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COMMENTARY

RGS2 determines the preventive effects of ARBs against vascular remodeling: toward personalized medicine of anti-hypertensive therapy with ARBs

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The clinical goal of anti-hypertensive therapy is not the reduction of blood pressure, but the prevention of cardiovascular diseases (CVDs). In practical terms, as blood pressure is closely associated with CVDs, anti-hypertensive medications are chosen by considering their effectiveness at reducing blood pressure; however, cynically speaking, even if some cardiovascular events occur in medicated patients, it is impossible to ascertain that the medication is inadequate for each patient because no 'control' treatment exists in the individual case. Therefore, personalized medicine is expected to improve the outcome of hypertension treatment. To that end, much effort has been made to establish predictive biomarkers for drug response to prevent CVDs.

In this issue, Matsumoto *et al.*[1] demonstrated that low-dose telmisartan, an angiotensin receptor blocker (ARB), clearly prevents angiotensin (Ang) II-induced vascular remodeling in regulator of G protein signaling (Rgs2) -deficient mice (Figure 1). Rgs2 regulates the signal transduction of seven-transmembrane domain receptors (7TMRs), including the angiotensin type I receptor (AT1R).[2] Stimulation of ATR1 by Ang II results in the activation of Gαq proteins. Rgs2 accelerates the inactivation of Gαq by activating GTPase-activating proteins. In addition, recent studies have shown that Rgs2 influences the activities of channels, scaffolds and kinases, and also stabilizes microtubules. Therefore, Rgs2 is not simply the inactivator of 7TMRs but also the coordinator of the 7TMR signaling network. Using Rgs2+/+, Rgs2+/− and Rgs2−/− mice, Matsumoto *et al.* generated an aortic aneurysm by infusing Ang II. Ang II infusion resulted in blood-pressure elevation and increased aneurysm incidence; however, there were no differences in these clinical phenotypes among the three groups. Surprisingly, low-dose telmisartan inhibited the development of aortic aneurysm and improved survival without reducing blood pressure in Rgs2−/− mice. In the aortic walls of Rgs2−/− mice, superoxide production and NAD(P)H oxidase activity were significantly suppressed by low-dose telmisartan.

Previously, it was reported that Rgs2−/− mice show a hypertensive phenotype.[3,4] Interestingly, Heximer *et al.*[4] demonstrated that candesartan more dramatically decreased blood pressure in Rgs2−/− mice than in wild-type mice, implying that the clinical effectiveness of ARBs in blood-pressure reduction depends on Rgs2 activity. Importantly, the article by Matsumoto *et al.* in this issue describes that low-dose telmisartan exhibits inhibitory effects on aneurysm formation without affecting blood pressure in Rgs2−/− mice, suggesting that *Rgs2* gene depletion alters the responsiveness to ARB and prevents aneurysm formation. Collectively, it can be concluded that Rgs2 activity influences vascular remodeling, at least partially, independently of blood-pressure elevation, and that Rgs2 determines the effectiveness of ARB not only in blood-pressure reduction but also in vascular protection. The findings in this animal model may be clinically informative, but, at the same time, they raise clinical questions. Even in patients whose elevated blood pressure is not reduced in response to ARBs, will ARBs show protective effects against vascular remodeling if the Rgs2 activity is low? Should these patients continue to take ARB in order to prevent vascular diseases? To answer these questions, we must establish clinical approaches to estimate Rgs2 activity in patients.

