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Osteomodulin silencing alleviates renal podocyte injury in membranous nephropathy by inhibiting pyroptosis

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Membranous nephropathy (MN) is an autoimmune disorder primarily characterized by renal podocyte injury. The emerging role of pyroptosis, a novel form of regulated cell death, in the pathogenesis of podocyte damage in MN underscores the need to identify additional regulators and inhibitors of pyroptosis to optimize MN treatment. This study examined osteomodulin (OMD) as a potential regulator of pyroptosis in MN using a passive Heymann nephritis (PHN) rat model. OMD silencing in PHN rats resulted in an alleviation of nephrotic syndrome, as evidenced by reductions in 24-h urine protein and low-density lipoprotein levels, and increased albumin levels. Additionally, OMD silencing mitigated podocyte injury, as indicated by the restoration of podocyte foot process architecture, enhanced expression and normalization of Nephrin and Podocin, and reduced Desmin expression in glomeruli. Mechanistically, OMD silencing led to the inhibition of renal p38 MAPK activation and pyroptosis, demonstrated by decreased expression of intrarenal p-p38 MAPK (Thr180/Tyr182) and key pyroptosis markers, including NLRP3, ASC, Caspase-1, Caspase-1 p20, IL-1β, IL-18, GSDMD, and GSDMD-N, as well as lowered serum levels of IL-1β and IL-18. In conclusion, this study suggests that OMD silencing attenuates renal podocyte injury in MN through inhibiting pyroptosis, highlighting a promising new therapeutic approach for MN.

Keywords: Osteomodulin, Membranous nephropathy, Renal injury, Pyroptosis