Functional genomics of peri- and post-implantation stage stem cells

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Pioneered by the classical mouse embryonic stem cells (ESCs), various stem cell lines representing the peri- and post-implantation stages of embryogenesis have been established. To obtain insight into the gene regulatory network operating in these cells, we first investigated epiblast stem cells (EpiSCs), which are the immediate precursors of all somatic lineages. For this purpose, we performed ChIP-seq analysis for five major transcription factors (TFs) involved in epiblast regulation using biotinylated TFs.

A remarkable finding was that an alternating pattern of genomic domains of megabase scale exists, with those rich in ZIC2 ChIP-seq peaks and genes and those rich in POU3F1 peaks but sparse in genes. The distribution and overlap of individual ChIP-seq peaks indicated that ZIC2 and OTX2 form one group of functionally cooperating TFs in EpiSCs, whereas SOX2 and POU form a second group, which are consistent with the sequence motifs enriched in the TF-binding regions. The identified TF-binding regions, particularly those of overlapping TFs, likely participate in enhancer functions, as indicated by comparison with histone modification signatures.

The SOX2–POU5F1 TF pairs highlighted in mouse ESCs were not the major players in other stem cells. By analysis of the differences of SOX2- and POU5F1-binding genomic regions, the stem cell lines of the epiblastic lineage of peri- and post-implantation stages were arranged in the following developmental order: mouse ESCs, EpiLCs, human ESCs, and then EpiSCs. Despite these differences, several hundred genomic regions were invariably bound by SOX2 in all ESCs, EpiSCs, and neural progenitors and may play a major role in the regulation of somatic lineage development.

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