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## Impact of Conditional Deletion of Microglial ADAM17 on Kidney Fibrosis in Salt-Sensitive Hypertension

In DOCA-salt hypertension, the brain and kidney interact through a complex interplay involving the renin-angiotensin system (RAS) and the autonomic nervous system, contributing to elevated blood pressure. Our lab previously demonstrated that microglial ADAM17 plays a role in regulating salt-sensitive hypertension and the associated inflammatory response. More recently, our lab observed that deletion of ADAM17 from microglia mitigates neuronal hyperactivity and sympatho-excitation in salt-sensitive hypertension. The brain RAS can also influence the kidney RAS, further promoting sodium and water retention. However, the precise mechanisms underlying microglia and kidney communication remain unclear. In the DOCA-salt hypertension model, kidney fibrosis is a prominent feature, alongside inflammation and structural damage, contributing to renal dysfunction. Our aim is to investigate the impact of ADAM17 deletion in microglia on renal kidney fibrosis in salt-sensitive hypertension. To investigate this, we analyzed the mRNA expression levels of collagen 1A in the kidney, as collagen 1A serves as a biomarker for kidney fibrosis. DOCA group shows an increase in collagen 1A mRNA expression compared to mice lacking microglial ADAM17 exposed to DOCA (25.93 ±3.3 *vs* 4.61 ±0.8). In addition, the deletion of ADAM17 in microglia + DOCA group showed ACE2 upregulation (Angiotensin-converting enzyme 2) while ACE2 was downregulated in wild type (WT) mice exposed to DOCA (1.7 ±0.13 vs 1.2 ±0.1). ACE2 plays a significant role in preventing kidney fibrosis, primarily through its interaction with the renin-angiotensin system (RAS) and is downregulated when the RAS becomes overactivated. Additionally, our group previously reported that ACE2 is shed by ADAM17. Interestingly, the protein level of mature ADAM17 was downregulated in the microglia ADAM17 deletion with DOCA group, whereas it was upregulated in the WT+DOCA group (0.9 ±0.3 *vs* 2.1 ±0.3). A possible explanation is that reducing sympathetic activity decreases circulatory norepinephrine levels and inhibits the maturation of ADAM17 in the kidney thus reducing the shedding of ACE2 and activating the local compensatory RAS. Therefore, we conclude that the microglia and kidneys are interconnected through the autonomic nervous system, which regulates involuntary functions like heart rate and blood pressure. Therefore, ADAM17 in microglia contributes to renal fibrosis in salt–sensitive hypertension.