Therapeutic effects of blocking TNFR1 and TNFR2 signaling in experimental membranous nephropathy by using TNFR preligand assembly domain (PLAD) and etanercept

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Background

Idiopathic membranous nephropathy (MN) is an autoimmune-mediated glomerulonephritis and a common cause of nephrotic syndrome in adults. Tumor necrosis factor α (TNF-α) mediated inflammatory response by binding to the extracellular domains of TNF receptor I (TNFRI; p60) and TNFRII (p80) were recognized as an important pathogenic factor. We assessed the efficacy of Therapeutic effects of blocking TNFR1 and TNFR2 signaling in experimental membranous nephropathy by using TNFR preligand assembly domain (PLAD) and etanercept.

Methods

Murine MN was experimentally induced by daily subcutaneous administration of cationic bovine serum albumin, with phosphate-buffered saline used in control mice. MN mice were treated by inhibition of tumor necrosis factor using etanercept or the PLAD.Fc which is a small fusion protein that could preferentially block TNFR1 signal. Disease severity and pathogenesis was assessed by determination of metabolic and histopathology profiles, lymphocyte subsets, immunoglobulin production, oxidative stress, and apoptosis. .

Result

MN revealed typical nephrotic syndrome and renal histopathology. The progressive increase of proinflammatory and TNF expression during MN both in splenocytes and kidneys indicated that TNF may participate in MN process. Purified recombinant PLAD. Fc of TNFR1 revealed effectively attenuation of TNF-α induced cell death and TNF-α induced IκB phosphorylation. MN mice from both given etanercept or the PLAD.Fc revealed significant reduction of proteinuria, but did not show amelioration of glomerular lesions or attenuation of immunocomplex deposition. There were also no changes of immune cell subsets and serum immunoglobulin levels as well as production of reactive oxygen species (ROS), and cell apoptosis. There were significant immune cell infiltration in kidneys from MN mice both given etanercept or the PLAD.Fc.

