

Unveiling the impact of epigenetic regulation in disease pathogenesis with iPS cell technology

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Stepwise epigenetic reorganization occurs during reprogramming of somatic cells into induced pluripotent stem cells. The faithful shutdown of the somatic program occurs in the early stage of reprogramming. Taking advantage of such properties of cellular reprogramming, we examined the effect of *in vivo* reprogramming on *Kras*-induced cancer development. We show that the transient expression of reprogramming factors in pancreatic acinar cells results in the transient repression of acinar cell enhancers, which are similarly observed in pancreatitis. We next demonstrate that *Kras* and *p53* mutations are insufficient to induce ERK signaling in the pancreas. Notably, the transient expression of reprogramming factors in *Kras* mutant mice is sufficient to induce pancreatic ductal adenocarcinoma. In contrast, the forced expression of acinar cell-related transcription factors inhibits the pancreatitis-induced activation of ERK signaling and development of precancerous lesions in *Kras*-mutated acinar cells. These results underscore a crucial role of dedifferentiation-associated epigenetic regulations in the initiation of pancreatic cancers. We propose that iPS cell technology could be a powerful tool to study the impact of epigenetic regulation in disease pathogenesis.