Cytokine Actions of Angiotensin II

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In this issue of Circulation Research, Ruiz-Ortega et al.12 show that Ang II activates nuclear factor-κB (NF-κB) through both AT1 and AT2 in vascular smooth muscle cells. NF-κB is a ubiquitous transcription factor of particular importance in inflammatory responses.13 Many stimuli relevant to cardiovascular diseases, including proinflammatory cytokines (interleukin [IL]-1β and tumor necrosis factor-α [TNF-α]), signals elicited by ischemic stress (nitric oxide [NO] and reactive oxygen species), and mechanical forces, have been shown to activate NF-κB. Activation of NF-κB leads to coordinated increases in the expression of many genes whose products mediate inflammatory responses, including cytokines, chemokines, and adhesion molecules.13 Although activation of NF-κB by AT1 has been demonstrated previously,14 the study by Ruiz-Ortega et al.12 is the first to show the linkage between AT1 and NF-κB and thus potentially clarifies the mechanism of many presently unexplained cardiovascular phenomena known to be mediated by AT2.

Functional Roles of the AT2/NF-κB Pathway

As Ruiz-Ortega et al.12 point out, many inflammatory cytokines (TNF-α, IL-6, and IL-8), chemokines (monocyte chemoattractant protein-1 [MCP-1]), cell adhesion molecules (vascular cell adhesion molecule-1 and intercellular adhesion molecule-1), and other molecules (tissue factor) relevant for cardiovascular remodeling are regulated by NF-κB. Other important candidates regulated by the AT2/NF-κB pathway include inducible NO synthase15 and cyclooxygenase-2,16 which mediate NO and prostaglandin and thromboxane production, respectively, in inflammatory diseases. NO synthesis and subsequent production of cGMP are stimulated by AT2 in many organs.17 Induction of cyclooxygenase-2 and activation of NF-κB have been observed in fibrotic scars in the myocardium of failing human hearts.18 Remarkably, AT2 is predominantly localized in fibroblasts present in the interstitial region,1 suggesting that AT2 may be responsible for progression of inflammation and interstitial fibrosis during cardiac remodeling. Stimulation of AT2 generally inhibits growth of vascular smooth muscle cells3 and cardiac myocytes,4 but, paradoxically, it may also be involved in cell growth. For example, AT2 blockade inhibits medial smooth muscle hypertrophy and fibrosis in the thoracic aorta of Ang II–infused rats7 and spontaneously hypertensive rats.19 Because these growth stimulatory effects are seen only in vivo (and have not been reported in pure smooth muscle cell cultures), upregulation of cytokines and cell adhesion molecules by the AT2/NF-κB pathway, attraction of inflammatory cells, and additional amplification of trophic (paracrine) factors in vivo may be responsible for these AT2-mediated cell growth responses. Recently, a preliminary study suggested that pressure overload–induced cardiac hypertrophy is completely suppressed in mice with targeted
AT1 and AT2 have distinct downstream targets, which counteract each other and mediate opposite cellular functions. AT1 and AT2 also have shared downstream targets, such as arachidonic acid and NF-κB. Whether the shared downstream targets mediate the same cellular functions is unknown. PKC indicates protein kinase C; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MKP-1, mitogen-activated protein kinase phosphatase-1; PP2A, serine/threonine phosphatase 2A; and SHP-1, Src homology 2 protein containing tyrosine phosphatase-1.

Unresolved Questions

Several important questions remain unanswered. First, in cultured smooth muscle cells, Ang II–induced increases in MCP-1 and angiotensinogen, well-known targets of NF-κB, were mediated predominantly by AT1, despite both AT1 and AT2 stimulation activating NF-κB in this cell type.12 Because AT1 is the predominant Ang II receptor subtype in cultured aortic vascular smooth muscle cells, the possibility remains that these NF-κB targets may be regulated more potently by AT1 when expression of AT1 is upregulated in pathological conditions. It is also possible that AT1 and AT2 regulate different molecules through NF-κB. For example, the AT1/NF-κB pathway may regulate predominantly proinflammatory cytokines, whereas the AT2/NF-κB pathway may have different targets. The mechanisms by which AT1 and AT2 regulate distinct NF-κB targets remain to be clarified. Because NF-κB is known to function in concert with other transcription factors such as AP-1 and C/EBP, these cofactors may be regulated differentially by AT1 and AT2.

Another important question is whether the AT1/NF-κB pathway always exerts a beneficial action in cardiovascular diseases.1 The answer is not simple, considering that NF-κB activation can be both beneficial and detrimental. For example, NF-κB activation is essential for the development of the cardioprotective effects of preconditioning.27 On the other hand, many studies have shown that inhibition of NF-κB can also have a salutary effect on cardiovascular diseases. For example, in vivo transfer of NF-κB decoy oligonucleotides reduces the extent of myocardial infarction and reperfusion injury.28,29 Inhibition of NF-κB reduces Ang II–induced organ damage in the heart and kidney by preventing inflammatory mediators.30 In the vasculature, inhibition of NF-κB suppresses development of atherosclerotic lesions by preventing inflammation,31 smooth muscle cell proliferation,32 and dysregulation of apoptosis.33 In a recent review, Matsubara1 discussed the potential advantages of shunting Ang II toward thereby inactivating tyrosine kinases and mitogen-activated protein kinases stimulated by AT1.2 It is interesting that NF-κB activation is one of the few examples reported thus far in which AT1 and AT2 share the signaling mechanism at least in part (Figure). Although both AT1 and AT2 stimulation cause degradation of inhibitor κB (IκB),12 an essential step for nuclear translocation of NF-κB, the mechanism leading to IκB degradation by AT1 and AT2 stimulation remains to be clarified. Degradation of IκB depends on phosphorylation of the two N-terminus serines by IκB kinase, and the phosphorylated IκB undergoes polyubiquitination and proteasome degradation.25 Degradation of IκB can be also mediated by phosphorylation of IκB at tyrosine 42 or by unknown mechanisms involving protein tyrosine phosphatases.25,26 Therefore, it will be interesting to determine whether NF-κB activation by AT1 and AT2 is mediated by either IκB kinase–dependent mechanisms or other mechanisms in which tyrosine kinases or phosphatases (directly or indirectly) modulate IκB degradation. Ruiz-Ortega et al12 suggest that oxygen radicals and ceramide are common mediators of NF-κB activation by AT1 and AT2. However, how AT2 stimulates production of oxygen radicals and ceramide in cardiovascular cell types remains to be elucidated.

Signaling Mechanism of NF-κB Activation by Ang II

Another interesting aspect of the work by Ruiz-Ortega et al12 is that both AT1 and AT2 are able to activate NF-κB. AT1 activates protein phosphatases, including SHP-1, PP2A, and MKP-1,
AT1 (during AT1 blockade) in the treatment of cardiovascular diseases. This hypothesis is well supported by the results of a recent study showing that losartan was associated with a lower mortality rate than captopril in the treatment of older heart failure patients. It has been shown that cardioprotective effects of AT1 antagonists in a rat model of heart failure are prevented by AT1 blockade. It will be extremely important to identify the targets of the AT1/NF-κB pathway in each disease condition and evaluate in which disease states stimulation of AT1 could be beneficial.

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References

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