Endothelial WT1 and the epicardium in cardiac development and disease

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English summary

In **Chapter 1** we provide an overview of the heart in general and about development and myocardial infarction in more detail. In addition, we describe the development of the epicardium, the cell layer which is situated around the heart and characterized by the expression of the transcription factor Wilms' tumor-1 (WT1) during development.

In **Chapter 2** of this thesis we studied the spatiotemporal expression pattern of WT1 during developmental stages and after cardiac injury. Our results show that WT1 is expressed in cardiac endothelial cells in the developing, adult and post-infarcted heart in a spatial and temporal expression pattern and is not exclusively for epicardial cells and EPDCs as has been suggested previously. In vitro experiments show that WT1 plays an important role in endothelial proliferation and formation of the vascular network. We suggest a role for WT1 in angiogenesis and conclude that, in addition to the essential role of WT1 in the epicardium, WT1 has an active role in cardiac endothelial cells.

In **Chapter 3** of this thesis we provide a detailed description of the expression of WT1 protein during human cardiac development. we studied the expression of WT1 during human cardiogenesis. We show that human expression of WT1 is present in cells that are crucial for the proper formation of the cardiac vessels and ventricular myocardium, i.e. epicardial, endothelial and endocardial cells [3].

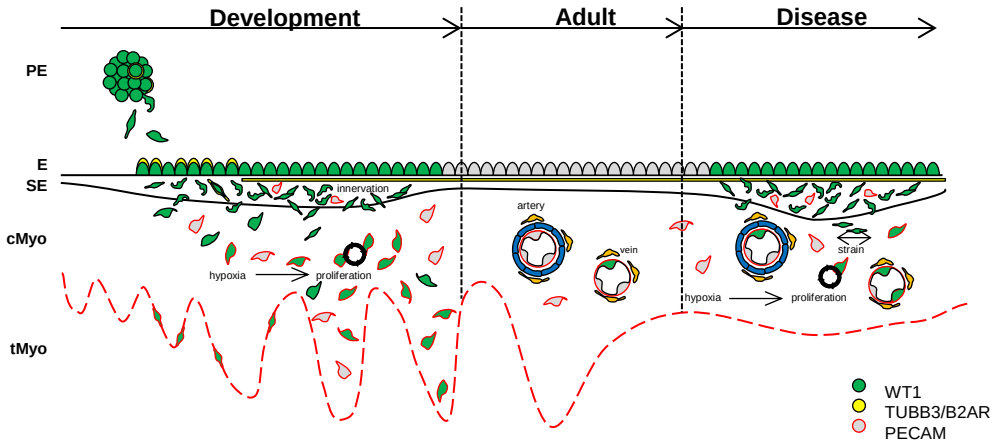
In **Chapter 4** of this thesis we provide a review of the many aspects of WT1 within the heart during development and after injury and propose a working model for the role of WT1 in endothelial cells, based on our own experiments, which are described in this thesis and previous literature.

In **Chapter 5** of this thesis we studied the role of the epicardium in autonomic modulation of the developing heart prior to innervation. Our results show that the epicardium expresses the neuronal markers TUBB3, NCAM and β2AR during early development. Using an ex-ovo model we show that inhibition of epicardial outgrowth results in a disturbed response to epinephrine. Together, these results show for the first time that the epicardium plays a role in modulating the cardiac autonomic response prior to innervation.

In **Chapter 6** of this thesis we studied the response of EPDC to mechanical stimulation. Using an *in vitro* straining model, we show that mechanical stimulation slightly stimulates the differentiation of EPDCs into myofibroblasts, but does not result in the deposition of ECM. On

the other hand, injection of EPDCs in the heart after MI results in a fast deposition of collagen, indicating that factors additional to stretch determine the behavior of EPDCs.

Finally, the results and conclusions of the previous chapters of this thesis are discussed in **Chapter 7** (Discussion), together with the future implications deriving from this work.



The expression of WT1 in the heart during development, in the adult heart and after cardiac injury. The expression of WT1, during different cardiac conditions, as described in this thesis is illustrated in green. PE, proepicardium, E; epicardium, SE; subepicardium, cMyo; compact myocardium, tMyo; trabeculated (non-compacted) myocardium.