Nature Reviews Cardiology published online 5 May 2015; doi:10.1038/nrcardio.2015.6-c1

ACE2–angiotensin-(1-7)–Mas axis might be a promising therapeutic target for pulmonary arterial hypertension

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We read with great interest the Review by Latus *et al.* (Treatment of pulmonary arterial hypertension in children. *Nat. Rev. Cardiol.* **12**, 244–254; 2015),[1] in which the authors thoroughly summarize the latest developments in drug therapy for patients with pulmonary arterial hypertension (PAH). They mention some novel therapeutic targets in PAH; however, they do not discuss the angiotensin-converting enzyme (ACE) 2–angiotensin-(1-7)–Mas axis in their article.

The ACE2–angiotensin-(1-7)–Mas receptor axis is an important component of the renin–angiotensin system. ACE2 is highly expressed in the lungs, and converts angiotensin II into angiotensin-(1-7). Angiotensin-(1-7) mediates vasodilatation, antiproliferation, antiapoptosis, and antifibrosis by stimulating the receptor Mas, which counterbalances the vasoconstrictive, proliferative, and fibrotic pathways (ACE–angiotensin II–type 1 angiotensin II receptor [AT_1R] axis). Studies have indicated that an imbalance between the mechanisms of the ACE–angiotensin II–AT_1R and the ACE2–angiotensin-(1-7)–Mas pathways involved in the pulmonary circulation might lead to the development of PAH.[2–5]

ACE inhibitors and AT_1R blockers inhibit the ACE–angiotensin II–AT_1R axis, but their primary effects are to reduce systemic blood pressure. Consequently, these drugs are unsuccessful in treating patients with PAH, who are already at high risk of developing hypotension owing to right ventricular overload. Some studies have shown that ACE2 or angiotensin-(1-7), in the form of a synthetic molecule, continuous injection of resorcinolnaphthalein, or gene transfer, can induce beneficial pulmonary outcomes in a monocrotaline-induced model of PAH, with no adverse effects on systemic blood pressure.[6–9] Our studies have shown that serum ACE2 and angiotensin-(1-7) levels were decreased in patients with PAH due to congenital heart disease, and mean pulmonary artery pressure is negatively correlated with serum levels of ACE2 and angiotensin-(1-7).[10,11] Shenoy and colleagues have developed a system to generate human ACE2 and angiotensin-(1-7) within plant chloroplasts using transplastomic technology, and observed substantial functional and structural cardiopulmonary improvements with oral delivery of ACE2 and angiotensin-(1-7) in protocols for both prevention and reversal of PAH.[12,13] In the reversal protocol, combination therapy with ACE2 and angiotensin-(1-7) was better than single therapy, particularly at the higher combined dose.[12]

On the basis of these findings, the ACE2–angiotensin-(1-7)–Mas axis is a potential new target for treating PAH. Currently, a clinical trial to assess the mechanism, safety, and efficacy of ACE2 in the treatment of PAH is underway.[14]

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Acknowledgements
H.D. has received research grants from the National Natural Science Foundation of China (No.81360037), Natural Science Foundation of Yunnan (No.2012FB009, 2013FZ284), and Dr Academic Award of Yunnan. L.J. has received research grants from the National Natural Science Foundation of China (No.31160230), and Natural Science Foundation of Yunnan (No.2011FB166). Z.X. has received a Monash Professorial Fellowship and the Talent Program of Yunnan.

Competing interests
The authors declare no competing interests.

1. Latus, H., Delhaas, T., Schranz, D. & Apitz, C. Treatment of pulmonary arterial hypertension in children. *Nat. Rev. Cardiol.* **12**, 244–254 (2015).
2. Kleinsasser, A. *et al*. Recombinant angiotensin-converting enzyme 2 suppresses pulmonary vasoconstriction in acute hypoxia. *Wilderness Environ. Med*. **23**, 24–30 (2012).
3. Li, G. *et al.* ACE2 activation confers endothelial protection and attenuates neointimal lesions in prevention of severe pulmonary arterialhypertension in rats. *Lung* **191**, 327–336 (2013).
4. Rondelet, B. *et al.* Prevention of pulmonary vascular remodeling and of decreased BMPR-2 expression by losartan therapy in shunt-induced pulmonary hypertension. *Am. J. Physiol. Heart Circ. Physiol.* **289**, H2319–H2324 (2005).
5. Shenoy, V. *et al.* Diminazene attenuates pulmonary hypertension and improves angiogenic progenitor cell functions in experimental models. *Am. J. Respir. Crit. Care Med.* **187**, 648–657 (2013).
6. Ferreira, A. J. *et al.* Evidence for angiotensin-converting enzyme 2 as a therapeutic target for the prevention of pulmonary hypertension. *Am. J. Respir. Crit. Care Med.* **179**, 1048–1054 (2009).
7. Li, G. *et al.* Angiotensin-converting enzyme 2 activation protects against pulmonary arterial hypertension through improving early endothelial function and mediating cytokines levels. *Chin. Med. J.* **125**, 1381–1388 (2012).
8. Yamazato, Y. *et al.* Prevention of pulmonary hypertension by angiotensin-converting enzyme 2 gene transfer. *Hypertension* **54**, 365–371 (2009).
9. Shenoy, V. *et al.* The angiotensin-converting enzyme 2/angiogenesis-(1-7)/Mas axis confers cardiopulmonary protection against lung fibrosis and pulmonary hypertension. *Am. J. Respir. Crit. Care Med.* **182**, 1065–1072 (2010).
10. Dai, H. L. *et al.* The changes of serum angiotensin-converting enzyme 2 in patients with pulmonary arterial hypertension due to congenital heart disease. *Cardiology* **124**, 208–212 (2013).
11. Dai, H. *et al.* Decreased levels of serum angiotensin-(1-7) in patients with pulmonary arterial hypertension due to congenital heart disease. *Int. J. Cardiol.* **176**, 1399–1401 (2014).
12. Shenoy, V. *et al.* Oral delivery of angiotensin-converting enzyme 2 and angiotensin-(1-7) bioencapsulated in plant cells attenuates pulmonary hypertension. *Hypertension* **64**, 1248–1259 (2014).
13. Grobe, J. L. & Sigmund, C. D. Another reason to eat your greens: cardiopulmonary protection by dietary delivery of angiotensin-converting enzyme-2 and angiotensin-(1-7) made in plants. *Hypertension* **64**, 1182–1183 (2014).
14. US National Library of Medicine. *ClinicalTrials.gov* [online], https://clinicaltrials.gov/ct2/show/NCT01884051 (2014).