Activation of podocyte-specific MC5R signaling by melanocortin therapy protects against THSD7A-associated membranous nephropathy

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Backgrounds: Melanocortins, exemplified by adrenocorticotropic hormone, have demonstrated a unique beneficial effect in membranous nephropathy (MN). The underlying mechanism remains elusive and this study tested the role of melanocortin 5 receptor (MC5R), one of the five MCRs of the melanocortin system.

Methods: Wild-type (WT) and MC5R knockout (KO) mice were injected with a rabbit anti-THSD7A antibody to develop MN. Beforehand, some KO mice received hydrodynamic transfer of a plasmid encoding MC5R driven by Nphs2 promoter. Subsequently, melanocortins were given, including repository corticotropin injection (RCI), the nonsteroidogenic pan-MCR agonist NDP-MSH, and the selective MC5R agonist PG901. In vitro, primary podocytes from WT or KO mice were exposed to the anti-THSD7A antibody in the presence or absence of melanocortins. Glomerular and cellular injury was assessed.

Results: After anti-THSD7A antibody insult, WT mice developed massive proteinuria and a pathology resembling human MN. Despite granular subepithelial deposition of the rabbit IgG in glomeruli to a comparable extent, KO mice sustained more severe glomerular injury, as evidenced by heavier proteinuria, worsened podocytopathy, and increased expression of the podocyte injury marker. Melanocortin treatment with RCI, NDP-MSH or PG901 ameliorated proteinuria and glomerular damage in WT mice, coinciding with an improvement in podocyte injury. The beneficial efficacy of melanocortins was drastically blunted in KO mice. Mechanistically, MC5R is expressed in glomeruli in WT mice, and co-localized with podocyte markers. Melanocortin treatment directly protected the WT podocytes against

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the antibody-elicited cytopathic changes, including cytoskeleton disruption, cellular hypermotility, oxidative stress, and apoptosis. This protective effect was abolished in cultured KO podocytes. In contrast, glomerular podocyte-specific reconstitution of MC5R in KO mice attenuated the experimental MN, and restored the beneficial efficacy of melanocortins.

Conclusions: Our findings suggest that podocyte-specific MC5R signaling protects against glomerular injury and proteinuria in MN, and may serve as a novel therapeutic target for treating MN.

Keywords: Thrombospondin Type 1 Domain Containing 7A, Membranous Nephropathy, Melanocortin 5 Receptor, Melanocortin Therapy

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