Published in final edited form as:

Hypertension. 2014 November ; 64(5): 933–934. doi:10.1161/HYPERTENSIONAHA.114.04047.

Linking Angiotensin II to NF- κ -induced Cardiovascular Damage: Bad CARMAs

Steven D. Crowley

Division of Nephrology, Department of Medicine, Duke University and Durham Veterans Affairs Medical Centers, Durham, NC

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 ligation culminates in the translocation of nuclear factor kappa light chain enhancer of activated B cells (NF- κ B) to the nucleus where it drives transcription of a broad array of inflammatory mediators.² Accordingly, activation of the NF- κ B signaling pathway by Ang II potentiates target organ damage in hypertension.³ Nevertheless, the upstream mechanisms through which Ang II stimulates NF- κ B in hypertension have awaited further investigation.

In one paradigm of NF- κ B activation, the “CBM signalosome” promotes ubiquitination of an I κ B subunit that would otherwise sequester the rest of the NF- κ B complex in the cytoplasm, allowing a heterodimer composed of NF- κ B's p50 and p65 subunits to translocate to the nucleus and direct transcription of inflammatory cytokines.⁴ In lymphocytes, the CBM signalosome includes CARMA1 (caspase recruitment domain 11), Bcl10 (B cell lymphoma/leukemia 10), and MALT1 (mucosa-associated lymphoid tissue lymphoma translocation protein 1). In non-immune cells, CARMA3 substitutes for CARMA1 in the CBM signalosome, but either of these CARMAs must complex with Bcl10 to trigger the NF- κ B inflammatory signaling cascade.⁵ Therefore, as part of the CBM signalosome, Bcl10 functions to amplify antigen receptor-driven responses in lymphocytes and NF- κ B-dependent pathologies in target tissues including fibrosis in the liver and atherosclerosis in the vasculature.^{5, 6}

In this context, the experiments of Marko and colleagues 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.⁷ They find that Bcl10-deficient mice have a preserved hypertensive response leading to robust cardiac hypertrophy

Correspondence to Steven D. Crowley, Box 103015 DUMC, Durham, NC 27710, Phone: 919-684-9788. Fax 919-684-3011. steven.d.crowley@duke.edu.

Disclosures
None

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 non-immune 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. While 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- κ B activation by the CARMA3 CBM signalosome in endothelial cells may facilitate recruitment of pro-fibrotic 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 and colleagues demonstrate *in vitro* and *in vivo* that Bcl10-deficient macrophages have reduced migratory capacity.⁷ On the other hand, the known importance of the CBM signalosome within T lymphocytes to drive inflammatory signals following antigen-specific stimulation of the T cell receptor¹⁰ introduces the possibility that cardiac fibrosis in hypertension, like 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} Since CARMA1 expression is restricted primarily to lymphocytes,⁴ 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 since non-inducible 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.⁷ 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- κ -B activation. In the original clinical trials demonstrating efficacy of RAS inhibitors for the treatment of congestive heart failure (CHF), hypertension was the leading cause of CHF.¹⁴ Thus, the Marko experiments may at long last have pinpointed a precise molecular mechanism underlying the remarkable mortality benefit of ACE inhibition in patients with moderate and severe CHF.^{14, 15} Preventing AT₁ receptor activation through the disruption of Ang II-generation reduces the occurrence of potentially fatal arrhythmias accruing from CARMA signalosome-induced NF- κ -B nuclear translocation. Nevertheless, understanding whether a “1st hit” of blood pressure elevation is necessary to set this molecular machinery in motion will require experiments with Bcl10-deficient animals in non-hypertensive models of cardiomyopathy.

A fundamental question emanating from the Marko studies is whether Bcl10-dependent NF- κ -B 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.⁵ In the liver and kidney, Ang II upregulates angiotensinogen via an NF- κ -B-dependent pathway,^{16, 17} but whether Bcl-deficiency disrupts intra-renal 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 kidney disease patients,¹⁸ in which pathogenic signaling through CBM signalosomes in one 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.

Acknowledgments

Sources of Funding

This work was supported by funding from (1) National Institutes of Health Grant DK087893-01, (2) the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Biomedical Laboratory Research and Development, Grant BX000893-01A2, (3) the Edna and Fred L. Mandel Center for Hypertension and Atherosclerosis Research, and (4) a Grant-in-Aid from the American Heart Association.

References

1. Nataraj C, Oliverio MI, Mannon RB, Mannon PJ, Audoly LP, Amuchastegui CS, Ruiz P, Smithies O, Coffman TM. Angiotensin ii regulates cellular immune responses through a calcineurin-dependent pathway. *J Clin Invest.* 1999; 104:1693–1701. [PubMed: 10606623]
2. Wolf G, Wenzel U, Burns KD, Harris RC, Stahl RA, Thaiss F. Angiotensin ii activates nuclear transcription factor-kappa through at1 and at2 receptors. *Kidney Int.* 2002; 61:1986–1995.
3. Muller DN, Dechend R, Mervaala EMA, Park J-K, Schmidt F, Fiebeler A, Theuer J, Breu V, Ganten D, Haller H, Luft FC. Nf- κ b inhibition ameliorates angiotensin ii-induced inflammatory damage in rats. *Hypertension.* 2000; 35:193–201. [PubMed: 10642297]

