"Mechanisms of iPS cell generation and beyond"

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The generation of induced pluripotent stem cells (iPSCs) achieved by overexpression of Oct4, Sox2, Klf4 and c-Myc, transformed our classical views of the cellular epigenetic landscape and delivered a new concept for cell and tissue engineering. In addition to iPSCs, several other cell types have also been generated by master transcription factor (TF)-mediated transdifferentiation. However, the critical molecular mechanisms amongst diverse cellular identity changes are not well understood. Through the investigation of reprogramming mechanisms, we recently revealed that over-expression of constitutive active Smad3 boosted not only iPSC generation, but also 3 other master TF-mediated conversions, from B cells to macrophages, myoblasts to adipocytes, and human fibroblasts to neurons. This demonstrated that there were common mechanisms underlying different master TF-mediated cell conversions. To illuminate such mechanisms further, we have recently performed CRISPR/Cas9-mediated genome-wide knockout screening during reprogramming with a lentiviral gRNA library containing 90,000 gRNAs. This screening provided us with ~15 novel reprogramming roadblock genes as well as ~20 candidate genes essential for the reprogramming process but not for ES cell self-renewal. This data set will be a valuable resource to further understand how overexpression of master TFs alters cellular identity, and to achieve more faithful, efficient cell conversions for regenerative medicine.