Buffering meta-stable pluripotent states in embryonic stem cells

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Abstract

Self renewal of embryonic stem cells *in vitro* illustrates how a meta-stable, otherwise transitional, state of differentiation may be fixed in time and maintained indefinitely. The stability of the pluripotent state is governed by a transcriptional gene regulatory network, linking together core pluripotency transcription factors Oct4, Nanog, Sox2, Esrrb, Sall4 and many others. However, the exact topology of the pluripotency gene network and mechanisms of its functioning are not known. Developing theory explaining behavior of the core pluripotency network is essential for both theoretical and translational/medical science.

Based on analysis of gene expression and transcription factor binding data, a hierarchical organization has been proposed for the transcriptional gene network, controlling pluripotency state in mouse embryonic stem cells (mESC). Analysis of the network revealed several network motifs, which conform to structure of incoherent feed-forward loop (iFFL). One of the identified network motifs connects the core transcriptional regulators Oct4 and Nanog, occupying the top levels of transcriptional hierarchy (inputs), with transcription factor Sall4 at the bottom level of hierarchy (output). Recently published data suggested regulation of Oct4 by Sall4, thus emphasizing importance of a feedback control of the highest network levels (Oct4, Nanog) from the downstream components such as Sall4. Theoretical analysis of the identified iFFL with the feedback predicted buffering of the Oct4 concentration for an extremely wide range of the network model parameters, thus suggesting a possible mechanism of buffering pluripotency in mESC.

Analysis of gene expression in a large number of single embryonic stem cells grown under LIF-serum conditions revealed two major subpopulations of the pluripotent cells, presumably corresponding to two meta-stable pluripotency states. Theoretical scenarios describing interactions between the Oct4 Nanog and Sall4 in the context of iFFL with feedback fit well with the single cell gene expression data and consistent with effects observed in mutant mouse embryonic stem cells. Several network motifs have been detected, linking the core pluripotency factors in a way similar to the Oct4-Nanog-Sall4 loop, and perhaps, contributing to the buffering of the meta-stable pluripotency state as well.