arthritis research&therapy

EDITORIAL

Angiotensin-converting enzyme 2 autoantibodies: further evidence for a role of the renin–angiotensin system in inflammation

Mark C Chappell*

See related research by Takahashi *et al*., http://arthritis-research.com/content/12/3/R85

Abstract

Traditionally viewed as important in the regulation of blood pressure, the renin–angiotensin system – and specifically the angiotensin-converting enzyme (ACE)–angiotensin (Ang) II–AT_1 receptor axis – may play a prominent role to promote inflammation and fibrosis. ACE2, a new component of the renin–angiotensin system, has emerged as a key enzyme that selectively degrades Ang II and generates Ang-(1–7), a bioactive peptide with anti-inflammatory and anti-fibrotic actions. Takahashi and colleagues demonstrate circulating titers of inhibitory autoantibodies against ACE2 in patients with systemic sclerosis. The current study reveals a potentially novel mechanism to attenuate the catalytic activity of ACE2, thereby promoting the actions of Ang II.

The discovery of the angiotensin-converting enzyme (ACE) homolog ACE2 [EC 3.4.15.1] has provoked intensive efforts to elucidate the role of this enzyme in various pathologies, including hypertension, diabetes, heart failure, viral infection, pulmonary injury and liver fibrosis. The biological relevance of ACE2 reflects its critical location in the enzymatic cascade of the renin–angiotensin system to directly govern the local expression of angiotensin (Ang) II and Ang-(1–7), two bioactive hormones with significant and opposing actions.

In the present issue of *Arthritis Research & Therapy*, Takahashi and colleagues assessed circulating levels of ACE2 in patients with connective tissue pathologies including pulmonary hypertension and persistent digital ischemia [1]. In comparison with normal controls, patients with overt vasculopathy expressed significantly higher amounts of ACE2 protein in the circulation. These patients, however, exhibited reduced ACE2 activity in serum and circulating autoantibodies against the enzyme. There are few reports on the circulating levels of ACE2 in humans or experimental models, possibly reflecting the difficulty of obtaining a consistent measurement of the enzymatic activity. The current study reveals a potentially novel mechanism to attenuate the catalytic activity of ACE2, thereby promoting the inflammatory actions of Ang II.

ACE and ACE2 are both chloride-activated metallopeptidases that are predominantly associated with the cell membrane and are widely distributed in various tissues and vascular beds. In contrast to ACE, which cleaves two amino acid residues from the carboxyl terminus of Ang I to form Ang II, ACE2 hydrolyzes a single amino acid from the carboxyl end of Ang II to form Ang-(1–7) [2]. ACE is considered the primary enzymatic pathway that catalyzes the generation of Ang II in the circulation and tissues. ACE inhibitors, which have become standard therapies in the treatment of hypertension and other cardiovascular disease, have little or no inhibitory activity against ACE2, but they reduce the metabolism of Ang-(1–7) [2]. Circulating levels of ACE activity are readily measurable in humans and other species using synthetic substrates or assessing the direct conversion of Ang I to Ang II.

In comparison with serum ACE, Rice and colleagues reported that the circulating levels of ACE2 were 100-fold lower and that <10% (40 out of 494) of their patients expressed measurable ACE2 activity [3]. Nevertheless, families with detectable circulating ACE2 exhibited a greater incidence of cardiovascular pathologies although the overall sample population was low. More recent studies by Epelman and colleagues find that circulating levels of ACE2 are highly associated with increasing severity of progressive heart failure [4]. However, patients

*Correspondence: mchappel@wfubmc.edu
Hypertension and Vascular Disease Center, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27015, USA

were chronically treated with inhibitors of the renin–angiotensin system including aldosterone antagonists which may increase basal ACE2 expression potentially contributing to the protective mechanisms of these therapies.

There is increasing evidence for the interplay of the renin–angiotensin system and inflammatory events [5]. Pre-eclampsia is associated with circulating autoantibodies against the AT_1 protein that act as functional receptor agonists to promote vasoconstriction and inflammation [5]. Studies by Harrison and colleagues suggest that T-cell expression of the AT_1 receptor contributes to inflammatory events and the development of hypertension. Moreover, activated T cells may themselves generate Ang II locally to influence cell function in an autocrine manner [6]. In experimental encephalomyelitis, AT_1 expression was increased and subsequent AT_1 receptor blockade or ACE inhibition ameliorated the autoimmune inflammation [7].

The present findings by Takahashi and colleagues reveal increased expression of circulating ACE2 in patients with vasculopathy utilizing a novel protein capture assay [1]. Despite the increased levels of the enzyme, ACE2 activity was markedly lower in comparison with the control group. Indeed, the authors report the presence of circulating levels of ACE2 antibodies that exhibit inhibitory activity *in vitro*. Previous studies showed that commercial sources of antibodies against ACE2 also inhibit enzyme activity, suggesting the epitope may encompass the catalytic site [4]; however, the present study is the first to identify autoantibodies that attenuate enzyme activity in a patient population.

