Role of B7.1 in Hypertensive Nephropathy

Seth A, Liarte E, Heasman S, Sulikowski M, Conway J, Slidel T, Coghlan M, Baker D, Moreno C.

Cardiovascular & Metabolic Diseases, Medimmune Cambridge, UK

MedImmune
A member of the AstraZeneca Group

Introduction

Progressive loss of renal function is mostly observed in diabetic and hypertensive patients. Activation of the immune system, in particular T-cells, is emerging as a possible mechanism underlying CKD progression in humans and animal models[1,2]. We have shown that inhibition of T-cell activation ameliorates diabetes-induced renal damage[3], and we hypothesize that it will also ameliorate hypertension-induced renal damage.

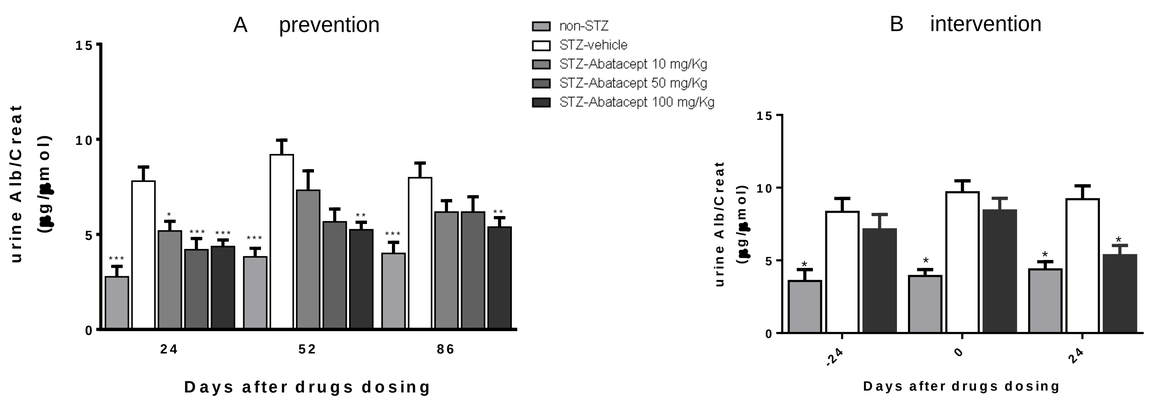
Interaction of B7-1/2 (CD8081) on the surface of antigen presenting cells with its binding partners, CTLA4 (CD152) and CD28 on T-cells, is essential for T-cell activation. In this study we used a soluble CTLA4-Fc fusion protein to block cell surface B7-1, preventing the cellular interaction and inhibiting T-cell activation.

Methods

Male 129S1/SvImJ (129) mice underwent 5/6 nephrectomy (NPX) and eight weeks after, either Abatacept (CTLA4-Fc, 50 mg/kg, EOD, i.p.), or Losartan (10 mg/kg/day, drinking water) was given for four weeks. Blood pressure was measured by tail cuff; urinary albumin-to-creatinine ratio (ACR) was used to assess renal damage, together with histological scoring. Immune cell infiltrate was assessed by IHC. Urinary kidney damage biomarkers were measured by Luminex panels.

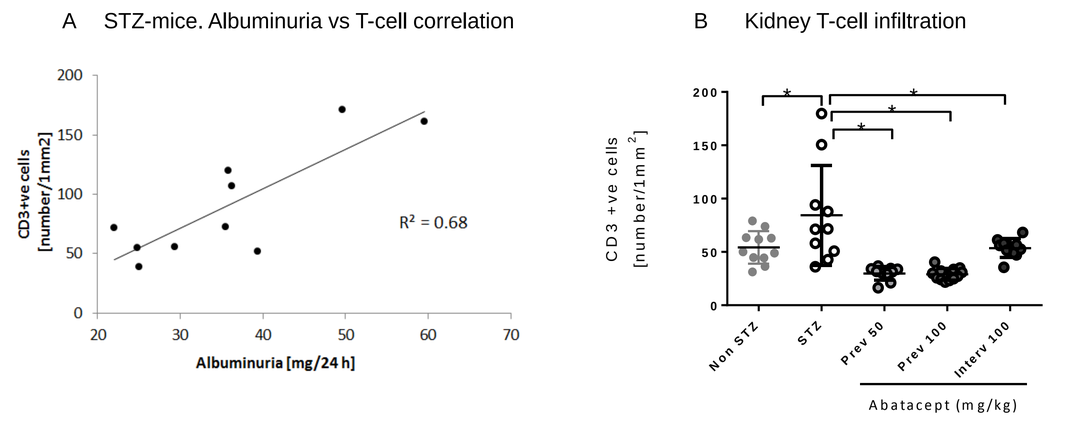
Results

Figure 1. CTLA4-Fc attenuated diabetic nephropathy in the STZ-induced diabetes mouse model



