Liver X receptor in the cardiovascular system

Kuipers, Irma

General Introduction

CARDIOVASCULAR DISEASE

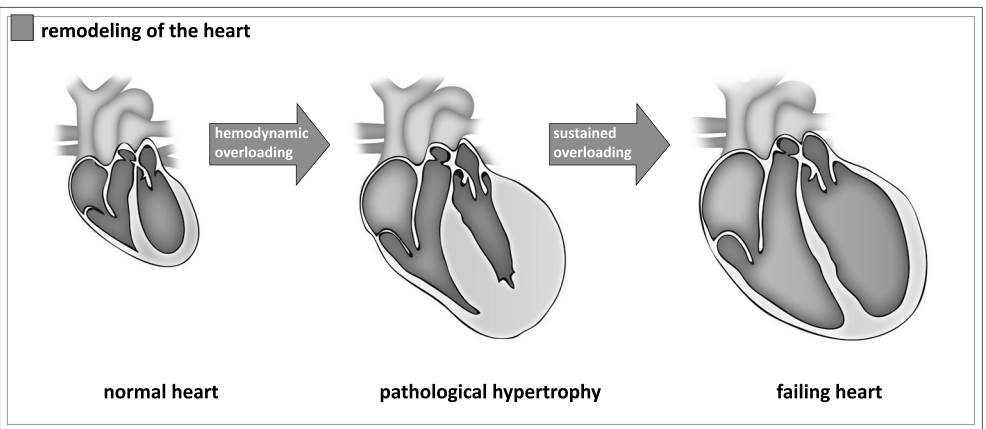
Cardiovascular diseases are leading causes of morbidity and mortality in industrialized countries. They are based on genetic and environmental factors and are associated with substantial abnormalities in metabolic and inflammatory pathways.[1] Different etiological triggers, like arterial hypertension, myocardial infarction, or valvular disease, ultimately all culminate in a phenotypcically identical form of end-stage disease, which is referred to as heart failure (figure 1). The prevalence of heart failure is estimated at 1-2% in the Western world, with an incidence that approaches 10 per 1000 persons per year.[2] Although survival of patients with cardiovascular diseases has started to improve,[3,4] mortality rates after onset of heart failure remain high.

LIVER X RECEPTORS

Liver X receptors (LXRs) are nuclear hormone receptors that act as ligand-activated transcription factors.[5] They are critically involved in cholesterol metabolism[6] and their natural ligands are oxysterols; oxidized cholesterol derivatives.[7] There are two known isoforms of LXRs; LXR-α (mainly expressed in liver, spleen, intestine, macrophages, heart and kidney) and LXR-β (expressed ubiquitously).[8] LXRs form a heterodimer with the retinoid X receptor (RXR). This complex binds to specific parts of the genome called LXR response elements (LXREs). In the non-active state, the LXR/RXR complex is occupied by corepressor complexes (figure 2A). However upon ligand binding, the corepressor complexes are exchanged by coactivator complexes, which results in the transcription of specific target genes of LXR (figure 2B).

Over the last decade, research on LXRs was mainly focused on their role in cholesterol metabolism. It was discovered that LXRs play a crucial role in the process of 'reverse cholesterol metabolism'; the efflux of cholesterol from peripheral tissues towards the liver for excretion.[6] More recent studies show that LXRs also exert pleiotropic properties. They have been shown to attenuate proliferative pathways,[9] blunt inflammatory responses,[10] and influence the renin-angiotensin-aldosterone system

Figure 1



Remodeling of the heart. The heart undergoes continual remodeling in response to fluctuations in functional demand. Pathological hemodynamic overloading (e.g. hypertension and myocardial infarction) induces pathological hypertrophy. Adapted and modified from Dr. Kalpana Vijayan (downloaded from www.abcam.com).

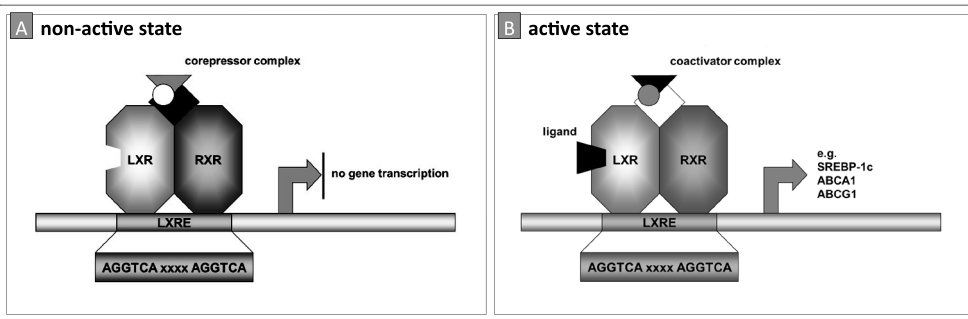
(RAAS).[11] An extensive overview of LXRs and their potential role in cardiovascular disease is described in chapter 1.

SCOPE OF THIS THESIS

Metabolic and inflammatory pathways highly influence the onset and development of cardiovascular disease. Both pathways are controlled by complex mechanisms, in which LXRs play a critical role.[12] However, knowledge of the direct effects of LXRs on the cardiovascular system remains scarce.

