7. Summary

Previous unpublished in vivo studies showed that $Id2^{-/-}$ mice with NMRI background infused with Angiotensin II are resistant to hypertension. Reconstitution of immune cells by bone marrow transplant did not restore the hypertension, indicating that Id2 in circulating blood cells regardless of their Id2 expression does not modulate blood pressure. Kidney transplant experiments demonstrated that extra-renal Id2 is also not responsible for the lack of blood pressure sensitivity. Alternatively, the vessel wall could be a candidate tissue, which might have determined for the insensitivity to maintain Ang II-induced hypertension.

The main focus of this thesis was to elucidate the role of Id2 in VSMC and to examine if primary VSMC from $Id2^{-/-}$ mice show a more protective behaviour than VSMC from wildtype mice. Further unpublished studies suggested that in contrast to Ang II-infused NMRI mice, European C57BL/6 mice infused with Ang II although maintained normal blood pressure and failed to develop cardiovascular diseases. Therefore, another aim of the present work was to examine a possible parallel in the behaviour of VSMC from $Id2^{-/-}$ mice with NMRI backround and VSMC from C57BL/6 mice.

Within the bounds of this work Affymetrix-Genechip analyses were done to elucidate the differences between $Id2^{+/+}$- (NMRI), $Id2^{+/-}$- and $Id2^{-/-}$ VSMC. Gene expression profiling analyses revealed a cluster of gene expression related to cell cycle and senescence. The senescence biomarkers p16 and collagen1a1 nearly are transcripted in Id2 deficient-VSMC. Furthermore, $Id2^{+/-}$ and $Id2^{+/-}$ VSMC show characteristics of cellular senescence like an enlarged and flattened morphology, increased senescence associated β-galactosidase activity and reduced cell proliferation. In contrast, Id2 deficient-VSMC develop an antisenescence phenotype. The results of the present study are the first that demonstrate a senescent effect of Id2 and provide evidence that Id2 deletion inhibits the genesis of a senescence phenotype.

Comparative studies of VSMC from NMRI and C57BL/6 mice suggest that there is no difference in status of senescence. But an analogy between VSMC from C57BL/6 and $Id2^{-/-}$ mice could be demonstrated in the cell cycle regulation. Both show increased proliferation, which is due to an elevated S-phase-entry and the levels of the cell cycle inhibitor p21 and Id2 are abrogated. This is the first work demonstrating a link between the decrease of p21 expression and an abrogated Id2 level. This correlation suggests that Id2 participates in the p21-mediated cell cycle regulation.

The present study identifies a new role for the HLH-Factor Id2. Id2 deficient-VSMC show an antisenescence phenotype and therefore a more protective behaviour in comparison to wild-type VSMC. Presumably these data could help to develop an antisenescent therapy. The maintenance of the proliferation status could be a contribution to wound healing of ruptured plaques in advanced atherosclerotic lesions. In addition the role of vascular senescence in the genesis of hypertension is an attractive speculation, but needs to be addressed in the future.