Mechanisms by which angiotensin-receptor blockers increase ACE2 levels

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We read with interest the well-balanced Comment by Zheng and colleagues (COVID-19 and the cardiovascular system. *Nat. Rev. Cardiol.* **17**, 259–260; 2020)[1] and their Reply (Reply to: 'Interaction between RAAS inhibitors and ACE2 in the context of COVID-19'. *Nat. Rev. Cardiol.* **17**, 313–314; 2020)[2] to the Correspondence written by Mourad and Levy (Interaction between RAAS inhibitors and ACE2 in the context of COVID-19. *Nat. Rev. Cardiol.* **17**, 313; 2020)[3].

We have reported the capacity of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) to increase the left ventricular levels of *Ace2* mRNA when given to normotensive rats either under normal conditions[4] or following coronary artery ligation[5]. This work revealed the existence of a negative feedback mechanism in which the angiotensin-converting enzyme 2 (ACE2)–angiotensin-(1–7)–Mas receptor axis counterbalances the pathological effects of angiotensin II[6]. In their Reply[2], Zheng and colleagues suggest that the mechanism underlying the increase in levels of cardiac *Ace2* mRNA and ACE2 activity by these drugs was undetermined; we wish to clarify that we did elucidate the mechanism by which these medications augment the expression of ACE2 (REFS[7–9]).

In these studies, the inhibitory effect of angiotensin II on the transcription of *Ace2* in cultured cerebellar or medullary astrocytes from rats was prevented by exposure to losartan or valsartan but not PD123319 (a blocker of angiotensin II receptor type 2)[7]. A similar finding was obtained in cultured cardiomyocytes and cardiac fibroblasts from neonatal rats[8]; in these in vitro experiments, the inhibitory effect of angiotensin II on the transcription of *Ace2* and on ACE2 enzymatic activity was replicated by the treatment of cardiomyocytes with exogenous endothelin 1 (REF.[8]). The inhibitory effect of angiotensin II on *Ace2* transcription is mediated by activation of extracellular signal-regulated kinase 1 (ERK1; also known as MAPK3) and ERK2 (also known as MAPK1)[8,9]. In addition, treatment of rat neonatal cardiomyocytes in vitro with atrial natriuretic peptide reversed the downregulation of *Ace2* transcription induced by angiotensin II or endothelin 1 (REF.[8]). We have also shown that angiotensin II reduces *Ace2* transcription and ACE2 activity in rat aortic smooth muscle cells in vitro via activation of a MAPK phosphatase pathway[9], as confirmed by others[10].

These experiments show that *Ace2* expression in cardiac tissues in rats depends on the balance and concentration of regulatory molecules. We appreciate the opportunity to highlight the cellular signalling mechanisms by which ARBs increase *Ace2* expression and ACE2 activity, especially given that ACE inhibitors and ARBs have opposite effects on the plasma and tissue concentrations of angiotensin II and angiotensin-(1–7) (REF.[6]).

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1. Zheng, Y.-Y., Ma, Y.-T., Zhang, J.-Y. & Xie, X. COVID-19 and the cardiovascular system. *Nat. Rev. Cardiol.* **17**, 259–260 (2020).
2. Zheng, Y.-Y., Ma, Y.-T., Zhang, J.-Y. & Xie, X. Reply to: 'Interaction between RAAS inhibitors and ACE2 in the context of COVID-19'. *Nat. Rev. Cardiol.* **17**, 313–314 (2020).
3. Mourad, J.-J. & Levy, B. I. Interaction between RAAS inhibitors and ACE2 in the context of COVID-19. *Nat. Rev. Cardiol.* **17**, 313 (2020).
4. Ferrario, C. M. et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* **111**, 2605–2610 (2005).
5. Ishiyama, Y. et al. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. *Hypertension* **43**, 970–976 (2004).
6. Ferrario, C. M., Ahmad, S., Joyner, J. & Varagic, J. Advances in the renin angiotensin system focus on angiotensin-converting enzyme 2 and angiotensin-(1–7). *Adv. Pharmacol.* **59**, 197–233 (2010).
7. Gallagher, P. E., Chappell, M. C., Ferrario, C. M. & Tallant, E. A. Distinct roles for ANG II and ANG-(1–7) in the regulation of angiotensin-converting enzyme 2 in rat astrocytes. *Am. J. Physiol. Cell Physiol.* **290**, C420–C426 (2006).
8. Gallagher, P. E., Ferrario, C. M. & Tallant, E. A. Regulation of ACE2 in cardiac myocytes and fibroblasts. *Am. J. Physiol. Heart Circ. Physiol.* **295**, H2373–H2379 (2008).
9. Gallagher, P. E., Ferrario, C. M. & Tallant, E. A. MAP kinase/phosphatase pathway mediates the regulation of ACE2 by angiotensin peptides. *Am. J. Physiol. Cell Physiol.* **295**, C1169–C1174 (2008).
10. Koka, V. et al. Angiotensin II up-regulates angiotensin I-converting enzyme (ACE), but down-regulates ACE2 via the AT1-ERK/p38 MAP kinase pathway. *Am. J. Pathol.* **172**, 1174–1183 (2008).

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Competing interests
The authors declare no competing interests.