Wt1 is involved in pancreas development and adult pancreatic homeostasis

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The embryonic mesothelium lining the visceral organs gives rise to mesenchymal cells through a localized epithelial-mesenchymal transition (EMT). This has been extensively studied in some cases, such as the heart, where the epicardium gives rise to epicardial-derived cells that contribute to the cardiac vascular and connective tissues. In other organs, such as the lungs, liver and gut, the developmental fate of the mesothelial-derived mesenchyme and their importance for visceral morphogenesis has also been demonstrated (reviewed in Ariza et al., *Dev Dyn*, 2016, 245:307-22).

Hepatic stellate cells (HSC) are located in the perisinusoidal space of the liver. It has been described that cells derived from the liver mesothelium through an EMT contributes to the HSC population and also to the sinusoidal endothelium during development (IJpenberg et al. *Dev Biol,* 2007, 312: 157–170; Asahina et al., *Hepatology*, 2011, 53:983-95). Thus, we checked is a similar developmental origin accounts for pancreatic stellate cells (PSC), a population of pancreatic stromal cells that share many features with HSC. In normal adult pancreas, PSC are quiescent, star-shaped cells with a periacinar distribution. When activated by profibrogenic stimuli such as inflammatory cytokines or oxidative stress, PSC transform into myofibroblast-like cells. Thus, PSC are the major source of extracellular matrix in the adult pancreas, but their embryonic origin remains unknown.

The Wilms' tumor suppressor gene (*Wt1*) is highly expressed in the embryonic mesothelium. For this reason, we have used two lines of transgenic mice for lineage tracing of mesothelial-derived cells, systemic ($Wt1^{Cre}$; $R26R^{EYFP}$), tamoxifen-inducible ($Wt1^{ERT2}$; $R26R^{EYFP}$) and we have also used the inducible driver for conditional deletion of *Wt1* ($Wt1^{ERT2}$; $Wt1^{flox}$) in adult mice.

Our results confirm that WT1 protein is only expressed in the mesothelium of the developing pancreas, allowing for reliable tracing of the mesothelial-derived cells. During the early stages of pancreas morphogenesis, its mesothelium shows the typical features of EMT. Mesothelial-derived cells, identified by constitutive YFP expression, differentiate into a major part of the PSCs and also contribute to other connective and vascular cell type, including endothelium. Thus, mesothelial-derived cells originated by EMT seem to constitute an important subpopulation of mesodermal cells during pancreas development, contributing to its morphogenesis.

On the other hand, systemic deletion of Wt1 in adult mice causes a severe atrophy of the pancreas, although this factor is only expressed in the pancreatic mesothelium. In addition, we have observed that adult PSC express Wt1 in the caerulein-induced pancreatitis model. Our results suggest that: 1) normal pancreatic function is maintained by a Wt1-dependent signaling mechanism acting from the mesothelium and 2) Wt1 plays a role in PSC activation in adult mice. These observations point to a relevant function of the Wt1 gene in pancreatic development and function.