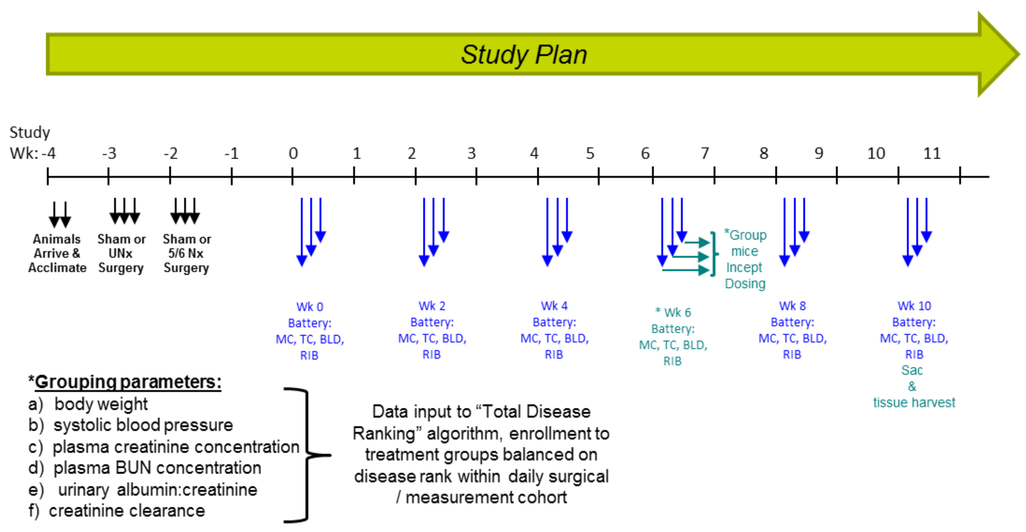
Effect of the CTLA4-Fc (Abatacept) on urinary albumin/creatinine ratio. Type 1 diabetes was induced in C57Bl6/J male mice fed a high fat diet by 5 consecutive daily injections of 50 mg/Kg Streptozotocin (i.p.). Dosing with Abatacept (Orencia) started 7 days later for the prevention arms and 9 weeks later for the intervention arm. Urine and blood was collected 3, 7 and 12 weeks (prevention arm) and 4 weeks (intervention arm) after dosing started. At all doses, Abatacept was efficacious at attenuating albuminuria when administered every 2 days (s.c) in both, prevention (A) and intervention (B) modes. CTLA4-Fc did not modify plasma glucose or HbA1c levels.

Figure 2. Renal T-cell infiltration correlated with albuminuria in the STZ-induced diabetes mouse model and CTLA4-Fc reduced T-cell infiltration in the DN kidney.



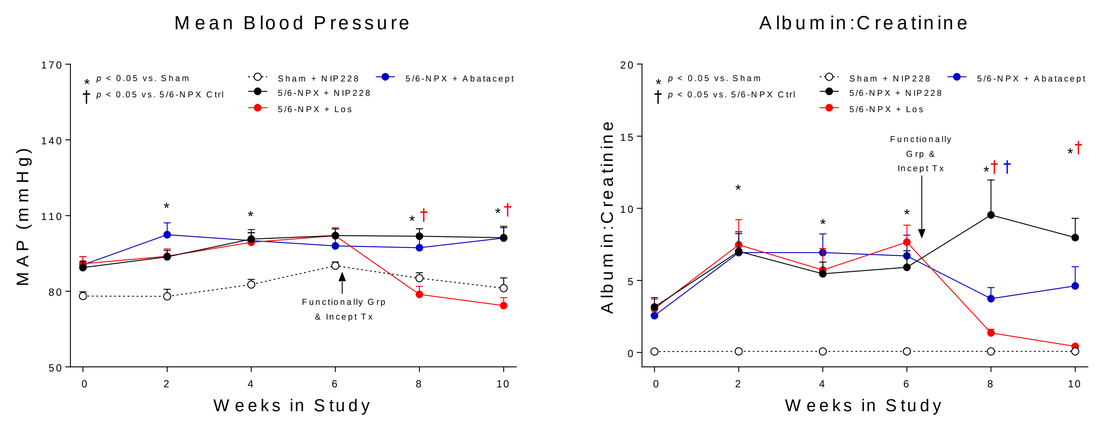
Positive correlation between the number of lymphocytes present in the kidney versus the degree of albuminuria in STZ-induced diabetic nephropathy animals (A). Effect of the CTLA4-Fc (Abatacept, across different regimens) on the number of lymphocytes (CD3+ve cells) infiltrating the kidney (B) in diabetic nephropathy animals.

