Effect of Anti-P-selectin Monoclonal Antibody (mAb) on Renal Injury in Experimental Lupus Nephritis

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Objectives

Inflammatory reactions contribute to the development and evolution of lupus nephritis (LN) [1]. P-selectin, a selectin member of cell adhesion molecules that is widely accepted as critical modulator for various biological processes including inflammation and immunity, mediating initial leukocyte adhesion to activated platelet and endothelium [2,3]. Our previous work found that P-selectin was highly expressed in both plasma and renal tissue of LN patients.

In this study, we aimed to explore the effect of anti-P-selection mAb on renal injury in an experimental model of mice with established LN and the underlying mechanism.

Methods

Female MRL/lpr were treated with either anti-P-selectin mAb (2mg/kg) (n=5) or the same amount of saline control (n=4) by intraperitoneal injection twice per week from 12 to 16 weeks old until being euthanized.

Urinary protein, albumin to creatinine ratio (ACR), renal function, serum anti-double-stranded DNA (anti-dsDNA) antibody, complement C3, histopathology, as well as hypoxia and endothelial cell marker were evaluated.

Results

Compared with saline-treated mice, urinary protein was much lower in anti-P-selectin mAb treated mice (1.19±0.58 *vs* 4.22±1.70 mg/24h, *P*=0.02) at 16 weeks of age. Furthermore, urinary ACR was significantly decreased by anti-P-selectin mAb intervention (2.67±0.45 *vs* 1.14±0.10 mg/mmol, *P*=0.048).

The levels of serum creatinine (Scr) were much lower in anti-P-selectin mAb treated mice than those in saline-treated mice (32.97±9.75 *vs* 90.67±18.03 μmol/l, *P*=0.003) at 14 weeks old. Anti-P-selectin mAb treated mice had significant reduction of Scr levels from12 to 16 weeks old (86.28±8.16 *vs* 61.46±17.99 μmol/l, *P*=0.03).

There were no statistical differences in the levels of anti-ds-DNA and complement C3 between two groups.

Anti-P-selectin mAb treated mice exhibited a significant improvement in glomerular and tubulointerstitial lesions in comparison with saline-treated control. (Figure 1)

The expression of hypoxia-inducible factor 1 alpha (HIF-1α) was actually down-regulated in renal tissues of MRL/lpr mice treated with anti-P-selectin mAb, however, the expression of CD31 or peritubular capillary (PTC) density was elevated in anti-P-selectin mAb treated mice. (Figure 1 and 2)

