Angiotensin II Type 1a–Deficient Bone Marrow–Derived Dendritic Cells Produce Higher Levels of Monocyte Chemoattractant Protein 1

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Letter to the Editor

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To the Editor:

We read with interest the article from Crowley et al,[1] who studied the role of angiotensin II type 1 (AT_1) receptors ($AT_{1a}R$) on immune cells in the pathogenesis of angiotensin II–induced hypertension by generating bone marrow chimeras with wild-type (WT) donors or donors lacking $AT_{1a}R$. Interestingly, they found that the group of donors lacking $AT_{1a}R$ had more albuminuria and higher expression of a number of inflammatory mediators, including monocyte chemoattractant protein 1 (MCP-1), with persistent infiltration of macrophages in the kidney, concluding that $AT_{1a}R$ on bone marrow–derived cells had protective actions.

The absence of a functional renin-angiotensin system, like in mice genetically lacking renin, angiotensinogen, angiotensin-converting enzyme, or $AT_{1a}R$, is associated with microvascular disease and tubulointerstitial inflammation. Ouyang et al[2] described that AT_{1a} knockout (KO) mice spontaneously develop glomerular and tubulointerstitial diseases. They observed increased expression of proinflammatory mediators like MCP-1 in renal tissue of AT_{1a} KO mice compared with WT mice. Crowley et al[3] studied the role of AT_{1a} in autoimmune glomerulonephritis using MLR-$Fas^{lpr/lpr}$ mice. They found that AT_{1a} deficiency accelerated mortality and kidney pathology, showing higher expression of inflammatory mediators, including MCP-1 in the kidneys, when compared with WT mice.

Recruitment of leukocytes plays a crucial role in the progression to irreversible damage in inflammatory states, such as cardiovascular and kidney diseases. Increased expression of MCP-1 is a critical link between angiotensin II and target organ inflammation. Dendritic cells (DCs) are highly specialized antigen-presenting cells with the ability to activate resting T lymphocytes and to initiate primary immune responses. We studied the production of cytokines by bone marrow–derived DCs deficient in $AT_{1a}R$, $AT_{1b}R$, or in both AT_1 receptors. In line with the reports by Crowley et al,[1,3] we found that DCs derived from AT_{1a} KO and double KO mice released significantly higher levels of MCP-1 when compared with control mice. The difference remained significant even after stimulation with lipopolysaccharides (Figure). In contrast, no differences in the production of interleukin 10 and interleukin 12p70 were found between AT_1KO-DC and WT-DC (data not shown).

Contrasting with the results described above, Hisada et al[4] observed in experimentally induced immune mediated renal injury that glomerular expression, proteinuria, and tissue damage were markedly reduced in AT_{1a}KO mice compared with WT mice. Moreover, Koga et al[5] found that AT_{1a} deficiency impaired MCP-1 and vascular cell adhesion molecule 1 expression in the arterial wall in angiotensin II–induced atherogenesis in apolipoprotein E–deficient mice. It seems difficult to reconcile these opposing results, but it is clear that the impact of AT_1R on MCP-1 production has been evaluated in different experimental models, and AT_1-deficient mice being used in the different experimental settings have been generated by independent KO approaches.

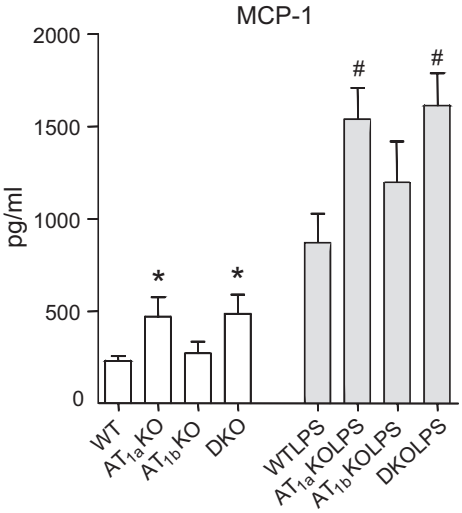

Figure. $AT_{1a}R$-deficient DCs release higher levels of MCP-1. Bone marrow cells isolated from mice lacking AT_{1a} (AT_{1a}KO), AT_{1b} (AT_{1b}KO), or both receptor isoforms (DKO) and control littermates (WT) were cultured for 6 days in the presence of recombinant murine granulocyte macrophage-colony stimulating factor (200U/mL, R&D Systems) to generate myeloid immature DCs in vitro. Then, harvested cells were analyzed by flow cytometry and ≈70% expressed major histocompatibility complex class II and CD11c, a characteristic expression profile in DCs (BD Pharmingen). At day 6, immature DCs were further stimulated for 24 hours with 100 ng/mL of lipopolysaccharide (Sigma) to obtain mature DCs. Concentrations of MCP-1 were determined in the culture supernatant using ELISA (Quantikine, R&D Systems). Results are expressed as mean±SE in picograms per milliliter. Data were analyzed with an unpaired *t* test. Experiments were performed in duplicates, with n=5. **P*<0.05 vs WT and #*P*<0.05 vs WT lipopolysaccharide.

The hypothesis that AT_1R may also have "protective effects" based on the findings of Crowley et al[1,3] and our findings is surely challenging. Our results support the notion that AT_{1a} isoform activation selectively inhibits MCP-1. We can demonstrate for the first time that, other than the described effects in macrophages, DCs being deficient in AT_{1a} produce more MCP-1. In advance to the approach by Crowley et al,[1,3] we also incorporated AT_{1b} and double KO mice that excluded a direct involvement of AT_{1b} in the AT_1-mediated MCP-1 regulation.

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Disclosures

None.

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1. Crowley SD, Song YS, Sprung G, Griffiths R, Sparks M, Yan M, Burchette JL, Howell DN, Lin EE, Okeiyi B, Stegbauer J, Yang Y, Tharaux PL, Ruiz P. A role for angiotensin II type 1 receptors on bone marrow-derived cells in the pathogenesis of angiotensin II-dependent hypertension. *Hypertension*. 2010;55:99–108.
2. Ouyang X, Le TH, Roncal C, Gersch C, Herrera-Acosta J, Rodriguez-Iturbe B, Coffman TM, Johnson RJ, Mu W. Th1 inflammatory response with altered expression of profibrotic and vasoactive mediators in AT1A and AT1B double-knockout mice. *Am J Physiol Renal Physiol*. 2005;289: F902–F910.
3. Crowley SD, Vasievich MP, Ruiz P, Gould SK, Parsons KK, Pazmino AK, Facemire C, Chen BJ, Kim HS, Tran TT, Pisetsky DS, Barisoni L, Prieto-Carrasquero MC, Jeansson M, Foster MH, Coffman TM. Glomerular type 1 angiotensin receptors augment kidney injury and inflammation in murine autoimmune nephritis. *J Clin Invest*. 2009;119: 943–953.
4. Hisada Y, Sugaya T, Yamanouchi M, Uchida H, Fujimura H, Sakurai H, Fukamizu A, Murakami K. Angiotensin II plays a pathogenic role in immune-mediated renal injury in mice. *J Clin Invest*. 1999;103: 627–635.
5. Koga J, Egashira K, Matoba T, Kubo M, Ihara Y, Iwai M, Horiuchi M, Sunagawa K. Essential role of angiotensin II type 1a receptors in the host vascular wall, but not the bone marrow, in the pathogenesis of angiotensin II-induced atherosclerosis. *Hypertens Res*. 2008;31: 1791–1800.