). This work is of immediate interest to my research focus on understanding the mechanism of self-renewal and the role of NS in this event [2-5]. It raises several fascinating points that speak generally on the issue of ESC state and thus warrants further discussion. First, is the pluripotency loss of NS-depleted ESC operated by a selective or instructive mechanism? In the selective model, NS loss causes cell death predominantly in pluripotent cells, thereby favoring the survival of cells exiting the pluripotent state. In the instructive model, NS loss disrupts the maintenance of pluripotency, which then leads to cell differentiation, or triggers cell cycle exit first, followed by cell differentiation. If the instructive mechanism is in play, the result would indeed indicate a pluripotent connection of NS to the downstream events of Nanog or Esrrb, which may act in serial or in parallel to these two factors. However, since the loss-of-pluripotency effect of NS depletion is invariably coupled with changes in cell death, slowed cell proliferation, and/or cell cycle exit, it is unclear which of the mechanisms (instructive vs. selective) is the event-driving force. Some scenarios, such as the selective or cell cycle exit one, may suggest an indirect link between NS and pluripotency. The key to resolve this issue resides in clone-based time-course analyses and depends on the lineage homogeneity of NS tet-off ESC.

Next, how important is the role of NS-mediated genome protection in the reduced survival of NS tet-off ESC? The authors propose a yet unidentified NS program that acts independently of RAD51 or genome protection and more critically for ESC survival. This argument is based on Fig. 6A-C. To dismiss the genomic damage effect of NSKO reported

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in other stem/progenitor and cancer cells [6-10] as a minor one in ESC, one needs better assays to detect DNA damage foci (*i.e.* a higher image resolution and wider list of DNA damage markers). Given the distinct culture characteristics of ESC vs. monolayer cells, the detached cell population should be included in this analysis as well. It is also worth noting that DNA damage is not a lone member in the category of late-appearing phenotypes (showing up 4 days post-Dox) in NS tet-off ESC. Almost all NS loss-related changes, including growth perturbation and pluripotency loss, do so in this model.

Third, should one expect RAD51 to perform sufficiently or necessarily in rescuing the self-renewal of NS tet-off ESC? Self-renewal is governed by a multitude of molecular events, and RAD51 is likely involved in the protection against replication-associated genomic damage only. Therefore restoring RAD51 expression will be quite different from that of Nanog or Esrrb in reversing a complex phenotype like self-renewal. The involvement of RAD51 in different aspects of self-renewal can and should be better understood by quantitative and time-control readout on DNA damage, cell death, and self-renewal, as opposed to a single snapshot of ALP signal. Finally, self-renewal and pluripotency are two distinct but overlapping properties of ESC. While some self-renewal events may not directly participate in pluripotency maintenance of ESC, their perturbation will likely prevent ESC from staying in the pluripotent state.

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