Articles in this series:


**Introduction on the ATVB Review Series “Nuclear Receptors in Metabolism and Cardiovascular Disease”**

Bart Staels

Over the last decades, dramatic changes in lifestyle habits have precipitated a worldwide obesity epidemic. The decrease in exercise and increase in caloric intake results in a higher prevalence of central obesity, which is often accompanied by metabolic derangements, including dyslipidemia and diabetes and, as a consequence, an increased risk for cardiovascular disease. Organisms adapt their metabolism to environmental changes by modulating signaling pathways, including several transcription factor pathways. Although these adaptations are initially meant to maintain physiological homeostasis, chronic overactivation may result in the dysregulation of pathways, leading to insulin resistance, dyslipidemia, inflammatory responses, etc. A thorough knowledge of the regulatory mechanisms of these adaptive metabolic pathways is required for a proper understanding of the pathophysiological bases of these diseases and to open up perspectives for their management.

Nuclear receptors (NRs) are transcription factors that respond to hormonal and environmental signals by inducing adaptive transcriptional responses. The human NR superfamily contains 48 members, all with conserved modular structures containing, among other features, a DNA-binding zinc finger domain and a ligand-binding domain. The first identified, and hence termed “classical” NRs, are the hormone receptors, which include the estrogen, androgen, mineralocorticoid, and glucocorticoid receptors. Although theoretically all NRs may be ligand-activated, a large number of NR family members, identified mainly by homology screening, are (still) orphans. However, over the last years, several of them have been deorphanized. Interestingly, many of these are activated by dietary-derived compounds, such as fatty acids and derivatives for the peroxisome proliferator-activated receptors, oxysterols for the liver X receptors (LXRs), bile acids for farnesoid X receptor (see the reviews in this series for details). More recently, oxysterols and heme have been identified as ligands for the retinoid acid receptor-related orphan receptor and Rev-erbs. These findings have opened up exciting new avenues in the understanding of the dietary control of transcription. This review series aims at highlighting the recent findings on the control of metabolism and vascular function by NRs, as illustrated by a selection of examples.

The series kicks off with an article by Arnal et al discussing the role of classical hormone receptors, the estrogen receptorα and estrogen receptorβ in vascular biology. The authors discuss new data on how estrogen receptors influence endothelial function and atherogenesis by modulating the interplay of cells of the immune system and the endothelium. The use of genetically modified animal models expressing different functional domains of these NRs has greatly advanced our understanding of the effect of estrogens on the vasculature and may open perspectives for the future development of selective modulators, devoid of sexual, proinflammatory, and procoagulant activities, but retaining the beneficial effects on bone and the endothelium, which may be of use in postmenopausal women.
The following set of articles addresses the functions of a number of deorphanized lipid-regulated NRs. LXRα and LXRβ are oxysterol receptors that were initially identified to play major roles in cholesterol and fatty acid homeostasis. More recently, these receptors were also found to control innate immunity and inflammation. Calkin and Tontonoz discuss how LXRs modulate atherosclerosis development via regulating genes of cholesterol and fatty acid metabolism, inflammation, and apoptotic cell phagocytosis. Interestingly, distinct roles for the 2 LXRs in these processes are now emerging.

Bile acids are cholesterol metabolites, which for a long time were considered as simple detergents necessary for the intestinal absorption of lipids and lipophilic molecules, such as certain vitamins. However, the discovery in 1999 of the NR farnesoid X receptor as a bile acid receptor, followed, a few years later, by the identification of a membrane G-protein coupled receptor, G-protein coupled bile acid receptor opened an entirely new field, identifying bile acids as molecules exerting also signaling functions. Hageman et al discuss results, obtained during the decade following these initial discoveries, on the metabolic control of lipid, glucose, and energy homeostasis by farnesoid X receptor, as well as recent findings on the vascular actions of this receptor with particular attention to the control of inflammatory pathways and atherosclerosis, opening up interesting perspectives for pharmacological application of these pathways, as already exemplified by the use of bile acid sequestrants.

Many physiological processes undergo circadian variations in amplitude. Examples are metabolic pathways, such as cholesterol and bile acid metabolism, as well as cardiovascular activities, such as blood pressure. Perturbation of these rhythms, as occurs after a jetlag, in night-shift workers, or in relation to sleep restriction, results in metabolic complications resembling the metabolic syndrome. Recent findings, discussed by Duez and Staels, have identified the existence of molecular clock components, many of which are transcription factors, acting not only in central, but also peripheral tissues. The NRs Rev-erbα and RORα are integral parts of the clock machinery and display, together with peroxisome proliferator-activated receptors and other NRs, circadian rhythmicity. Emerging evidences identify several of these NRs also as controllers of metabolic pathways and vascular function. These findings open interesting perspectives for the development of approaches aimed at “resetting” these altered rhythms, with the ultimate goal to correct the associated metabolic disorders.

The NR4A nuclear subfamily, including Nurr77 (NR4A1), Nurr1 (NR4A2), and NOR1 (NR4A3), are orphan NRs. They, however, respond to stimuli as immediate early response genes. Although initially shown to control processes such as differentiation, proliferation, and apoptosis, linking them to central nervous system disorders, such as Parkinson disease, recent observations also identified roles for the NR4As in the control of metabolism and vascular remodeling and inflammation. Zhao and Bruemmer discuss how NR4As control hepatic and skeletal muscle glucose metabolism, plasma and hepatic lipid metabolism, white and brown adipocyte differentiation and function, as well as their direct vascular actions.

In addition to regulating the transcription of target genes via binding to NR response elements, many NRs display antiinflammatory activities, as already mentioned in several of the series contributions. The classical example is the glucocorticoid receptor, which mediates the effects of glucocorticoids, widely used antiinflammatory drugs. Huang and Glass discuss our current understanding of the molecular mechanisms behind these antiinflammatory actions, taking the glucocorticoid receptor, peroxisome proliferator-activated receptors, LXRs, and NR4A family members as examples. Recent technological developments provide the means to study these mechanisms in more detail and at the “whole genome” level, thus opening up interesting pharmacological perspectives.

We hope that the selection of review articles in this series will introduce the reader to the exciting world of NRs, with its wide spectrum of actions, from the control of lipid and glucose metabolism over immunoinflammatory to vascular activities. A better understanding of their physiological roles, their response to environmental changes, and their potential to reprogram pathways altered in pathological conditions should spawn further interest in this family of transcription factors as pharmacological targets.

**Key Words:** nuclear receptors | dietary lipids | gene regulation | metabolism | atherosclerosis
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