Figure 3. CTLA4-Fc attenuated hypertensive nephropathy in the 5/6 nephrectomy mouse model without changes in blood pressure



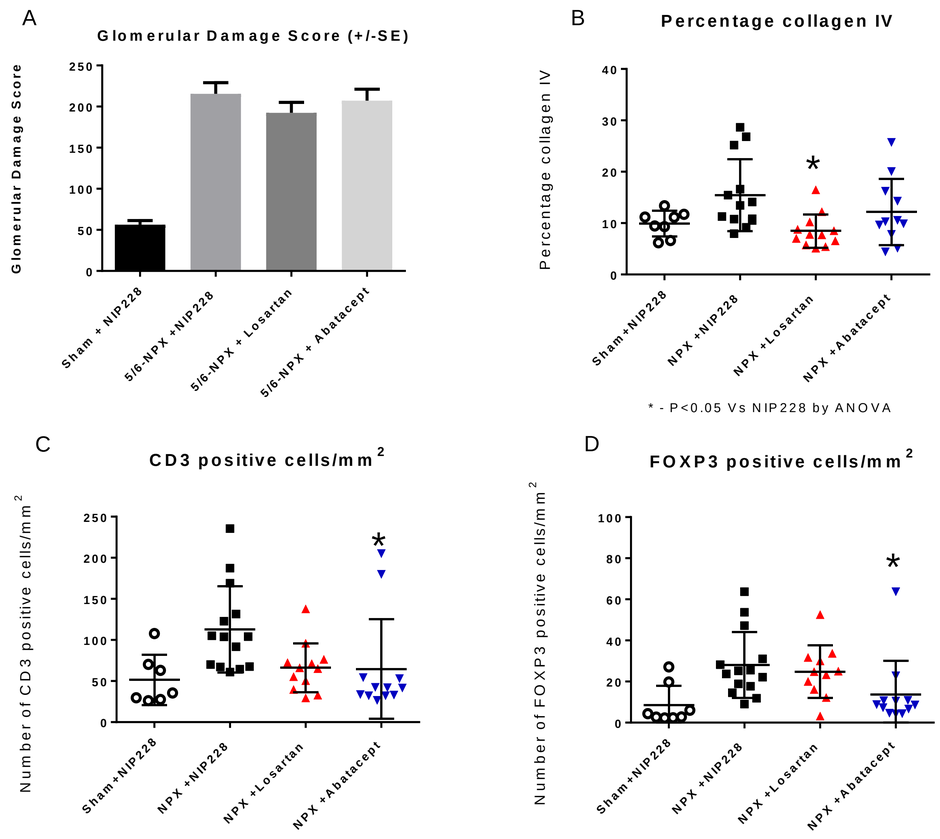
Key: BLD: Blood Collection; MC: Metabolism Cage Housing; RIB: Renal Injury Biomarker Sample Collected (urine creatinine, albumin, protein, Biweekly); TC: Tail Cuff BP Measures; UNx: Unilateral Nephrectomy; Sac: Sacrifice; 5/6 Nx: remnant kidney subtotal ablation

Figure 3. CTLA4-Fc attenuated hypertensive nephropathy in the 5/6 nephrectomy mouse model without changes in blood pressure



