Sox2-dependent transcriptional control in neural stem cells in vitro and in vivo

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The Sox2 transcription factor is essential to preserve the pluripotent stem cells of the early embryo, and to reprogram them by reprogramming. Sox2 is also expressed in neural stem cells (NSC) in the developing central nervous system (CNS) and in neurogenic regions of the adult brain. In humans, Sox2 heterozygous mutation leads to a spectrum of CNS defects (involving eyes, hippocampus, seizures, motor control problems and intellectual disability).

We addressed Sox2 function in the CNS and in NSC by conditional mutagenesis in the mouse. By Sox2 ablation at mid-gestation (E11.5), we demonstrated that Sox2 plays a critical role for the maintenance of brain-derived NSC, in vitro long-term culture, and in vivo, in the postnatal hippocampus. By earlier Sox2 deletion with different Cre transgenes, we further found important defects of the developing ventral telencephalon, hippocampus primordium, cerebral cortex, thalamus and cerebellum, pointing to a stage- and region-specific requirement for Sox2 for the development of different, disease-relevant CNS regions.

We found that Sox2 is also required to maintain neural cancer stem cells, in a mouse model of high-grade oligodendroglioma: following Sox2 ablation, tumour cells lose proliferation and differentiate in vitro, and lose their tumor-initiating properties in vivo.

To understand Sox2 function, we are investigating Sox2 targets. Shh (encoding a cytokine), and Nkx2.1 (encoding a transcription factor, known regulator of Shh) are important regulators of ventral forebrain and hippocampal development, and we found they are regulated by Sox2. More recently, we used genomic approaches to compare normal and Sox2-ablated NSC, and we found an unexpected role for Sox2 in the maintenance of a global pattern of long-range interactions in chromatin, mediated by RNA pol II, by ChIA-PET analyses. Sox2-dependent long-range interaction “anchors” are highly enriched in Sox2 binding, and in epigenetic enhancer marks, and most contain new enhancers that guide expression of reporter transgenes to the forebrain in vivo.

Reduction of gene expression observed in mutant cells is accounted for by the loss of Sox2-mediated activation via promoter-enhancer interactions. Genes controlled by Sox2-dependent interactions also identify new mediators of Sox2 function, able to rescue the self-renewal defect of Sox2-ablated neural stem cells. They also include genes involved in Sox2-related human brain disease. Our results highlight the maintenance of long-range interactions as a new aspect of Sox2 function as a lineage-specific transcription factor, and give access to thousands of novel distal enhancers of potential relevance for brain development and disease, by the definition of their connectivity to specific target genes.

Friday
June 16th
h 17:00
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