NR4A nuclear receptors in vascular disease

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Preface and Outline of the thesis

Cardiovascular diseases including coronary artery disease (CAD) and stroke are the leading cause of death worldwide. In 2001, the number of deaths from CAD alone was around 7.1 million, comprising 12.2% of the 56.2 million people who died in this year. These statistics reflect the global epidemic of cardiovascular disease, which has a considerable impact on individuals and society as a whole. Population growth and aging, of which the latter also affect many Western countries including the Netherlands, will result in an increasing prevalence of cardiovascular disease and booster health care expenses. As a consequence of these statistics, worldwide research efforts have been undertaken to unravel the pathophysiological mechanisms that underlie cardiovascular disease, and more importantly to discover solutions to this increasingly important health care problem. These research efforts have resulted in many successful prevention and treatment modalities and therefore the mortality rates of cardiovascular disease in Western countries are steadily declining. In CAD, these modalities include, next to life-style modification programs, treatment with anti-platelet aggregation drugs, anti-hypertensive drugs and 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)-reductase inhibitors (statins) and invasive treatment strategies including coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI). Nevertheless, a considerable level of risk to cardiovascular disease remains in patients subjected to these prevention and treatment options as we age. Moreover, changes in demographic population composition in combination with an increasing prevalence of diabetes and obesity in both Western and developing countries will contribute to an increasing burden of cardiovascular disease. In line with this, projections designed to predict causes of death till 2030 foresee that CAD will stay the main cause of death in all scenarios used. These scenarios indicate that although certain advances are made, there is an increasing need for improved prevention and treatment strategies for cardiovascular disease. The studies described in this thesis have a strong focus on the function of NR4A nuclear receptors in vascular disease and aim to contribute to a better understanding of cardiovascular disease and ultimately to new, innovative treatment options.

Part I contains a general introduction (Chapter 1) on atherosclerosis and vascular diseases closely related to atherosclerosis: restenosis and vein-graft disease. Next, the NR4A nuclear receptors are introduced by two published reviews. To better serve as an introduction of my thesis the reviews have been modified. The first review (Chapter 2) describes the structure of NR4A nuclear receptors as well as their expression regulation and function in macrophages and smooth muscle cells (SMC) in atherosclerosis and vein-graft disease. The second review (Chapter 3) focuses on NR4A function in metabolism and vascular cells, including endothelial cells and describes the current knowledge on 6-mercaptopurine.
(6-MP), an active metabolite of the immunosuppressive drug azathioprine, that has been shown to enhance the transcriptional activity of NR4A nuclear receptors.

**Part II** contains three chapters that cover several aspects on the expression and function of NR4A nuclear receptors in atherosclerosis. **Chapter 4** describes the expression of all three NR4A nuclear receptors (Nur77, Nurr1 and NOR-1) in human atherosclerotic lesions and explores NR4A nuclear receptor function in cultured macrophages in inflammation and lipid-loading, key cellular processes in atherosclerosis. In **Chapter 5**, the expression and function of Nur77 in SMCs in arterial remodeling, a critical feature of vascular disease, including atherosclerosis, is studied. For this purpose transgenic mice that overexpress Nur77 in arterial SMCs are subjected to contralateral, right carotid artery ligation, which results in flow-induced, outward remodeling of the left carotid artery. Next, the effect of 6-MP on monocyte/macrophage function *in vitro* and atherosclerotic lesion formation in ApoE*3-Leiden mice is studied in **Chapter 6**.

In **Part III**, a switch is made towards restenosis, a major complication of PCI including stent placement. In **Chapter 7**, we demonstrate expression of Nurr1 in human in-stent restenosis lesions and explore the function of Nurr1 in proliferation and inflammatory responses in SMCs *in vitro* and in wire-injury-induced restenotic lesion formation in mice. Also the association of Nurr1 genetic haplotypes with in-stent restenosis risk is described, linking bed-side restenosis to bench-side experiments. **Chapter 8** describes the effects of 6-MP on restenotic, SMC-rich lesion formation in femoral arteries in a drug-eluting cuff model in mice, which is shown to involve Nur77. Finally, in **Chapter 9** we describe the association of a single nucleotide polymorphism (SNP) in the *p27kip1* gene, a downstream target of Nur77 and Nurr1 in SMCs, with in-stent restenosis risk and demonstrate that this SNP modulates the promoter activity of this gene.

In the final part (**Part IV**), interesting selected aspects, and future perspectives of the NR4A nuclear receptors in atherosclerosis and restenosis, are discussed (**Chapter 10, general discussion**) along with a summary per chapter (**Chapter 11**).
References


