Ph.D. Thesis abstract:

Diabetes mellitus is a chronic disease characterized by a metabolic disorder in which there is a low level or complete lack of the insulin. Diabetes mellitus type 1 (DM1) is caused by an autoimmune reaction leading to the destruction of the insulin producing beta cells in the pancreas. In consequence, low or non-existent insulin production leads to a complete dependence on exogenous insulin supplementation. DM1 causes serious long-term complications. Although strict control of blood sugar could prevent the onset and development of diabetic complications only 5% of diabetic patients are able to achieve such control. Hence it is evident that the current methods of treatment are neither sufficient to treat this disease, nor prevent late complications in most patients. The most promising therapeutic approach in the treatment of diabetes is the restoring of insulin production. One such method is the transplantation of insulin-producing tissue. However, a lack of available insulin-producing tissue limits such therapeutic approach. Therefore an alternative source of insulin producing cells have to be found to obtain a sufficient amount of safe and efficient insulin producing tissue.

Pancreatic stem/progenitor cells could represent such an available alternative source. Despite the evidence of permanent beta cell neogenesis during the adult life a putative pancreatic stem cell (PSC) has not yet been identified. With the aim to expend a list of available PSC markers we have focused on the characterization of pancreatic cell populations based on the expression of stem cell markers. In our work we have identified two new markers of adult pancreatic stem/progenitor cells which allow their isolation. Population of CXCR4 positive pancreatic cells express markers and transcription factors of pluripotent and adult stem cells. Upon in vitro differentiation CXCR4 positive pancreatic cells are able to differentiate into insulin producing cells. Similarly CD133 positive pancreatic cells also express transcription factors of pluripotent stem cells and are able to differentiate into insulin producing cells.

We have also focused on the role of phosphoinositide 3 kinase signaling pathway (PI3K) on beta-cells differentiation, in the attempt to improve the process of pancreatic stem/progenitor cells differentiation into beta-cells. We found that activation of PI3K significantly increase a number of beta-cells differentiated from adult pancreatic progenitor cells.
With the same aim we have also studied the effect of epigenetic factors on differentiation of adult pancreatic progenitor cells. We found that inhibition of DNA and histone methylation also improves the rate of differentiation into beta-cells.

Finally we have examined the potential of human umbilical cord blood cells (HUCB) to differentiate into insulin producing cells with the aim to evaluate their possible clinical application for the treatment of diabetes. We found that HUCB cells are able to differentiate into insulin producing cells upon irradiation of transplanted animals. However the number of insulin producing cells derived from HUCB was not significantly high.

In conclusion our results provide new information about pancreatic adult stem/progenitor cells, about their differentiation into insulin producing beta cells and also about suitability of HUCB cells for the treatment of diabetes