

## Epigenetic reprogramming of human skin fibroblasts into insulin secreting cells – Brief Communication

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The cells of an adult organism acquire their differentiated state through the epigenetic regulation of gene expression that leads to a progressive restriction in their options. Among the different mechanisms involved in lineage specification, DNA methylation plays a major role. Therefore, the use of a demethylating agent can be used to facilitate the transition of mature cells to a higher plasticity state and thus allow the direct conversion of an adult cell into another differentiated cell type. In our talk, we will describe the use of the DNA methyltransferase inhibitor 5-azacytidine (5-aza-CR) to revert fibroblasts from their lineage commitment to a more pluripotent state. We will show that the short exposure to the epigenetic modifier is enough to trigger a transient higher plasticity window in fibroblasts that can then be re-addressed towards the endoderm lineage and pancreatic differentiation. At the end of the

treatment, fibroblasts become pancreatic converted cells (PCC) that show an epithelial morphology, produce insulin, release the hormone in response to a physiological glucose challenge in vitro and are able to protect recipient mice against streptozotocin-induced diabetes, restoring normal processing of glucose. The conversion into pancreatic phenotype is obtained without any transgenic modification and avoids a stable pluripotent state which is unphysiological, inherently labile and makes cells prone to alterations. All these aspects, together with the easy accessibility of fibroblasts makes these cells excellent candidates for regenerative medicine and patient-specific cell therapy (*the authors performed the experiments with the support of Network Lombardo iPS (NetLiPS) Project ID 30190629 and are members of the COST Action FA1201 Epiconcept: Epigenetics and Periconception environment*).