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The novel renin-angiotensin system, inflammation and hypertension

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Hypertension is one of the most important risk factors for cardiovascular disease and stroke and has become an increasingly important contributor to the global health burden. However, the risk factors for hypertension are still largely unknown. Recently, chronic low grade low-grade inflammation has been identified as an integral part in the pathogenesis of vascular disease, including hypertension, either as a primary or secondary event. Reactive oxygen species (ROS) may directly alter vascular function or cause changes in vascular tone by several mechanisms including altered nitric oxide bioavailability and signaling and enhanced pro-inflammatory factors, which may contribute to vascular injury, remodeling and end-organ damage in hypertension. In the renin-angiotensin system (RAS), the activation of angiotensin II (Ang II) is an important mediator of oxidative stress and inflammation in hypertension. The newly-discovered angiotensin-converting enzyme 2 (ACE2), a carboxy-peptidase structurally related to ACE but resistant to ACE inhibitors. The key peptidase action of ACE2 is degradation of Ang II to Ang-(1-7), which exerts vasodilatory/ anti-proliferative/anti-inflammatory actions and functions effectively as a negative regulator of the RAS. In our recent research work, we have demonstrated that loss of ACE2 enhances the adverse pathological remodeling susceptibility to Ang II with elevated oxidative stress and inflammation in mice. Expression of proinflammatory cytokines, interleukin-1β and chemokine (C-C motif) ligand 5, were increased in heart and kidney in ACE2 knockout mice in association with greater activation of extracellular-regulated kinase 1/2 and increase of protein kinase C levels. In contrast, human recombinant ACE2 prevents Ang II-induced oxidative stress, inflammation and pathological signaling in hypertension. Interventions such as ACE2 replenishment or augmentation of its actions have proven successful in reducing hypertension, and cardiac damage in a range of different models. ACE2 is abundantly expressed in the cardiovascular tissue and emerging evidence suggests a beneficial role for this enzyme against hypertension and cardiovascular diseases. Targeting the novel renin-angiotensin system by gene therapy or antibody treatment may provide a longer-term treatment for Patients with chronic inflammatory disease such as hypertension. This work was supported by National Natural Science Foundation of China (30973522 & 81170246), Shanghai Pujiang Talents Plan Project (11PJ1408300) and the Canadian Institute for Health Research Project (G.Y.O. 86602).