Stress-induced adverse remodeling of the myocardium is a major mechanism leading to heart failure, a leading and rapidly escalating source of morbidity and mortality worldwide.1,2 As a result, much work is underway to dissect molecular mechanisms governing cardiac remodeling in hopes of identifying novel therapeutic targets. In recent years, much of this work has focused on the hypertrophic growth response of the cardiac myocyte. Initially adaptive, cardiac hypertrophy compensates for declines in cardiac performance and increases in wall stress; sustained hypertrophy, however, is a major risk factor for emergence of systolic dysfunction and clinical heart failure.3 On the bright side, numerous preclinical studies have demonstrated that abrogation of the hypertrophic response is well tolerated, and even beneficial.4

One potential target of therapy in the pathologically remodeled, hypertrophied heart is the transcription factor nuclear factor κB (NF-κB). First discovered more than 20 years ago, NF-κB has been linked to numerous neurohormonal, pathophysiological, and stress stimuli responses, and it has been characterized most extensively in the immune system. In the heart, activation of NF-κB–dependent transcription has been detected in numerous disease contexts, including hypertrophy, ischemia/reperfusion injury, myocardial infarction, allograft rejection, myocarditis, apoptosis, and more.5,6 Within coronary vessels, NF-κB has been implicated in atherosclerosis and restenosis.5,6 However, parsing the specific role(s) of NF-κB in these diverse disease processes has been hampered by the embryonic lethality of inactivation of several NF-κB components.7–9

In heart, the NF-κB family of transcription factors comprises 4 members: p50, p52, p65, and RelB. All are capable of multimerization, forming either homo- or heterodimers, but the ubiquitously expressed p50 and p65 (herein termed NF-κB) are responsible for the majority of NF-κB binding activity in the myocardium. Activation of cytoplasmic NF-κB requires phosphorylation and subsequent proteasome-dependent degradation of its repressor, inhibitor of κB (IκB). The essential step in this so-called canonical pathway, degradation of IκB, is initiated by a multicomponent IκB kinase (IKK) complex, comprising a regulatory scaffolding subunit NEMO (NF-κB essential modifier) (also known as IKKγ) and 2 catalytic subunits, IKKα and IKKβ. Then, the p50/p65 complex, released from the repressive influence of IκB, migrates to the nucleus, where it binds cognate DNA sequences (κB sites) in target genes.

The NF-κB response is often transient, because it is governed by at least 2 negative feedback loops. In one, the protein IκBα, a product of NF-κB transcription, binds NF-κB, and the newly formed IκBα/NF-κB complex is translocated out of the nucleus, obviating NF-κB–dependent gene transcription. In another, the NF-κB–responsive, zinc finger protein A20 inhibits initiation of the NF-κB/caspase by inactivating IKK in the cytoplasm. In addition, p50/p50 homodimers can attenuate NF-κB transactivation.10,11 Thus, expression of NF-κB-dependent genes is tightly regulated by multiple, interlacing control processes.

In the myocardium, it remains puzzling the extent to which NF-κB promotes cell survival or cell death. Some evidence points to important cardioprotective effects. For example, NF-κB activation attenuates the hypertrophic response to pressure overload,12 minimizes infarct size during late-phase ischemic preconditioning,13 and lowers tumor necrosis factor–α–dependent apoptotic myocyte death.14 By contrast, other evidence suggests that cardioprotection can be brought about by blocking essential components of the NF-κB pathway; suppression of the NF-κB cascade decreases cardiac hypertrophy15–17 and prevents stress-induced ventricular dilatation.15,16,18,19 In addition, NF-κB activation is required for doxorubicin-induced cardiomyocyte apoptosis.20 Clearly, the multifaceted roles of NF-κB in the heart require clarification.

NF-κB is so pleiotropic that it has traditionally been considered a “general,” nonspecific transcription factor: a diverse array of stimuli activates NF-κB, and NF-κB, in turn, regulates more than 200 genes. More recent evidence, however, suggests that NF-κB serves as a nodal point of signaling, governing a network of circuits to integrate sundry inputs and elicit precise outputs via specific downstream targets. Consistent with this is our ever-growing understanding of the complexity of NF-κB feedback and feedforward control loops. Very recently, microRNAs have entered the NF-κB control picture.21 This work has uncovered an entire network of genes involved in cardiovascular development and reprogramming enriched for NF-κB binding sites in their proximal promoter regions.

Much of the work to delineate NF-κB functions in heart has been conducted using transgenic models of cardiac-specific expression of mutant p50 and/or unphosphorylatable (undegradable) IκB. However, conclusions drawn from these studies have been conflicting.12,13,15–18 For example, 2 independent groups studying mice exposed to ischemic stimuli and harboring degradation-resistant IκB mutants reported that NF-κB can be either maladaptive22 or cardioprotective.23 Although this discrepancy may stem from differences in
In light of these facts, the NEMO mutant complements the arsenal of existing mouse models with abrogated NF-κB signaling in the heart (ie, IκB degradation-resistant mutants). Because NEMO acts upstream of IκB in NF-κB activation, this model may provide new insights into the integration of NF-κB–activating signals and the selectivity of the output(s) of the NF-κB–dependent transcriptional network. Additional complexity in NEMO-dependent NF-κB activation is highlighted by the fact that NEMO harbors at least 7 reported sites of the NF-κB–activating signals and the selectivity of the output(s) of the NF-κB–dependent transcriptional network. Additional complexity in NEMO-dependent NF-κB activation is highlighted by the fact that NEMO harbors at least 7 reported sites of phosphorylation.

Non-standard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IκB</td>
<td>inhibitor of NF-κB</td>
</tr>
<tr>
<td>IKK</td>
<td>inhibitor of NF-κB kinase</td>
</tr>
<tr>
<td>NEMO</td>
<td>nuclear factor NF-κB essential modifier</td>
</tr>
<tr>
<td>NF-κB</td>
<td>nuclear factor NF-κB</td>
</tr>
</tbody>
</table>

Disclosures

None.
References


NEMO Nuances NF-κB
Andriy Nemchenko and Joseph A. Hill

_Circ Res._ 2010;106:10-12
doi: 10.1161/CIRCRESAHA.109.211185

_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/106/1/10

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/