4. Bertin J, Wang L, Guo Y, Jacobson MD, Poyet JL, Srinivasula SM, Merriam S, DiStefano PS, Alnemri ES. Card11 and card14 are novel caspase recruitment domain (card)/membrane-associated guanylate kinase (maguk) family members that interact with bcl10 and activate nf-kappa b. *J Biol Chem.* 2001; 276:11877–11882. [PubMed: 11278692]
5. McAllister-Lucas LM, Ruland J, Siu K, Jin X, Gu S, Kim DS, Kuffa P, Kohrt D, Mak TW, Nunez G, Lucas PC. Carma3/bcl10/malt1-dependent nf-kappab activation mediates angiotensin ii-responsive inflammatory signaling in nonimmune cells. *Proc Natl Acad Sci U S A.* 2007; 104:139–144. [PubMed: 17101977]
6. McAllister-Lucas LM, Jin X, Gu S, Siu K, McDonnell S, Ruland J, Delekta PC, Van Beek M, Lucas PC. The carma3-bcl10-malt1 signalosome promotes angiotensin ii-dependent vascular inflammation and atherogenesis. *J Biol Chem.* 2010; 285:25880–25884. [PubMed: 20605784]
7. Marko L, Henke N, Park J-K, Spallek B, Qadri F, Balogh A, Apel IJ, Oravecz-Wilson KI, Choi M, Przybyl L, Binger KJ, Haase N, Wilck N, Heuser A, Fokuhl V, Ruland J, Lucas PC, McAllister-Lucas LM, Luft FC, Dechend R, Muller DN. Bcl10 mediates angiotensin ii-induced cardiac damage and electrical remodeling. *Hypertension.* 2014 In Press.
8. Ishibashi M, Hiasa K-i, Zhao Q, Inoue S, Ohtani K, Kitamoto S, Tsuchihashi M, Sugaya T, Charo IF, Kura S, Tsuzuki T, Ishibashi T, Takeshita A, Egashira K. Critical role of monocyte chemoattractant protein-1 receptor ccr2 on monocytes in hypertension-induced vascular inflammation and remodeling. *Circulation Research.* 2004; 94:1203–1210. [PubMed: 15059935]
9. Tapmeier TT, Fearn A, Brown K, Chowdhury P, Sacks SH, Sheerin NS, Wong W. Pivotal role of cd4+ t cells in renal fibrosis following ureteric obstruction. *Kidney Int.* 2010; 78:351–362. [PubMed: 20555323]
10. McAllister-Lucas LM, Inohara N, Lucas PC, Ruland J, Benito A, Li Q, Chen S, Chen FF, Yamaoka S, Verma IM, Mak TW, Nunez G. Biml1, a maguk family member linking protein kinase c activation to bcl10-mediated nf-kappab induction. *J Biol Chem.* 2001; 276:30589–30597. [PubMed: 11387339]
11. Hermansson A, Ketelhuth DF, Strothoff D, Wurm M, Hansson EM, Nicoletti A, Paulsson-Berne G, Hansson GK. Inhibition of t cell response to native low-density lipoprotein reduces atherosclerosis. *J Exp Med.* 2010; 207:1081–1093. [PubMed: 20439543]
12. Rueda D, Gaide O, Ho L, Lewkowicz E, Niedergang F, Hailfinger S, Rebeaud F, Guzzardi M, Conne B, Thelen M, Delon J, Ferch U, Mak TW, Ruland J, Schwaller J, Thome M. Bcl10 controls tcr- and fcgamma-induced actin polymerization. *J Immunol.* 2007; 178:4373–4384. [PubMed: 17371994]
13. Acuto O, Cantrell D. T cell activation and the cytoskeleton. *Annu Rev Immunol.* 2000; 18:165–184. [PubMed: 10837056]
14. Effects of enalapril on mortality in severe congestive heart failure. Results of the cooperative north scandinavian enalapril survival study (consensus). The consensus trial study group. *N Engl J Med.* 1987; 316:1429–1435. [PubMed: 2883575]
15. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The solvd investigators. *N Engl J Med.* 1991; 325:293–302. [PubMed: 2057034]
16. Jamaluddin M, Meng T, Sun J, Boldogh I, Han Y, Brasier AR. Angiotensin ii induces nuclear factor (nf)-kappab1 isoforms to bind the angiotensinogen gene acute-phase response element: A stimulus-specific pathway for nf-kappab activation. *Molecular endocrinology.* 2000; 14:99–113.
17. Kobori H, Ozawa Y, Acres OW, Miyata K, Satou R. Rho-kinase/nuclear factor-kappabeta/angiotensinogen axis in angiotensin ii-induced renal injury. *Hypertens Res.* 2011; 34:976–979. [PubMed: 21633359]
18. Pun PH, Smarz TR, Honeycutt EF, Shaw LK, Al-Khatib SM, Middleton JP. Chronic kidney disease is associated with increased risk of sudden cardiac death among patients with coronary artery disease. *Kidney Int.* 2009; 76:652–658. [PubMed: 19536082]