Hypertension substantially increases the risk for coronary heart disease, stroke, retinopathy, and nephropathy. In patients, hypertension usually clusters with the other components of the metabolic syndrome, such as microalbuminuria, central obesity, insulin resistance, dyslipidemia, hypercoagulation, increased inflammation, and left ventricular hypertrophy. Of importance, obesity, atherosclerosis, insulin resistance, hyperinsulinemia, hyperlipidemia, essential hypertension, type 2 diabetes mellitus, and for coronary heart disease are components of the metabolic syndrome and are associated with elevated plasma levels of C-reactive protein, interleukin-6, and tumor necrosis factor-α, which are markers of inflammation. This suggests that the metabolic syndrome is a low-grade, systemic, inflammatory condition. Hence, instituting antiinflammatory measures might be beneficial in preventing or halting the progression of the metabolic syndrome in high-risk populations.

Therefore, numerous studies have been conducted to identify the relationship between hypertension and inflammation. Clinical data demonstrated that hypertension is clearly linked to inflammation, because C-reactive protein levels are reported to be associated with future development of hypertension. In addition, basic and clinical research have also demonstrated that upregulation of genes related to inflammation, such as tumor necrosis factor-α, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1, to name a few, was observed in target organs and/or circulation of hypertensive animals and patients. Increase in tissue and/or circulating levels of inflammatory cytokines suggest that the production of these cytokines increases the risk of plaque rupture.

However, how hypertension causes inflammation is not clear. Does high blood pressure directly cause inflammation, or do other humoral factors related to hypertension promote inflammation? Many researchers suspect that angiotensin II (Ang II) may be responsible for the inflammatory changes. Of importance, obesity, atherosclerosis, insulin resistance, hyperinsulinemia, hyperlipidemia, essential hypertension, type 2 diabetes mellitus, and for coronary heart disease are components of the metabolic syndrome and are associated with elevated plasma levels of C-reactive protein, interleukin-6, and tumor necrosis factor-α, which are markers of inflammation. This suggests that the metabolic syndrome is a low-grade, systemic, inflammatory condition. Hence, instituting antiinflammatory measures might be beneficial in preventing or halting the progression of the metabolic syndrome in high-risk populations.

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However, how hypertension causes inflammation is not clear. Does high blood pressure directly cause inflammation, or do other humoral factors related to hypertension promote inflammation? Many researchers suspect that angiotensin II (Ang II) may be responsible for the inflammatory changes. Ang II has direct effects on cellular proliferation, hypertrophy, apoptosis, and synthesis/degradation of matrix proteins and collagen that underlie development and progression of atherosclerosis as well as stability of the atherosclerotic plaque. Blockade of Ang II actions, therefore, offers the possibility of interfering with these direct and indirect effects and of lessening the progression of atherosclerosis, stabilizing vulnerable plaques, and even reversing the disease. Previous reports suggest that Ang II may play a pivotal role in the progression of inflammation in hypertension. However, the link between Ang II and inflammation in hypertension was missing.

In this issue of Hypertension, Zhao et al address the question of the missing link between inflammation and hypertension. In their report, they demonstrate that vascular endothelial growth factor (VEGF) is an essential mediator in Ang II–induced vascular inflammation and structural changes using a gene transfer approach. The role of VEGF in hypertension is still an enigma, because there is considerable debate over the vasculoprotective versus pro-inflammatory/arteriosclerotic effects of VEGF. Zhao et al used gene transfer to address this difficult question. Characterization of the role of the various factors involved in vivo is limited by the difficulty to manipulate individual components and by methodological limitations in studying their local function in the absence of contribution by VEGF in the circulation. In vivo gene transfer technology provides the opportunity to study the physiological responses to in vivo manipulation of the individual components related to hypertension (ie, by overexpression or inhibition) without changes in the circulating system. An important new observation has been made using transgenic/gene-targeting technology. Transgenic/gene targeting technology has many advantages, such as the ability to study specific gene function as systemic and developmental effects and to test specific gene function chronically. Nevertheless, this technology may have several potential disadvantages: (1) it is time-consuming and costly; (2) the effect of the overexpressed transgene is exerted throughout development; (3) it may be difficult to target the transgenic expression to a specific tissue; and (4) it may be difficult to exclude the potential contribution of the systemic effect of transgene expression for some cases. The targeted gene can cause a lethal effect, in which case it may be impossible to test its specific functions by transgenic or gene targeting techniques. For example, loss of a single VEGF allele is lethal in the mouse embryo. In addition, mice homozygous for mutations that inactivate either Flt-1 or Flk-1/KDR receptor also die in utero. Therefore, to dissect out the relation between hypertension and inflammation is quite difficult.

The gene transfer approach may be useful. Considering the lethality of VEGF knockout, in this study Zhao et al trans-
fected the gene of the soluble form of the VEGF receptor, Flt, into muscle of mice studied after Ang II infusion. Secretion of the soluble form of Flt into the circulation removed VEGF binding to the target receptor. Using this technique, they clearly demonstrated that VEGF is responsible for Ang II–induced vascular inflammation and structural changes such as wall thickening. However, unresolved questions still lie ahead. One of the missing links is how Ang II activated VEGF signaling. It is controversial whether Ang II directly activates VEGF. The relationship between VEGF and another transcription factor related to inflammation, NFkB, is also still unclear. In addition, the article by Zhao et al demonstrated the important finding that hypertension and cardiac hypertrophy were not affected by the blockade of VEGF signaling. Thus, there is still a missing link between inflammation and hypertension and cardiac hypertrophy. Further efforts to find the links between hypertension and other common diseases such as the acute coronary syndrome are necessary. Application of in vivo gene transfer will help provide further information to find these missing links.

References
Is Vascular Endothelial Growth Factor a Missing Link Between Hypertension and Inflammation?
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