Angiotensin II to macrophage: will you polarize? And when?

Philip Wenzel and Thomas Münzel
Department of Medicine 2, University Medical Center Mainz, Mainz, Germany

An activated immune system is increasingly regarded as a major contributor to hypertension in various animal models (spontaneously hypertensive rats, angiotensin II-induced hypertension, and salt-dependent hypertension to name a few). For example, activation of T cells, dendritic cells, and monocytes/macrophages has been observed in sympathetic outflow-dependent hypertension (8, 11), in conductance vessels (2, 3), in the kidney (1, 10, 14), and in the salt-challenged interstitium (7, 17). Also, end-organ damage seen in arterial hypertension is attributed significantly to activated immune cells (for review, see McMaster et al. (9)). Attenuating an inflammatory response has been shown to reduce sequela of hypertension like cardiac dysfunction (6), hypertensive kidney disease (12), and aortic aneurysm formation (15). Importantly, in many of these observations, angiotensin II is directly involved or at least implicated.

In particular, monocytes and macrophages have been identified as important contributors to vascular inflammation and hypertension elicited by angiotensin II. Mice that lack the mature macrophages because of macrophage-colony stimulating factor deficiency have a significantly blunted response to angiotensin II with less vascular oxidative stress, endothelial dysfunction, and arterial hypertension (2). Ablation of lysozyme-M+ myelomonocytic cells attenuates almost all consequences of angiotensin II, including vascular remodeling (16). Inflammatory monocytes typically express high levels of chemokine (C-C motif) receptor 2 (CCR2), the receptor for the monocyte chemoattractant protein 1 [chemokine (C-C motif) ligand 2]. CCR2-deficient mice have been reported to be protected from angiotensin II-induced vascular remodeling (4). Interestingly, CCR2−/− mice are protected from angiotensin II-induced abdominal aortic aneurysm, a late sequel of hypertension (15). However, it has been unclear whether inflammatory monocytes/macrophages undergo polarization or further (de)differentiation under continuous exposure to angiotensin II to exert these complex physiological roles.

In their article published in the American Journal of Physiology-Heart and Circulatory Physiology, Moore and coworkers (9a) describe mechanisms of vascular remodeling in the animal model of angiotensin II hypertension. In mice that were chronically infused with angiotensin II for 14 to 28 days, vascular fibrosis and collagen deposition were paralleled by elastin breakdown and infiltration of the vessel wall with macrophages, which were F4/80+ and preferentially CD206+. Additional mRNA analysis revealed that M2 markers outweigh M1 markers in angiotensin II-treated mice. Blockade of the CCR2 pathway prevented vascular elastin loss and M2 macrophage accumulation.

This study adds important information to the field and also broadens the concept of a crucial role of vascular inflammation in hypertension. The authors were able to confirm previous findings that angiotensin II selectively upregulates the number of Ly6C+ monocytes infiltrating the vessel wall (5). They show here that the majority of Ly6C+ monocytes express CCR2 but that over time (starting 7 to 14 days after beginning of the angiotensin II treatment), the infiltrating cells lose their inflammatory phenotype and adopt a “M2 like” macrophage phenotype with high levels of CD206, Arg-1, and Fcrls mRNA expression in the aorta. M2-polarized macrophages are regarded as “reparative” in classical wound healing or infectious disease systems; obviously, they also play a hitherto unrecognized role in vascular remodeling associated with chronically increased angiotensin II levels and arterial hypertension. While it is interesting and novel to notice that inflammatory monocytes change their polarization to M2 macrophages once they are inside the vascular wall, one must remember that the chronically increased angiotensin II levels will lead to continuous attraction of more M1-type monocytes. It is intriguing to see that the vasculature in hypertension is exposed to an immune response that has aspects of type 1 and type 2 inflammation in parallel: 14 days after the beginning of angiotensin II exposure, the aorta is inflamed with both proinflammatory (“M1”) Ly6C+ monocytes and alternatively activated (“M2”) CD11b+F4/80+CD206+iNOS− macrophages.

The precise molecular switches that direct the phenotypical changes in monocyte/macrophage differentiation still need to be defined. Presumably, adventitial fibroblasts play an important role in this process. It has been published that monocytes need to be cocultured with aortic fibroblasts to transform into vascular macrophages and to properly release cytokines (15). Recently, M2 macrophages have been associated with vascular smooth muscle cell proliferation occurring early in response to angiotensin II (13). Apparently, a tight spatial and temporal control is required in macrophage-dependent tissue remodeling in the vasculature exposed to angiotensin II. Future studies are needed to reveal which signals direct this tissue-specific form of sterile inflammation that drives arterial hypertension.

Grants
This work was supported by German Research Foundation Grant DFG WE 4361/4-1.

Disclosures
No conflicts of interest, financial or otherwise, are declared by the author(s).

Author Contributions
P.W. wrote manuscript; T.M. drafted, edited, revised, and approved final version of manuscript.

References
2. De Ciuceis C, Amiri F, Brassard P, Endemann DH, Touyz RM, Schiffrin EL. Reduced vascular remodeling, endothelial dysfunction, and oxidative stress in resistance arteries of angiotensin II-infused macrophage.
Editorial Focus

H738


