Epigenetics of reprogramming to induced pluripotency.

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Public Summary:
Studies of cell fate conversions experience a renaissance since Takahashi and Yamanaka's groundbreaking finding in 2006 describing the establishment of induced pluripotent stem cells (iPSCs) from differentiated cells, in vitro, by expression of a small set of transcription factors. The beauty of the iPSC technology lies in its simplicity and apparently unlimited power since virtually any cell type can be reprogrammed to pluripotency and subsequently be differentiated into desired cell types, yielding a powerful tool for the mechanistic dissection of cell fate conversions, disease modeling, as well as regenerative medicine. Improved reprogramming techniques in combination with genomic approaches, single cell studies, and genetic methods, have permitted a rapid progress in characterizing the reprogramming process. Here, we review current studies indicating that reprogramming is a step-wise process and that reprogramming factor binding, transcription and chromatin states change during reprogramming transitions. Particularly intriguing are findings that epigenetic priming events early in reprogramming are critical for the induction of pluripotency late in the process, comparable to developmental processes. Furthermore, chromatin and its regulators are important controllers of the process and contribute to reprogramming barriers. In addition, evidence is emerging that reprogramming factor levels, stoichiometry, and activity strongly influence the outcome of reprogramming. The improved mechanistic understanding enables the rational design of more efficient reprogramming strategies and novel reprogramming factor combinations, benefitting applications of iPSCs in the future. However, recent studies have also identified changes in the epigenetic state of the X chromosome in female iPSCs that warrant careful consideration before utilizing iPSCs.

Scientific Abstract:
Reprogramming to induced pluripotent stem cells (iPSCs) proceeds in a stepwise manner with reprogramming factor binding, transcription, and chromatin states changing during transitions. Evidence is emerging that epigenetic priming events early in the process may be critical for pluripotency induction later. Chromatin and its regulators are important controllers of reprogramming, and reprogramming factor levels, stoichiometry, and extracellular conditions influence the outcome. The rapid progress in characterizing reprogramming is benefiting applications of iPSCs and is already enabling the rational design of novel reprogramming factor cocktails. However, recent studies have also uncovered an epigenetic instability of the X chromosome in human iPSCs that warrants careful consideration.