Negative Modulation of B Cell Activation by MC1R Signaling Protects Against Membranous Nephropathy

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Background: The pituitary neuropeptide melanocortins, represented by ACTH, have recently emerged as a novel therapeutic modality for membranous nephropathy (MN). However, the mechanism of action remains elusive.

Methods: Passive Heymann nephritis (PHN), a model of MN, was induced in wild-type (WT) rats and melanocortin 1 receptor (MC1R) knockout (KO) rats generated by using the CRISPR/Cas9 technology, followed by treatment with various melanocortin agents, including the Repository Corticotropin Injection, the non-steroidogenic pan-MCR agonist NDP-MSH, and the selective MC1R agonist MS05. Some rats received adoptive transfer of syngeneic bone marrow-derived cells (BMDC) beforehand. Kidney function and injuries were evaluated.

Results: MC1R KO exacerbated proteinuria, podocyte injury and glomerulopathy, associated with enhanced glomerular deposition of autologous IgG and the C5b-9 complement complex, denoting a sensitized autologous humoral immune response. Melanocortin therapy ameliorated PHN in WT rats, coinciding with diminished glomerular deposition of autologous IgG and C5b-9. The beneficial efficacy of melanocortin therapy was blunted in KO rats but was restored by adoptive transfer of syngeneic BMDC derived from WT rats. Mechanistically, MC1R was evidently expressed in B lymphocytes, and negatively associated with B cell activation as revealed by gene set enrichment analysis. MC1R agonism triggered MITF induction in activated B cells in a cAMP-dependent mode, and repressed the expression of IRF4, resulting in suppressed plasma cell differentiation and IgG production.

Conclusion: MC1R signaling plays a key role in negative modulation of B cell activation and suppresses humoral immune response in PHN, representing a novel therapeutic target for MN.

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