In this context, pharmacogenomics (PGx) studies may provide important insight. Interestingly, Kamide *et al.*[5] reported that genetic polymorphisms of the *Rgs2* gene are associated with blood-pressure elevation. Considering the phenotypic alterations in *Rgs2*-null mice, they propose that the *Rgs2* gene polymorphisms that are associated with elevated blood pressure are likely to show reduced Rgs2 activity. To clinically apply the *Rgs2* genotype information, two problems must be solved. First, the association between Rgs2 polymorphisms and Rgs2 activity is somewhat speculative. Biological and biochemical characterization of these genetic polymorphisms is needed to prove these concepts. Next, it is essential to clinically address whether these polymorphisms are associated with the responsiveness to ARB in anti-vascular remodeling therapy as well as in blood pressure-reducing therapy. A number of PGx studies have examined the association between genetic polymorphisms and the effectiveness of anti-hypertensive drugs; however, in most of these studies, the primary end point is the reduction of blood pressure, but not the vascular protection. Thus, pharmacogenomic analysis should be more actively integrated into randomized controlled clinical trials of anti-hypertensive drugs, and the clinical importance of the pharmacogenomic information should be evaluated as anti-vascular remodeling therapy from the point of view of the prevention of CVDs.

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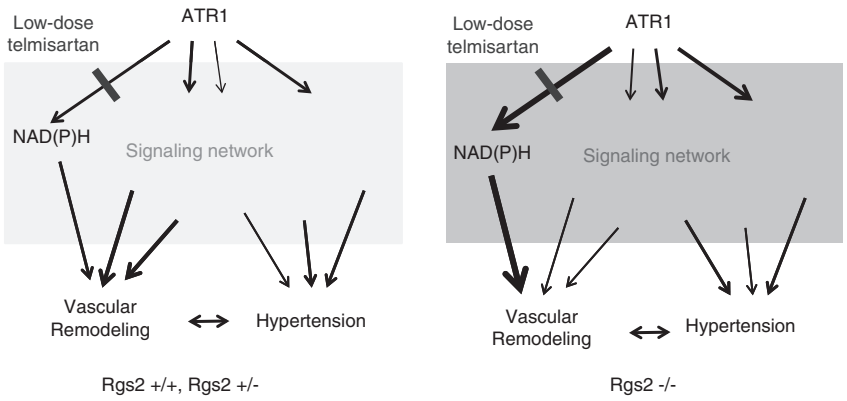

Figure 1 The responsiveness to low-dose telmisartan is determined by Rgs2 activity. Rgs2 activity regulates the signaling network downstream of AT1R. *Rgs2* gene ablation results in the enhancement of NAD(P)H activation. Low-dose telmisartan preferentially inhibits the NAD(P)H pathway and prevents vascular remodeling. In Rgs2−/− mice, vascular remodeling may depend largely on the NAD(P)H pathway, as compared with Rgs2+/+ or Rgs2+/− mice.

In spite of a number of difficulties, personalized medicine for ARB therapy is attractive. In addition to hypertension, the renin–angiotensin system (RAS) is involved in various types of diseases, including diabetes mellitus (DM)/insulin resistance. In the study by Matsumoto *et al.* in this issue, telmisartan treatment resulted in limited improvement of the metabolic profiles of Rgs2−/− mice; however, this finding does not necessarily indicate that Ang II-induced metabolic disturbances are independent of Rgs2 signaling. This argument is supported by the following ideas. First, this study was not designed to examine the effects of ARB on lipid or glucose metabolism. Calorie and lipid intake was not taken into account. Second, although recent clinical trials have shown that RAS blockade by telmisartan is clinically beneficial for reducing the risk of DM/insulin resistance,[6] it cannot be concluded that telmisartan-induced resistance to the metabolic disorder is derived exclusively from its agonistic effects on PPARs. Indeed, clinical studies have also shown that candesartan prevents the onset of DM.[7] Importantly, Ang II induces insulin resistance through reactive oxygen species.[8] Taken together with the result of this new study that Rgs2 activity influences the inhibitory effects of telmisartan on the production of reactive oxygen species, Rgs2 activity may also be considered to be a determinant of DM susceptibility. The genetic information of *Rgs2* gene polymorphisms might be more important than previously thought.

In conclusion, Matsumoto *et al.* propose the possibility that Rgs2 activity is a predictive biomarker for the inhibitory effects of ARBs on vascular remodeling. The clinical evaluation of the effects of the *Rgs2* genotypes on ARB responsiveness may contribute to the personalization of anti-hypertensive therapy.

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