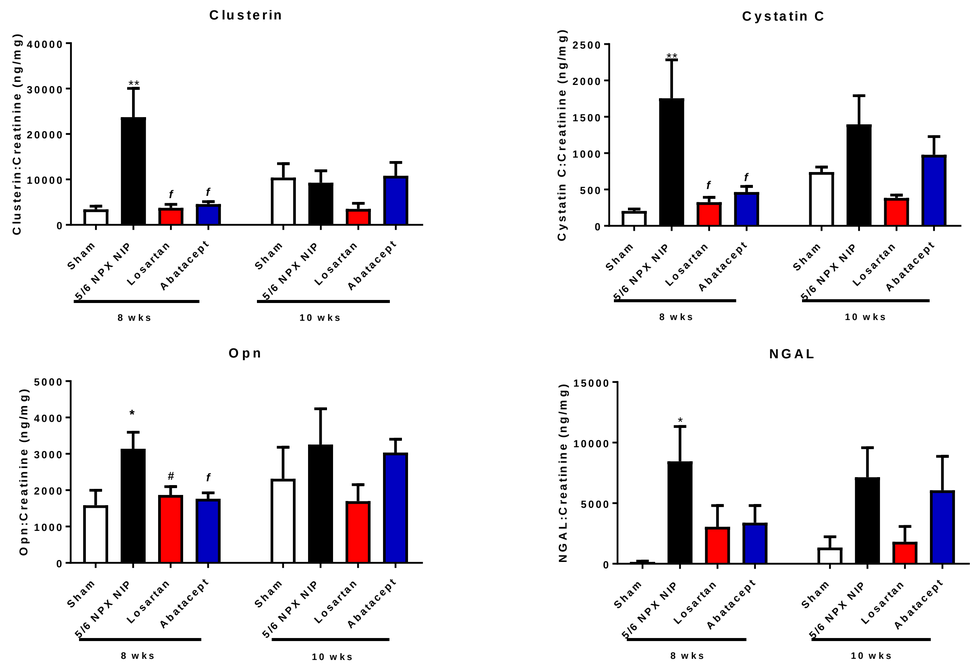
Effect of the CTLA4-Fc (Abatacept) on mean blood pressure and urinary albumin/creatinine ratio. Male 129S1/SvImJ (129) mice underwent 5/6-NPX (Uni-NPX 1 week prior to subtotal NPX via pole ablation) and eight weeks post-surgery, either Abatacept (CTLA4-Fc, 50 mg/kg, EOD, i.p.) or Losartan (10 mg/kg/day, drinking water) was administered for four weeks. Therapeutically administered Abatacept attenuated 5/6-NPX induced albuminuria without affecting blood pressure.

Figure 4. CTLA4-Fc treatment reduced T cell infiltrate in the 5/6 nephrectomy mouse model



Glomerular lesions were scored semi quantitatively (blinded) according to the scoring system described previously (Shek, et al., 2016). Significant differences in the mean GDS are observed among the groups that received the 5/6 surgical procedure (ANOVA p=0.0299) with a trend for decreased glomerular damage score in the Losartan treated mice (A). T-cell infiltrate (C, D) and fibrosis (collagen deposition) (B) were assessed by IHC. Semi-quantitative histopathological scoring revealed that 5/6 nephrectomy produced moderate to severe interstitial inflammatory response with fibrosis and tubular damage (not shown). Losartan and Abatacept reduced significantly these responses over the controls.

Figure 5. CTLA4-Fc treatment reduced the release of markers associated with kidney damage



*p<0.05 vs sham ANOVA Dunnets pht # p<0.05 vs 5/6 NPX NIP ANOVA *f* P<0.01 vs 5/6 NPX NIP ANOVA

Urine was collected at week 8 and 10 of study and analysed for urinary protein markers with MILLIPLEX® MAP Mouse Kidney Injury Magnetic Bead Panels. Urine concentration of each analyte is expressed as a ratio of the concentration of creatinine in each sample. At 8 weeks urinary clusterin, cystatin C, NGAL and opn were significantly elevated in the 5/6-NPX + NIP group compared to sham controls. Abatacept significantly decreased urinary clusterin, cystatin C, and opn compared to the 5/6-NPX + NIP group with a trend for reduced NGAL as well at 8 weeks.

Conclusions

CTLA4-Fc (Abatacept) ameliorates renal damage independently of blood pressure changes and reduces T-cell infiltration in a mouse model of hypertensive nephropathy

References

[1] Meng XM. et al, Nat Rev Nephrol. 2014 Sep;10(9):493-503
[2] Zheng Z. et al, J Diabetes Res. 2016;2016:1841690
[3] Herrera M. et al, Am J Physiol Renal Physiol. 2017 Apr 1;312(4):F748-F759

54 ERA
332--MP
CKD - Pathophysiology & progression II
Carol Moreno Quinn
DOI: 10.3252/pso.eu.54ERA.2017
ePosters supported by F. Hoffmann- La Roche Ltd.
54th ERA-EDTA CONGRESS Madrid, Spain June 3rd-6th 2017
PosterSessionOnline.com