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## Is Microglia the New Target for the Treatment of Resistant Hypertension?

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Despite a large array of drugs available, the number of patients with uncontrolled hypertension or drug-resistant hypertension keeps increasing. With it, also rises the risk of end-organ damage, such as stroke, chronic kidney disease, heart failure, and vascular pathologies, leading to increased morbidity and mortality. A common denominator to resistant hypertension is an increase in sympathetic activity. Initial drugs targeting the enhanced sympathetic activity (eg, reserpine,  $\alpha$ -methyl Dopa, clonidine) came with significant adverse effects, leading to a lack of compliance and the progressive disregard for this class of medications. Following was the development of other classes of drugs, able to preserve various organs function, but most of them unable to cross the blood brain barrier and therefore with limited impact on the sympathetic nervous system. The targeted scope of these medications resulted in combination therapies which ultimately are failing to achieve blood pressure control.

In the past 15 years, a major role for the immune system has been rediscovered in the development and maintenance of resistant hypertension. Beyond the obvious role of tumor necrosis factor- $\alpha$ , cytokines and other mediators of inflammation, immune-competent cells have been highlighted as pivotal players in hypertension.<sup>1,2</sup> It is now well recognized that in peripheral organs and tissues (eg, kidney and vasculature), T cells<sup>3</sup> and their downstream subsets play a role in the development and maintenance of hypertension. In addition, angiotensin-II (Ang-II) was shown to contribute, within the central nervous system (CNS), to T-cell activation, as part of a feed-forward mechanism leading to enhanced inflammation and enhanced hypertension.<sup>4</sup>

In this issue of *Hypertension*, Shen et al,<sup>5</sup> highlight a major role for another immune-competent cell type: microglia. Microglial cells are the resident inflammatory cells of the CNS. Derived from myeloid lineage progenitors, they represent a unique type of mononuclear phagocytes and >10% of the cells in the adult CNS. In the healthy CNS, they exist as resting or surveillant cells characterized by a ramified appearance, whereas in the injured tissue they are termed activated microglia and exhibit morphological (enlarged soma,

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short processes) and phenotypic changes. Interestingly, it is thought that in the healthy CNS, neurons exert some inhibitory effects on microglia, whereas in injured CNS this inhibitory effect disappears.<sup>6</sup>

This study<sup>5</sup> followed up on previous work from the same group showing that Ang-II<sup>7</sup> and prorenin<sup>8</sup> mediate hypertension via microglia activation and release of proinflammatory cytokines. Notably, these effects could be blocked by interleukin-10 or minocycline, a broad-spectrum and long-acting tetracycline antibiotic. Here, Shen et al,<sup>5</sup> investigated the requirement for microglia in the development of Ang-II dependent (Ang-II infusion) and Ang-II independent (L-N<sup>G</sup>-nitro-l-arginine methyl ester [L-NAME] via the mouth). They first observed that microglia has an activation profile different from macrophages, in that it expresses both M1 (interferon- $\gamma$  receptor, MHCII) and M2 (Tie2, Mannose receptor)-associated markers. The authors then used an elegant microglia depletion strategy, taking advantage of transgenic CD11b-DTR mice. In these mice, only microglial cells express the diphtheria toxin receptor under the control of the endogenous CD11b promoter. As a result, targeted deletion of microglia can be achieved by central injection of the toxin without affecting other cell types. Importantly, microglia depletion after development of hypertension resulted in a reduction of hypertension in both models, although the effect was delayed in L-NAME-treated mice. Nevertheless, this observation supports the idea that microglia contributes to the maintenance of hypertension and that the role of microglia is not specific to overactivity of the renin-angiotensin system. Intriguingly, normalization of cytokines levels after microglia depletion, throughout the CNS, suggests that baseline levels of cytokines originate from cells other than microglia. To further confirm the key role of microglia, the authors performed the reverse experiment, where they centrally injected an activated (lipopolysaccharide- or Ang-II-treated) microglia cell line 24 hours before challenging the mice with an Ang-II bolus. Although the pressor response to centrally administered Ang-II was not affected, the authors reported an increase in the duration of the effect for both Ang-II- and lipopolysaccharide-activated microglia, again suggesting that microglia is involved in the maintenance rather than the development of hypertension. Another interesting finding is that both endogenous and exogenous microglia activation resulted in a 2-fold increase in glutamate (GluN2A) receptors, a process that could be reversed by minocycline treatment. The authors suggested that activated microglia could promote changes in neuronal plasticity, as illustrated by the upregulation of glutamate receptors which was speculated to contribute to the observed increase in norepinephrine levels in the kidney.

Although Shen et al<sup>5</sup> convincingly made a case for activated microglia contribution to the maintenance of hypertension, several questions remain. As stated by the authors, data in humans are missing. It would be important to know whether drug-resistant hypertension is associated with microgliosis and if so, could it be reduced with something as simple as minocycline? Similarly, does minocycline reduce sympathetic activity?

At the cell level, the role of glutamate receptors upregulation needs to be further investigated. This study was not designed to identify which cell type overexpresses these receptors. In addition, if these receptors are increased in neurons, as speculated, are these presympathetic neurons and does this upregulation increase sympathetic drive? Although

increased norepinephrine levels in the kidney might suggest that it is the case, a more complete assessment of autonomic function is needed. However, there is no reason to think that microglia activation would trigger changes on a specific population of neurons, suggesting that other, yet to be identified, modifications might also take place.

This study by Shen et al<sup>5</sup> is a major contribution to the field of neurogenic hypertension. It clearly advances our knowledge of the central mechanisms contributing to the maintenance of hypertension by unequivocally highlighting the key role of activated microglia. The authors should be commended for their ingenious use of the CD11b-DTR transgenic mouse that allowed them to deplete a cell type notoriously difficult to target. Although some definitive link remains to be established between microglia activation and enhanced sympathetic drive, this study reminds us that the CNS plays a significant role in the maintenance of hypertension and significant efforts should be made to design new drugs capable of crossing the blood brain barrier and reducing sympathetic activity.

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