Editorial Commentary

Linking Angiotensin II to Nuclear Factor-κ Light Chain Enhancer of Activated B Cells–Induced Cardiovascular Damage

Bad CARMA3s

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See related article, pp 1032–1039

The capacity of agents that inhibit the renin–angiotensin system (RAS) to lower blood pressure and limit cardiac damage indicates that inappropriate RAS stimulation underlies the pathogenesis of hypertension and its associated complications. Although a key effector of the RAS, angiotensin II (Ang II), instigates hemodynamic injury to the heart by promoting blood pressure elevation, Ang II can also exacerbate end-organ damage independently of blood pressure by stimulating immune and inflammatory signaling cascades.1 One prominent inflammatory pathway responsive to angiotensin receptor ligand culminates in the translocation of nuclear factor-κ light chain enhancer of activated B cells (NF-κB) to the nucleus where it drives transcription of a broad array of inflammatory mediators.2 Accordingly, the activation of NF-κB signaling pathway by Ang II potentiates target-organ damage in hypertension.3 Nevertheless, the upstream mechanisms through which Ang II stimulates NF-κB in hypertension have awaited further investigation.

In one paradigm of NF-κB activation, the CBM signalosome promotes ubiquitination of an IκB subunit that would otherwise sequester the rest of the NF-κB complex in the cytoplasm, allowing a heterodimer composed of NF-κB’s p50 and p65 subunits to translocate to the nucleus and direct transcription of inflammatory cytokines.4 In lymphocytes, the CBM signalosome includes caspase recruitment domain 11 (CARMA1), B cell lymphoma/leukemia 10 (Bcl10), and mucosa-associated lymphoid tissue lymphoma translocation protein 1. In nonimmune cells, CARMA3 substitutes for CARMA1 in the CBM signalosome, but either of these CARMAs must complex with Bcl10 to trigger the NF-κB inflammatory signaling cascade.5 Therefore, as part of the CBM signalosome, Bcl10 functions to amplify antigen-driven responses in lymphocytes and NF-κB–dependent pathologies in target tissues including fibrosis in the liver and atherosclerosis in the vasculature.5,6

In this context, the experiments of Marko et al7 published in the current issue of Hypertension illustrate the requirement of CARMA-containing signalosomes for full induction of cardiac fibrosis during Ang II–dependent hypertension. They find that Bcl10-deficient mice have a preserved hypertensive response leading to robust cardiac hypertrophy but are protected from the scarring in the heart that disrupts cardiac conduction and raises the susceptibility to ventricular arrhythmia. Moreover, through bone marrow transfer studies, the authors show that Bcl10 in both immune and nonimmune cells potentiates cardiac fibrosis, suggesting the possible involvement of both the CARMA1- and CARMA3-containing CBM signalosomes in the pathogenic process.

The protection from cardiac fibrosis in the Bcl10-deficient recipients of wild-type bone marrow indicates that a population of cells resident in the heart directs CARMA3-dependent scar formation. Although the current experiments do not pinpoint in vivo the precise cell lineage in the heart responsible for these effects, the authors find that knocking down Bcl10 in endothelial cells in vitro blunts Ang II–induced adhesion of monocytes to the endothelium.7 Thus, NF-κB activation by the CARMA3 CBM signalosome in endothelial cells may facilitate recruitment of profibrotic inflammatory cells into the heart during hypertension. In this regard, the hypertensive bone marrow chimeras lacking Bcl10 on somatic cells have reduced cardiac accumulation of macrophages and T lymphocytes, both of which can promote tissue fibrosis.8,9