The current findings are of potential importance in our understanding of the role of circulating and tissue sources of ACE2, particularly in various disease states. Increased circulating levels of ACE2 may reflect a compensatory mechanism to alter the balance of the renin–angiotensin system to favor the ACE2–Ang-(1–7)–AT_7 receptor axis and promote the anti-fibrotic and anti-inflammatory actions of the heptapeptide, as well as attenuate the Ang II–AT_1 receptor pathway. Clearly, generation of endogenous antibodies with inhibitory activity against ACE2 may undermine this compensatory response. Indeed, identification of endogenous ACE2 inhibitors is important *in lieu* of optimizing the therapeutic benefits following administration of recombinant soluble ACE2, as recently demonstrated in models of diabetic nephropathy [8] and liver fibrosis [9] or in the genetic expression of ACE2 in pulmonary hypertension [10].

Although the ongoing study of the renin–angiotensin system has now surpassed the century mark, the characterization of this system and identification of the factors that regulate the expression or activity of its components continues to yield novel therapeutic targets in cardiovascular disease and other pathologies.

Abbreviations

ACE, angiotensin-converting enzyme; Ang, angiotensin.

Acknowledgements

These studies were supported in part by grants from the National Institute of Health (HL-56973).

Competing interests

The authors declare that they have no competing interests.

Published: 28 June 2010

References

1. Takahashi Y, Haga S, Ishizaka Y, Mimori A: **Autoantibodies to angiotensin converting enzyme 2 in patients with connective tissue diseases.** *Arthritis Res Ther* 2010, **12:**R85.
2. Chappell MC: **Emerging evidence for a functional angiotensin-converting enzyme 2-angiotensin-(1-7) mas receptor axis; more than regulation of blood pressure?** *Hypertension* 2007, **50:**596-599.
3. Rice GI, Jones AL, Grant PJ, Carter AM, Turner AJ, Hooper NM: **Circulating activities of angiotensin-converting enzyme, its homolog, angiotensin-converting enzyme 2, and neprilysin in a family study.** *Hypertension* 2006, **48:**914-920.
4 Epelman S, Tang WHW, Chen SY, Van Lente F, Francis GS, Sen S: **Detection of soluble angiotensin-converting enzyme 2 in heart failure: insights into the endogenous counter-regulatory pathway of the renin–angiotensin–aldosterone system.** *J Am Coll Cardiol* 2008, **52:**750-754.
5 Verlohren S, Muller DN, Luft FC, Dechend R: **Immunology in hypertension, preeclampsia, and target-organ damage.** *Hypertension* 2009, **54:**439-443.
6. Hoch NE, Guzik TJ, Chen W, Deans T, Maalouf SA, Gratze P, Weyand C, Harrison DG: **Regulation of T-cell function by endogenously produced angiotensin II.** *Am J Physiol* 2009, **296:**R208-R216.
7. Platten M, Youssef S, Hur EM, Ho PP, Han MH, Lanz TV, Phillips LK, Goldstein MJ, Bhat R, Raine CS, Sobel RA, Steinman L: **Blocking angiotensin-converting enzyme induces potent regulatory T cells and modulates TH1- and TH17-mediated autoimmunity.** *Proc Natl Acad Sci U S A* 2009, **106:**14948-14953.
8. Oudit GY, Liu GC, Zhong J, Basu R, Chow FL, Zhou J, Loibner H, Janzek E, Schuster M, Penninger JM, Herzenberg AM, Kassiri Z, Scholey JW: **Human recombinant ACE2 reduces the progression of diabetic nephropathy.** *Diabetes* 2010, **59:**529-538.
9. Osterreicher CH, Taura K, De Minicis S, Seki E, Penz-Osterreicher M, Kodama Y, Kluwe J, Schuster M, Oudit GY, Penninger JM, Brenner DA: **Angiotensin-converting-enzyme 2 inhibits liver fibrosis in mice.** *Hepatology* 2009, **50:**929-938.
10. Yamazato Y, Ferreira AJ, Hong KH, Sriramula S, Francis J, Yamazato M, Yuan L, Bradford CN, Shenoy V, Oh SP, Katovich MJ, Raizada MK: **Prevention of pulmonary hypertension by angiotensin-converting enzyme 2 gene transfer.** *Hypertension* 2009, **54:**365-371.

doi:10.1186/ar3052
Cite this article as: Chappell MC: Angiotensin-converting enzyme 2 autoantibodies: further evidence for a role of the renin–angiotensin system in inflammation. *Arthritis Research & Therapy* 2010, **12:**128.