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RETINOIC ACID INDUCES STEM CELL PLURIPOTENCY FLUCTUATION THROUGH COORDINATED MOLECULAR NETWORK

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ESCs are derived from the inner cell mass (ICM) of blastocysts. When cultured in appropriate conditions, they retain their pluripotent state, with the ability to differentiate into nearly all cell types. This condition is characterized by multiple metastable states that fluctuate between self-renewal and differentiation balance, and display a heterogenous differentiation potential. One of these populations retains high pluripotency capacity and it is marked by expression of 2-cell-like (2C) stage genes such as Zscan4 and its dependent/associated targets that altogether define the Zscan4 metastate molecular signature. We demonstrated that RA is necessary for ESCs to 2C-like transition. We further investigated the molecular network underlying RA-mediated Zscan4 activation by employing reverse engineering in silico analysis and found, a novel molecular network that mediates Zscan4 intermediates transition. In particular, we showed that such program sets the transition of ESCs of 2C-like ground-state by means of the simultaneous expression of two members of Dux family: Dux and Duxbl1. Moreover, we demonstrate that Zscan4 cells are hallmarked by oxidative and adaptable metabolism, which would, on one hand, fulfil a higher bioenergetic demand and, on the other hand, provide intermediate metabolites for epigenetic reprogramming. Our findings pave the way to the possibility to control the metastable state of stem cells with practical applications in regenerative medicine.

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