

## **In vivo GSK3 $\beta$ knockdown hastens endocrine and exocrine pancreatic regeneration in 90% pancreatectomized rats.**

**Jamileh MOVASSAT, Florence FIGEAC, Anissa ILIAS, Monique FARO and Bernard PORTHA**

### **Background and Aims**

The Wnt signaling pathway has been recently implicated in pancreas development as well as in beta cell biology. Glycogen synthase kinase 3  $\beta$  (GSK3  $\beta$ ), a pivotal partner of the Wnt signaling is a multifunctional enzyme that negatively regulates the growth and function of the beta cells. The aim of our study was to assess the impact of GSK3  $\beta$  downregulation on the stimulation of exocrine and endocrine regeneration after subtotal pancreatectomy in rat.

### **Methods:**

Adult Wistar rats underwent 90% pancreatectomy. In groups of pancreatectomized rats, either antisense oligonucleotides directed against GSK3  $\beta$  (AS-GSK3  $\beta$ ) or LiCl were injected directly within the remnant pancreatic tissue immediately after pancreatectomy. Two additional groups were administered with non specific standard oligonucleotides (Std group) or with saline and were used as control for the AS-GSK3  $\beta$  and LiCl treated groups respectively. Beta cell mass was assessed by morphometry 7 days and 4 weeks after pancreatectomy. Beta cell, ductal cells and acinar cell proliferation was measured by BrdU incorporation method 8h and 48h after surgery. Apoptosis was assessed in beta cells, ductal cells and acinar cells by the TUNEL method.

### **Results**

GSK3 $\beta$  down regulation via administration of LiCl or AS-GSK3  $\beta$  greatly improved the beta cell regeneration 7 days after surgery ( $p < 0.01$ ). Moreover the use of AS-GSK3  $\beta$  had sustained effect on the beta cell mass, since 4 weeks after surgery the beta cell mass in the remnant pancreas was found to be higher ( $p < 0.05$ ) in AS-GSK3  $\beta$  treated group compared to the Std treated group. The effect of GSK3  $\beta$  inactivation on the beta cell mass seemed to be mediated by the stimulation of beta cell proliferation. Regarding the exocrine pancreas, GSK3  $\beta$  knockdown significantly stimulated acinar cell proliferation. Interestingly, GSK3  $\beta$  inactivation reduced the number of apoptotic acinar cells compared to that found in the control Std group.

### **Conclusion**

Here we show that intra pancreatic in vivo knockdown of GSK3  $\beta$  promotes both endocrine and exocrine regeneration within the remnant pancreas and could have potential application in the treatment of diabetes and other pancreatic diseases such as pancreatitis.