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HYPERTENSION

Role of C3aR and C5aR in T_{reg} cells

Activation of the complement system is thought to be involved in the development of hypertension and target-organ damage. Now, Xiao-Hui Chen and colleagues report that complement 3a receptor (C3aR) and complement 5a receptor (C5aR) contribute to blood pressure regulation by modulating regulatory T (T_{reg}) cell functions.

In wild-type mice, the researchers show that angiotensin II (ANGII) infusion induced an increase in blood pressure, a decrease in the percentage of forkhead box protein P3 (FOXP3)$^+$ T_{reg} cells in the kidneys and blood, and a significant upregulation of C3aR and C5aR expression in FOXP3$^+$ T_{reg} cells. These effects were abrogated in mice with double knockout of C3aR and C5aR (DKO mice). ANGII-induced renal damage and vascular injury were also attenuated in DKO mice compared with wild-type controls; however, depletion of T_{reg} cells in DKO mice abolished these protective effects. By contrast, adoptive transfer of T_{reg} cells from DKO mice protected wild-type mice from ANGII-induced hypertension and target-organ damage.

In cultured CD4$^+$CD25$^+$ T_{reg} cells from wild-type mice, ANGII infusion induced an increase in the mRNA expression of C3aR and C5aR and a decrease in the expression of FOXP3. Stimulation with CD3 and CD28 antibodies also downregulated FOXP3 expression in T_{reg} cells from wild-type mice but not in those from DKO mice. In addition, the differentiation of DKO CD4$^+$CD25$^-$ T cells into FOXP3$^+$ T_{reg} cells was increased in comparison to that of wild-type CD4$^+$CD25$^-$ T cells. Based on these data, the researchers suggest that double knockout of C3aR and C5aR enhances the functions of T_{reg} cells.

Finally, the researcher report that the serum levels of C3a and C5a as well as C5aR expression in FOXP3$^+$ T_{reg} cells were increased in patients with hypertension compared with normotensive individuals. They conclude that "C3aR and C5aR play pivotal roles in [blood pressure] regulation and hypertension-related organ damage, likely through regulating T_{reg} cell functions," and suggest that targeting C3aR and C5aR on T_{reg} cells could be a novel strategy for the treatment of hypertension.

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> "targeting C3aR and C5aR on T_{reg} cells could be a novel strategy for the treatment of hypertension"

ORIGINAL ARTICLE Chen, X.-H. et al. Deficiency of complement C3a and C5a receptors prevents angiotensin II-induced hypertension via regulatory T cells. *Circ. Res.* https://doi.org/10.1161/CIRCRESAHA.117.312153 (2018)