ANG II receptor antagonists as modulators of macrophages polarization

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THE RENIN-ANGIOTENSIN SYSTEM (RAS) is well recognized for its key role in blood pressure, fluid homeostasis, vasoconstriction, hormone secretion, kidney function, and cellular growth. However, new roles for ANG II are being discovered, especially as it relates to how the RAS modulates immune cells. Indeed, inflammatory cells are equipped with all the components of the RAS and can produce ANG II. The ANG II receptor AT1A is expressed in a variety of splenocyte populations, including T cells, macrophages, and B cells. In addition, AT1 receptors are expressed in human circulating leukocytes, including polymorphonuclear leukocytes, monocytes, and B and T lymphocytes (10, 15). These discoveries have led to studies that are documenting a central role for the RAS in the control of the immune response.

Effect of ANG II on T Cells

One of the more important discoveries is that the RAS can modulate T cell function. For example, in a model of hypertension, ANG II increased CD69 expression, an early marker of T cell activation as well as tumor necrosis factor-α (TNF-α) production (7). In a model of autoimmunity, an inhibition of the RAS was associated with reduced expression of TH1 and TH17 cytokines and induced CD4+FoxP3+ regulatory T cells with inhibition of nuclear factor-κB1 (NF-κB1) transcription factor complex in this model (14). Inhibition of the RAS has also been reported to decrease the Th1-to-Th2 cytokine ratio and inflammatory cytokine production in patients with chronic heart failure. ANG II receptor blockers also suppress lymphocyte proliferation and interferon-γ (INF-γ) production, leading to suppression of the antigen-specific Th1 and Th2 immune responses (5, 9, 10, 17). Studies using ANG II receptor-deficient mice have further supported the role of ANG II in regulating cellular immune responses. For example, in Agt1a−/− mice that lack the AT1A receptor, the proliferation of splenic lymphocytes is prevented, and, in an in vivo model of cardiac transplantation, the absence of AT1 signaling increased the immunosuppressive effects of cyclosporine (10). Thus, the RAS may have a myriad of effects on T cell function.

Effect of ANG II on Monocytes/Macrophages

The RAS is also emerging as an important mechanism to regulate macrophage function. Not only do monocytes and macrophages produce components of the RAS, expression of ANG II AT1 and AT2 receptors is also expressed during the differentiation of monocytes to macrophages (4, 12). ANG II directly stimulates monocyte chemotactic protein (MCP)-1/CCL2 expression in monocytes/macrophages and MCP-2/CCL8 in macrophages through AT1 receptors, and blocking AT1 receptors decreases the secretion of MCP-1/CCL2 and the levels of CCR2 in PBMCs. In the U937 monocytic cell line, ANG II induces NF-κB activation and MCP-1/CCL2 and IP-10/CXCL10 expression (2, 13, 16, 19). Consistent with these observations, macrophages from ANG II-infused mice have an increased chemotactic response to MCP-1/CCL2 and ANG II amplified macrophage-driven atherosclerosis (3, 11).

In an issue of The American Journal of Physiology-Renal Physiology, Aki and colleagues (1) identify a novel effect of ANG II on macrophage phenotype. Macrophages comprise a heterogeneous population of cells that are important in the innate and adaptive immune response and also in the resolution of inflammation. On the basis of Th1/Th2 polarization concepts, phenotypically polarized macrophages are now generally termed proinflammatory M1 or classically activated and anti-inflammatory M2 or alternatively activated. In vitro, macrophages are polarized to the M1 state by treatment with IFN-γ and inducers of TNF-α. In contrast, macrophages are polarized to the M2 state by stimuli with interleukin (IL)-4, IL-13, IL-10, or glucocorticoids (6, 18).

The authors, using a model of anti-glomerular basement membrane (GBM) glomerulonephritis, in which there is an activation of the RAS in the acute phase, blocked ANG II signaling with olmesartan (8). Rats treated with high doses of olmesartan showed polarization of M1 to M2 macrophages with a Th2-predominant cytokine environment in the glomeruli and attenuation of the kidney injury. In contrast, the predominant macrophages in the glomeruli in control nephritic rats were M1 macrophages. This macrophage infiltration was associated with the expression of Th1 cytokines in the glomeruli. Interestingly, macrophages with both M1 and M2 markers could be observed in the nephritic glomeruli in olmesartan-treated rats and the control group. These data support that macrophages are able to reversibly and dynamically switch from one activation state to the other in response to a changing microenvironment.

Modulating macrophage phenotype reduces kidney injury in models of renal disease. Ex vivo macrophage modulation to the anti-inflammatory phenotype M2 resulted in attenuation of inflammatory lesion in experimental chronic inflammatory kidney disease (20). The study of Aki and colleagues (1) identifies a new fascinating mechanism to switching macrophages from inducers of inflammation toward its anti-inflammatory phenotype and targets ANG II receptor antagonists as a therapeutic strategy for macrophage-dependent diseases.

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REFERENCES


