Reviews

This Introduction is part of a thematic series on Nuclear Receptors, which includes the following articles:

- Control of Macrophage Activation and Function by PPARs [2010;106:1559–1569]
- PGC Coactivators in the Developing and Diseased Heart
- PPARs and the Vessel Wall
- LXR, Inflammation, and Vascular Disease
- Estrogen Receptor Signaling and Cardiovascular Disease

Daniel P. Kelly, Guest Editor

Introduction to the Nuclear Receptor Review Series

Daniel P. Kelly

Heart and vascular diseases comprise a worldwide health threat, despite significant advances in the treatment of some components of these lethal disorders. One barrier to effectively addressing modern cardiovascular disease relates to our lack of a full understanding of how multiple pathways converge to drive pathogenesis. The unique and aggressive forms of vascular and heart disease related to common metabolic disorders, such as diabetes, is one example of this complexity. Indeed, we are witnessing an emerging pandemic of obesity that is driving type 2 diabetes and its lethal cardiovascular complications.1–3 Evidence is emerging that the distinct forms of cardiovascular disease driven by the diabetic state involves the interaction of metabolic derangements with chronic inflammation, together with traditional etiologic determinants such as hypertension.4,5 The regulatory nodal points that connect these pathological processes must be defined to fully delineate the relevant disease mechanisms and to identify new drug targets.

An explosion of new information has revealed that members of the nuclear receptor (NR) superfamily serve a central role in directing gene regulatory programs that control metabolism, inflammation, and myriad other biological and physiological processes. NRs maintain cellular and organismal homeostasis by serving as ligand-activated transcription factors.6 NRs are now classified as “classical” (hormone receptors) or “nonclassical.”6 Members of the latter group were originally discovered as so-called “orphan” receptors because they had no known ligand. However, many of the “orphan” receptors have been “adopted” through identification of their ligands. Interestingly, the “adopted orphan” receptor ligands are, in most cases, intermediary metabolites that serve as feedback signals for the metabolic state of the cell and the entire organism. Alterations in levels of the metabolite ligands serve to activate, or in some cases deactivate, their cognate NRs to control the expression of genes involved in downstream metabolic pathways. For example, the peroxisome proliferator-activated receptors (PPARs) are activated by fatty acids and their derivatives (although the true endogenous ligands have not been fully determined).7 Elevation of fatty acids in the cardiac myocyte or hepatocyte instructs the PPARs to activate pathways involved in the burning of fat. The liver X receptors (LXRs) are activated by oxysterols.8,9 Changes in oxysterol levels lead to adjustments in the synthesis and disposal of cholesterol. In addition, the same NRs often serve as regulators of inflammatory processes and, thus, perform dual functions, linking control of metabolism with inflammation, a regulatory nodal point. In addition to the influence of ligands, we now know that specific transcriptional coregulators also serve to “boost” or put a “brake” on NRs in response to tissue-specific, developmental, and physiological cues.10,11 Taken together, NRs can be viewed as transducers of tissue-selective, physiological signals instructing downstream cellular responses to environmental changes.

Many of the biological pathways controlled by NRs are altered in common metabolic and cardiovascular disease states. Studies conducted in genetically modified mouse models have provided important information about the impact of dysregulated NR signaling, including delineation of phenotypes that mimic common vascular and myocardial diseases. These observations have triggered intense research efforts focused on NRs...
that control lipid metabolism, vascular function, and cardiac myocyte bioenergetics. The upcoming Circulation Research series on nuclear receptors will focus on a subset of NRs and coregulators relevant to the heart and vasculature, with emphasis on the control of the complex interplay between metabolism and pathogenic processes, such as inflammation. The review series has been designed to provide the reader with a current working knowledge about biological and physiological functions of NRs, with emphasis on links to cardiovascular disease. The reviews will also emphasize the potential for NRs, their coregulators, and downstream pathways as targets for novel therapeutic strategies aimed at uncoupling the pathological synergism between metabolic derangements and inflammation, processes known to drive common forms of cardiovascular disease.

In the first contribution to this series, Ajay Chawla will provide a current view of how the PPAR family of NRs function in the macrophage. Evidence has emerged that PPARs regulate genes involved in macrophage metabolism and function. Chawla will review the evidence that PPARs participate in both "classical" and "alternative" macrophage activation programs, which evolved as key components of the innate defense against pathogens. The PPARs likely contribute to, or in some cases protect against, dysregulated macrophage responses known to contribute to metabolic, autoimmune, and vascular diseases. Interestingly, recent data have shown that specific PPAR isofoms (PPARα, PPARβ/δ, and PPARγ), and their coregulators, may serve unique functions in the macrophage. Evidence has emerged that NRs and their coregulators control myocyte energy metabolism and mitochondrial functional capacity in the healthy and diseased heart. Zolt Arany will review the evidence that has identified the PPARγ coactivator-1 (PGC-1) family of NR coregulators as master regulators of heart and skeletal muscle bioenergetics. Recent evidence suggests that in several pathophysiological conditions that lead to heart failure, PGC-1 coactivators become deactivated. Genetic loss-of-function studies have begun to define the consequences of PGC-1 deficiency, including abnormalities in mitochondrial respiratory function and angiogenesis.

Two separate contributions will address the roles of NRs in vascular biology and disease. Jorge Plutzky will review PPAR-RXR signaling as it related to the vessel wall. Given that the PPARs are activated by lipid ligands, an important question for the field relates to the source and nature of such ligands and how they influence the cardiovascular system. New studies have shown that lipoproteins carry the ligand cargo for PPARs. Moreover, specific lipases may dictate the release of distinct PPAR ligands, which, in turn, orchestrate a variety of responses including, but not limited to, the control of lipid metabolism and inflammation. Tim Osborne will review the role of the LXRs in the broad regulation of lipid metabolism and inflammation. The author will address the importance of LXR-mediated transcriptional control in cholesterol and fatty acid metabolism under normal conditions and in disease states such as atherosclerosis. Recent evidence implicating LXRs in the control of inflammation will also be reviewed.

Finally, Richard Karas will review the biological actions of estrogen receptors (ERs), with emphasis on vascular and myocardial biology, and related disease states. In contrast to the other NRs highlighted in this series, the ERs are classical hormone receptors, rather than "adopted receptors." Indeed, this family of NRs has been extensively studied and roles in the control of physiological programs have been well delineated. However, recent studies have revealed the fascinating complexity of the ERs and their coregulators, ranging from nonclassical pathways of activation to selective downstream functions. Important roles for this group of receptors in cardiovascular biology and disease have been unveiled, including effects on vasodilatation, smooth muscle proliferation, and angiogenesis. Harnessing the selective beneficial actions of ERs remains an important goal for development of novel therapeutic strategies.

We hope that this review series provides the readership with a meaningful glimpse into the fascinating world of NR biology and stimulates discussion about new cross-disciplinary initiatives. We envision that this series will spark further interest in NR regulatory networks as therapeutic targets aimed at the complex processes that drive common diseases of the heart and vasculature.

Sources of Funding
Supported by NIH grants HL058493-12 and HL077113-05.

Disclosures
D.P.K. serves on the Scientific Advisory Boards of Eli Lilly and Johnson & Johnson.

References
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Circ Res. 2010;106:1557-1558
doi: 10.1161/CIRCRESAHA.110.221630
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/106/10/1557

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