In this thesis, several models of cardiac remodeling and cardiac failure have been used to investigate the role of LXRs in the pathophysiology of these conditions. **Chapter 1** provides an in-depth review on the role of LXRs in the cardiovascular system. In this review, we describe the potential role of LXRs in atherosclerosis, blood pressure homeostasis, and cardiac remodeling by summarizing recent literature on this topic combined with our findings described in the following chapters. **Chapter 2** describes how we identified LXRs as negative regulators of the RAAS, the main system regulating blood pressure homeostasis. With this study we confirmed earlier studies describing LXR-α as a regulator of renin transcription.[11] Chapter 2 describes the first long-term *in vivo* study focussing on LXR signalling in the RAAS. We further studied the role of LXRs in the cardiovascular system by activating LXRs in a model of cardiac remodeling (**chapter 3**). *In vitro* studies show that activation of LXRs attenuates hypertrophy in cultured cardiomyocytes. To corroborate these findings *in vivo*, abdominal aortic constriction (AC) was used as a pressure overload model to induce cardiac hypertrophy in wild-type and LXR-α-deficient (LXR-$\alpha^{-/-}$) mice. We show that also *in vivo*, LXR activation attenuates the development of LVH. Using the same model as in chapter 3, we studied the interaction of LXRs and statins in **chapter 4**. Statins are known to attenuate the development of LVH,[13] but the molecular mechanism through which this effect is exerted is still not fully elucidated. In chapter 4 we show that LXRs play an essential role in this mechanism and that without LXR-α (LXR-$\alpha^{-/-}$ mice) statins no longer exert their cardioprotective effects. In **chapter 5** we explore the effects of LXR activation in a model of myocardial infarction. Here we show that also in this model of cardiac remodeling activation of LXRs improves cardiac function and attenuates LVH. **Chapter 6** discusses the role of nuclear hormone receptors, including LXRs, in the RAAS. Several components of the RAAS (renin, angiotensinogen, angiotensin receptors) are discussed

Figure 2



LXR forms a heterodimer with RXR. This complex binds to specific parts of the genome (LXREs). LXREs consist of direct repeats of the core sequence AGGTCA separated by 4 nucleotides, hence denoted DR4. In the non-active state, the LXR/RXR complex is occupied by corepressor complexes (A). Upon ligand binding, the corepressor complexes are exchanged by coactivator complexes, which results in the transcription of specific target genes of LXR (B).

with respect to their transcriptional regulation and the way nuclear hormone receptors affect these processes. The findings reported in this thesis are summarized in the final chapter '**Summary and Future Perspectives**'.

REFERENCES

1. Bruemmer D, Law RE. Liver x receptors: potential novel targets in cardiovascular diseases. Curr Drug Targets Cardiovasc Haematol Disord 2005;5:533-540.
2. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007;93:1137-1146.
3. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347:1397–1402.
4. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. J Am Med Assoc 2004;292:344–350.
5. Janowski BA, Willy PJ, Devi TR, Falck JR, Mangelsdorf DJ. An oxysterol signaling pathway mediated by the nuclear receptor LXR alpha. Nature 1996;383:728-731.
6. Peet DJ, Turley SD, Ma W, Janowski BA, Lobaccaro JM, Hammer RE, Mangelsdorf DJ. Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXR alpha. Cell 1998;93:693-704.
7. Janowski BA, Grogan MJ, Jones SA, Wisely GB, Kliewer SA, Corey EJ, Mangelsdorf DJ. Structural requirements of ligands for the oxysterols liver X receptors LXRalpha and LXRbeta. Proc Natl Acad Sci USA 1999;96:266-271.
8. Peet DJ, Janowski BA, Mangelsdorf DJ. The LXRs: a new class of oxysterol receptors. Curr Opin Genet Dev 1998;8:571-575.
9. Blaschke F, Leppanen O, Takata Y, Caglayan E, Liu J, Fishbein MC, Kappert K, Nakayama KI, Collins AR, Fleck E, Hsueh WA, Law RE, Bruemmer D. Liver X receptor agonists suppress vascular smooth muscle cell proliferation and inhibit neointima formation in balloon-injured rat carotid arteries. Circ Res 2004;95:e110-123.
10. Joseph SB, Castrillo A, Laffitte BA, Mangelsdorf DJ, Tontonoz P. Reciprocal regulation of inflammatory and lipid metabolism by liver X receptors. Nat Med 2003;9:213-219.
11. Morello F, de Boer RA, Steffensen KR, Gnecchi M, Chisholm JW, Boomsma F, Anderson LM, Lawn RM, Gustafsson JA, Lopez-Ilasaca M, Pratt RE, Dzau VJ. Liver X receptors alpha and beta regulate renin expression in vivo. J Clin Invest 2005;115:1913-1922.
12. Calkin AC, Tontonoz P. Liver X receptor signalling pathways and atherosclerosis. Arterioscler Thromb Vasc Biol 2010;30:1513-1518.
13. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. Circulation 2004;109 (23 Suppl 1):III39-43.