# Homocysteine directly interacts and activates the angiotensin II type I receptor to aggravate vascular injury

With the support of the National Natural Science Foundation of China, Prof. Kong Wei (孔炜) from the Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Peking University Health Science Center and Prof. Sun JinPeng (孙金鹏) from the Department of Biochemistry and Molecular Biology, School of Medicine, Shandong University have made great advances in the study of the pathogenesis of abdominal aortic aneurysm and the mechanism of activation of AT1 receptor, which was published in *Nature Communications* (2018, 9: 11).

Homocysteine (Hcy) is the intermediate product of methionine metabolism. About 75% of Chinese patients with hypertension are associated with hyperhomocysteinemia due to genetic and dietary factors. Kong's group previously reported that hyperhomocysteinemia (HHcy) was an independent risk factor of abdominal aortic aneurysm by aggravating adventitial inflammation through NADPH oxidase and deubiquitinase CYLD (*Circ Res*, 2012, 111(10): 1261—73; *Arterioscler Thromb Vasc Biol*, 2017, 37(9): 1698—1709).

By performing the radio ligand receptor binding assay, molecular dynamics and site-directed muta-genesis experiments as well as *in vivo* study on AT1 receptor knock out mice, Kong's group found in the latest research that the pathological concentration of Hcy could bind to the AT1 receptor by forming a salt bridge and a disulfide bond with its Arg167 and Cys289 residues. They found that Hcy could directly activate AT1 receptor signaling by regulating the conformation of the AT1 receptor both orthosterically and allosterically. However, blocking the AT1 receptor by *AT1R* knock out or using ARB (telmisartan) could reverse the effect of Hcy, whereas using ACEI couldn't, which suggests that Hcy was a novel ligand of the AT1 receptor and its effect was independent of Ang II concentration.

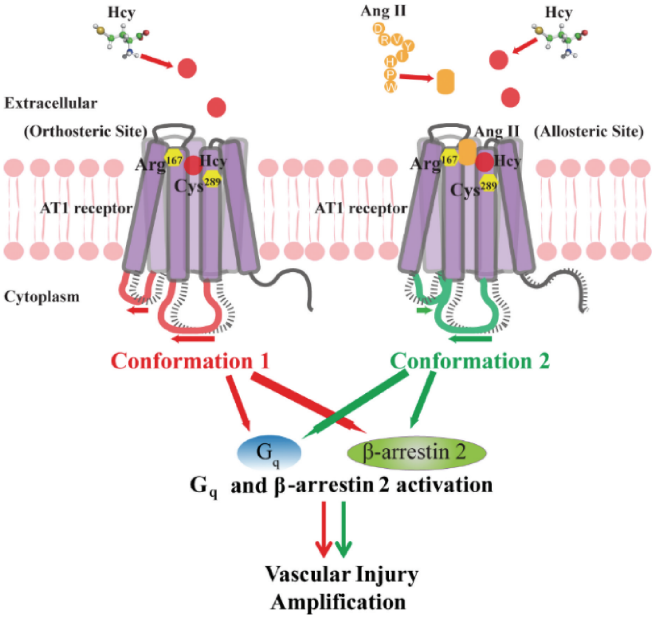


**Figure** Homocysteine directly binds to the AT1 receptor and activates the Gq and β-arrestin 2 signaling.

Taken together, these findings suggest that the strategies aimed at blocking the AT1 receptor may mitigate HHcy-associated aneurysmal vascular injuries.