Figure 1. Effect of TNF blockade on proteinuria and C3

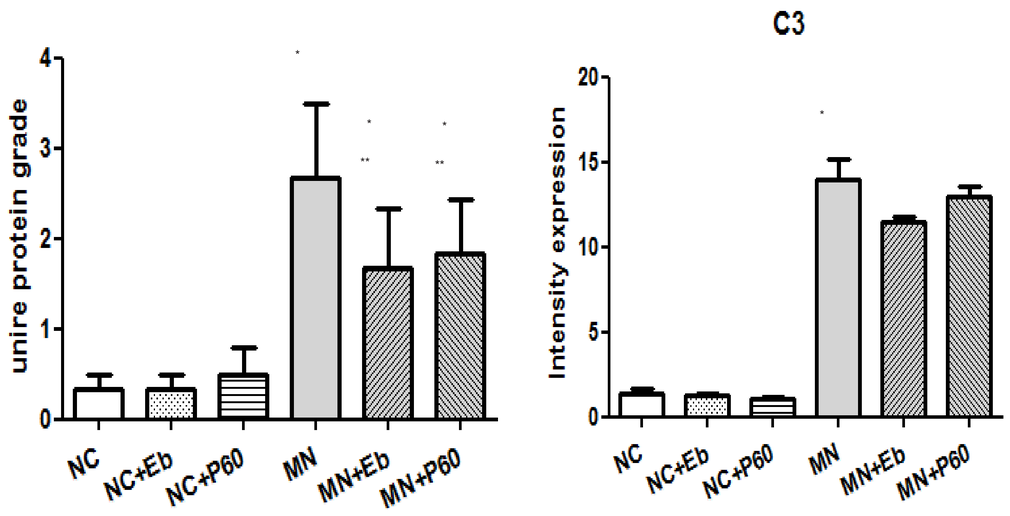


Figure 2. Effect of TNF blockade on IgG deposition

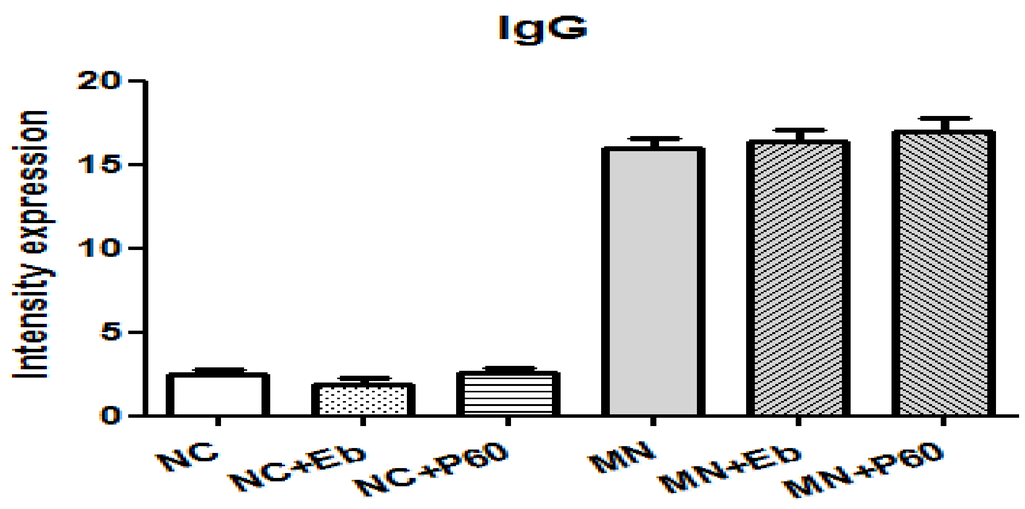


Figure 3. Effect of TNF blockade on ROS production

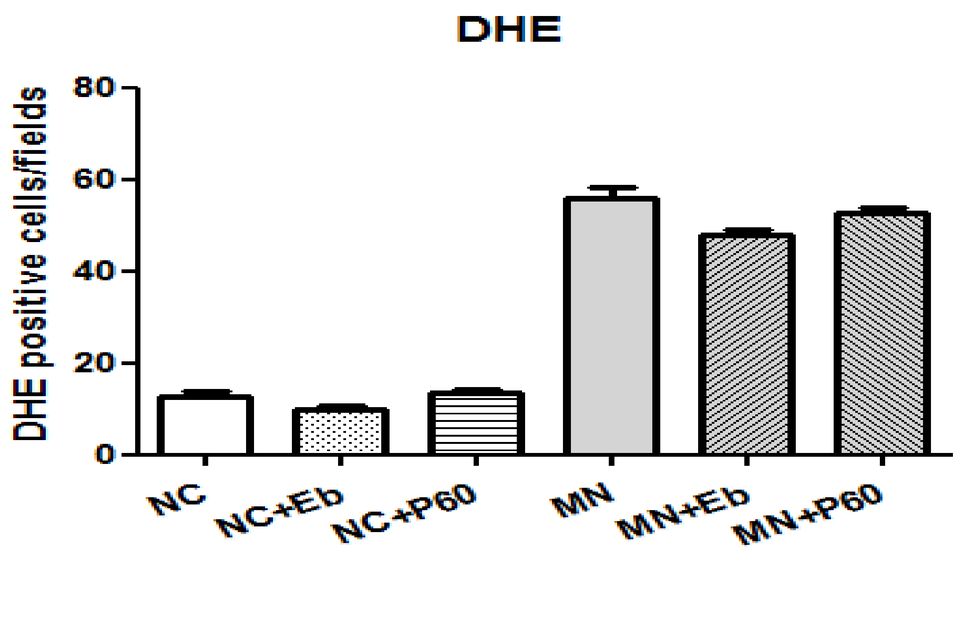


Figure 4. Effect of TNF blockade on Immune cells subsets

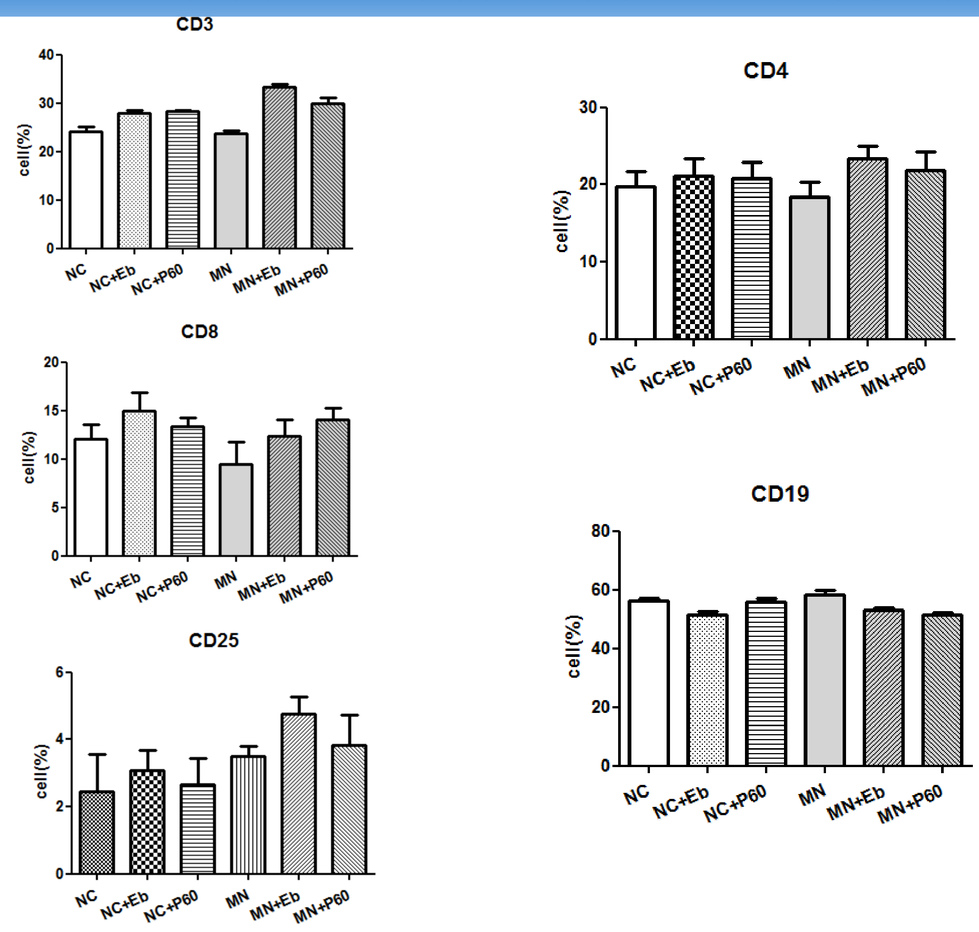
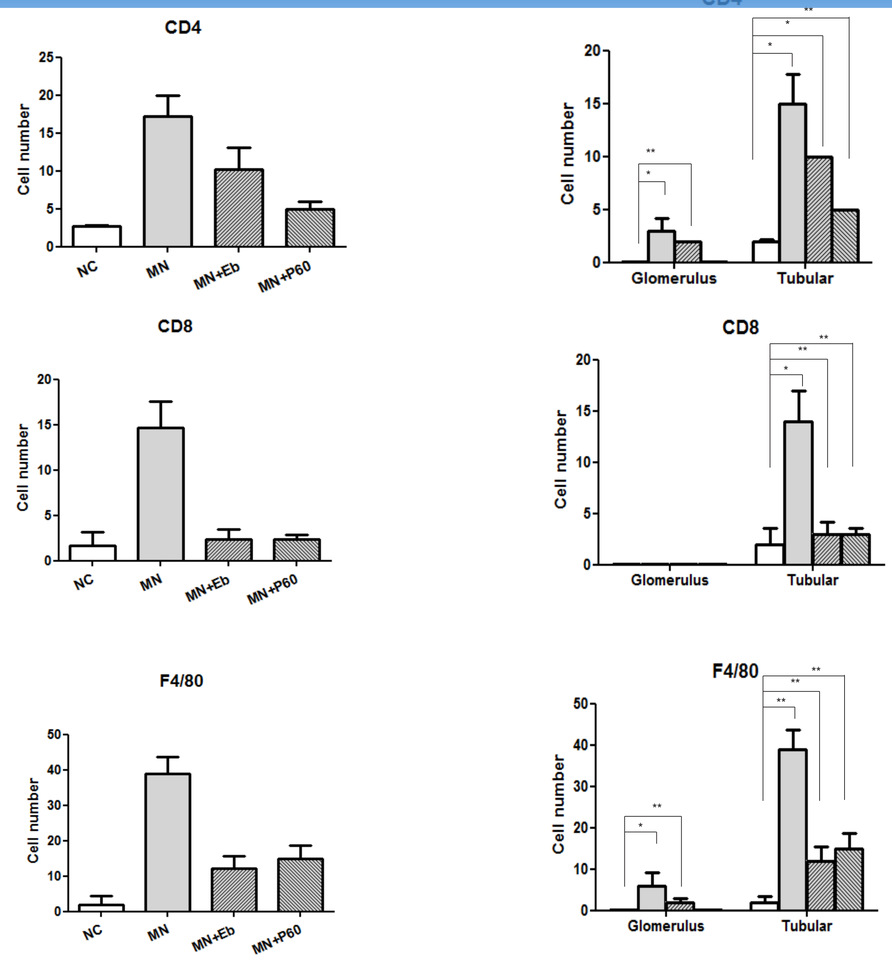


Figure 5. Effect of TNF blockade on renal immune cells



Conclusion

Our results show that there maybe therapeutic effects both blocking TNFR1 and TNFR2 signaling in experimental membranous nephropathy by using TNFR preligand assembly domain (PLAD) and etanercept.

53 ERA

75-MP

Renal pathology. Experimental and clinical.

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DOI: 10.3252/pso.eu.53era.2016

ePosters supported by F. Hoffmann- La Roche Ltd.

53rd CONGRESS ERA-EDTA VIENNA AUSTRIA MAY 21-24, 2016

Held jointly with Österreichische Gesellschaft für Nephrologie

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