Nevertheless, the protection from cardiac fibrosis during Ang II–induced hypertension in the bone marrow chimeras lacking Bcl10 solely on immune cells in the Marko studies7 and the recruitment of bone marrow–derived fibroblasts to sites of collagen deposition in the heart confirm the involvement of CARMA-containing signalosomes within circulating inflammatory cells in the disease process and raise the question as to which population of mononuclear cells drives cardiac fibrosis through actions of the CBM signalosome. Macrophages are critical players in directing tissue fibrogenesis,8 and Marko et al7 demonstrate in vitro and in vivo that Bcl10-deficient macrophages have reduced migratory capacity. On the other hand, the known importance of the CBM signalosome within T lymphocytes to drive inflammatory signals after antigen-specific stimulation of the T-cell receptor10 introduces the possibility that cardiac fibrosis in hypertension, as in atherosclerosis,11 may represent an autoimmune phenomenon triggered by classical activation of the cell-mediated adaptive immune response, particularly as Bcl10 regulates the cytoskeletal rearrangements required for full T-cell receptor activation.12,13 Because CARMA1 expression is restricted primarily...
to lymphocytes, analyzing whether the CBM signalosomes involved in cardiac fibrosis incorporate CARMA1 or CARMA3 may help to clarify whether Ang II–induced scarring in the heart is an antigen-driven process. However, determining the cell lineages infiltrating or residing in the heart that regulate hypertension-induced cardiac fibrosis through functions of CARMA1- or CARMA3-containing CBM signalosomes will ultimately require conditional gene targeting experiments in which CBM components are deleted from the endothelium or inflammatory cell populations in relevant hypertension models. The results of those studies will potentially inform translational gene therapy studies or identify more precise drug targets for the abrogation of cardiac fibrosis. However, caution must be taken in the design and interpretation of such experiments because noninducible strategies to delete target genes from the endothelium may also impact gene expression in circulating mononuclear cells.

In the Marko studies, Bcl10 deficiency limits Ang II–induced cardiac fibrosis without altering the degree of cardiac hypertrophy. The preserved cardiac enlargement in the Bcl10 knockouts presumably relates to their intact hypertensive response and suggests that fibrosis rather than hypertrophy of the heart disrupts electrical conduction pathways and raises susceptibility to ventricular arrhythmia. The current studies illustrate that cardiac fibrosis, QRS prolongation, and ventricular arrhythmias during RAS activation require CBM signalosome–dependent NF-xB activation. In the original clinical trials demonstrating efficacy of RAS inhibitors for the treatment of congestive heart failure, hypertension was the leading cause of congestive heart failure. Thus, the Marko experiments may at long last have pinpointed a precise molecular mechanism underlying the remarkable mortality benefit of angiotensin-converting enzyme inhibition in patients with moderate and severe congestive heart failure. Preventing Ang II receptor type 1 activation through the disruption of Ang II generation reduces the occurrence of potentially fatal arrhythmias accruing from CARMA signalosome–induced NF-xB translocation. Nevertheless, understanding whether a first hit of blood pressure elevation is necessary to set this molecular machinery in motion will require experiments with Bcl10-deficient animals in nonhypertensive models of cardiomyopathy.

A fundamental question emanating from the Marko studies is whether Bcl10-dependent NF-xB activation during RAS-mediated hypertension impacts damage to other target organs, such as the vasculature or the kidney. Collectively, the highest expression of the CARMA3 signalosome components is seen in the kidney. In the liver and kidney, Ang II upregulates angiotensinogen via an NF-xB–dependent pathway, but whether Bcl deficiency disrupts intrarenal RAS augmentation awaits elucidation. Nevertheless, the detection of CBM signalosome activity in the heart and kidney together invites a cardiorenal paradigm, relevant to the increased risk of sudden death among patients with kidney disease, in which pathogenic signaling through CBM signalosomes in 1 target organ promotes activation of CBM-dependent pathways in another. In this paradigm, pathogenic, instant CARMA3 induction in the heart or kidney would provoke indirect but sustained stimulation of CARMA1 signaling in circulating inflammatory cells that would in turn amplify CARMA3-dependent fibrosis in the other target organ, yielding cardiorenal damage that is both the cause and effect of Bcl10’s coupling with bad CARMAS.

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References
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