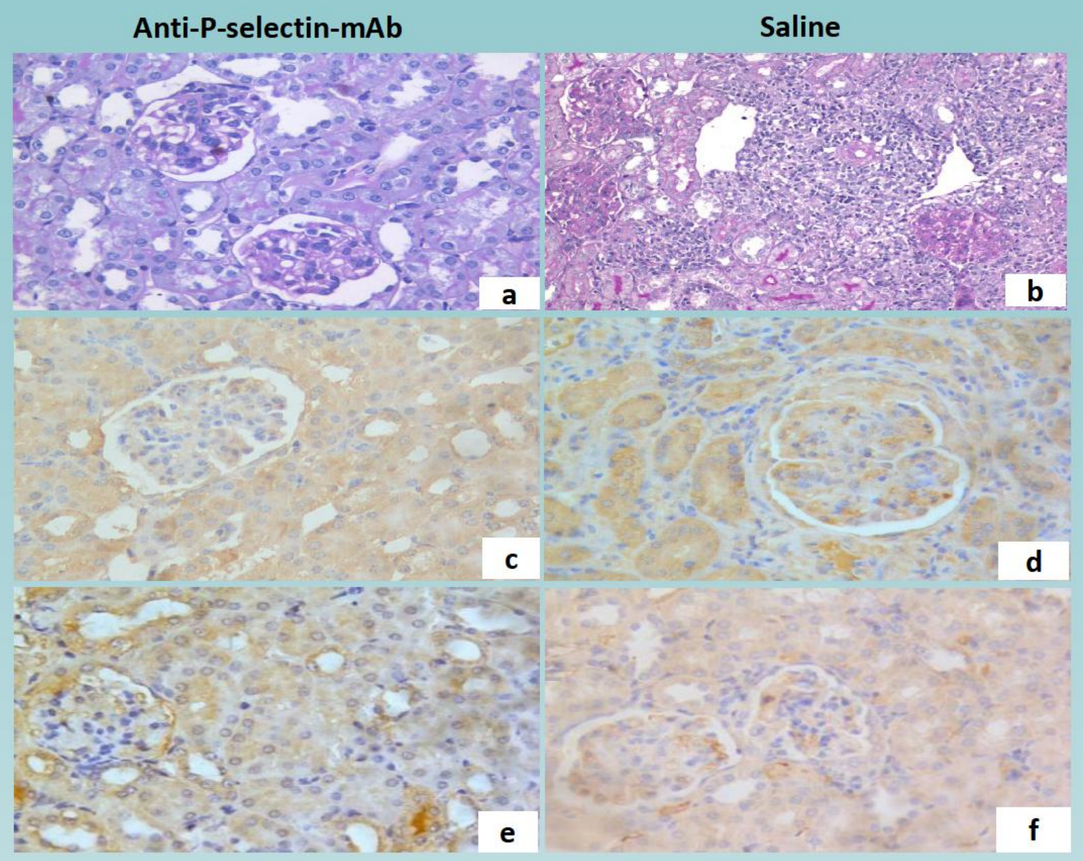

Figure 1 Renal Pathological changes (PAS-stained section: a, b; magnification: X400), the expression of HIF-1α (c, d) and PTC density marked by CD31 (e, f) in renal tissues of MRL/lpr mice (b, c, d, e: Immunohistochemistry, magnification: X400)

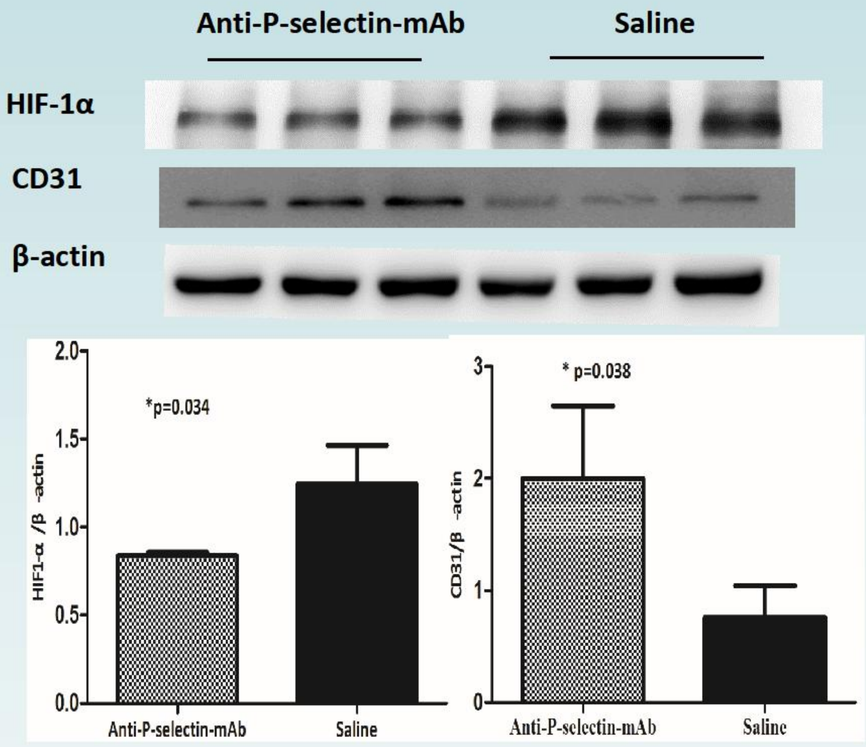

Figure 2 Expression of HIF-1α and CD31 in renal tissues of MRL/lpr mice (Western blot analysis) **P*<0.05, vs Saline

Conclusion

The results suggested that intervention with anti-P-selectin mAb may attenuate renal injury, hypoxia and the loss of PTC to some extent in MRL/lpr mice, and might be an emerging therapeutic method on lupus nephritis. Further studies are needed.

References

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