MC1R Deficiency Enhances Th1 Response and Impairs Regulatory T Cell Homeostasis In Nephrotoxic Serum Nephritis

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Background: The melanocortin neuropeptides, represented by adrenocorticotropic hormone, have recently emerged as a novel therapeutic choice for treating refractory glomerular diseases. As a key cognate receptor of the melanocortin hormone system, melanocortin 1 receptor (MC1R) plays a pivotal role in regulating immune response and inflammation, and has become a novel therapeutic target for a number of diseases. However, its role in the pathogenesis of immune-mediated glomerular disease remains unknown.

Methods: Wild-type (WT) mice and the recessive yellow mice (e/e) with the naturally occurring loss-of-function null mutation of MC1R received injection of the rabbit anti-mouse nephrotoxic serum (NTS) to develop the NTS nephritis and were examined 2 weeks later.

Results: The e/e mice developed more severe crescentic glomerulonephritis than WT mice, marked by aggravated proteinuria, kidney dysfunction, and renal lesions like glomerular hypercellularity, crescent formation, and renal inflammation and fibrosis. The exacerbated NTS nephritis in e/e mice was associated with greater levels of autologous IgG2c and IgG3 either deposited in glomeruli or in sera. In addition, profiling of signature cytokines of Th immunity revealed that e/e mice with NTS nephritis exhibited higher renal expression of IFN-γ, and an increasing trend in renal expression of TNF-α, as compared with WT mice, consistent with a reinforced Th1 immune response. Moreover, shown by immunohistochemistry staining, the number of FoxP3+ regulatory T cells in the NTS nephritic kidneys was diminished in e/e mice, as compared with WT mice. Mechanistically, MC1R was evidently detected in diverse renal leukocytes prepared from the diseased WT mice, including T lymphocytes, suggesting that T cells may be direct effector cells of the melanocortin hormones via MC1R signaling.

Conclusion: MC1R-mediated melanocortinergic signaling represses Th1 immune response and is required for regulatory T cell homeostasis in murine models of NTS nephritis, resulting in renal protection in experimental crescentic glomerulonephritis.

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