Oxidative Stress and efficacy of antioxidants in SLE

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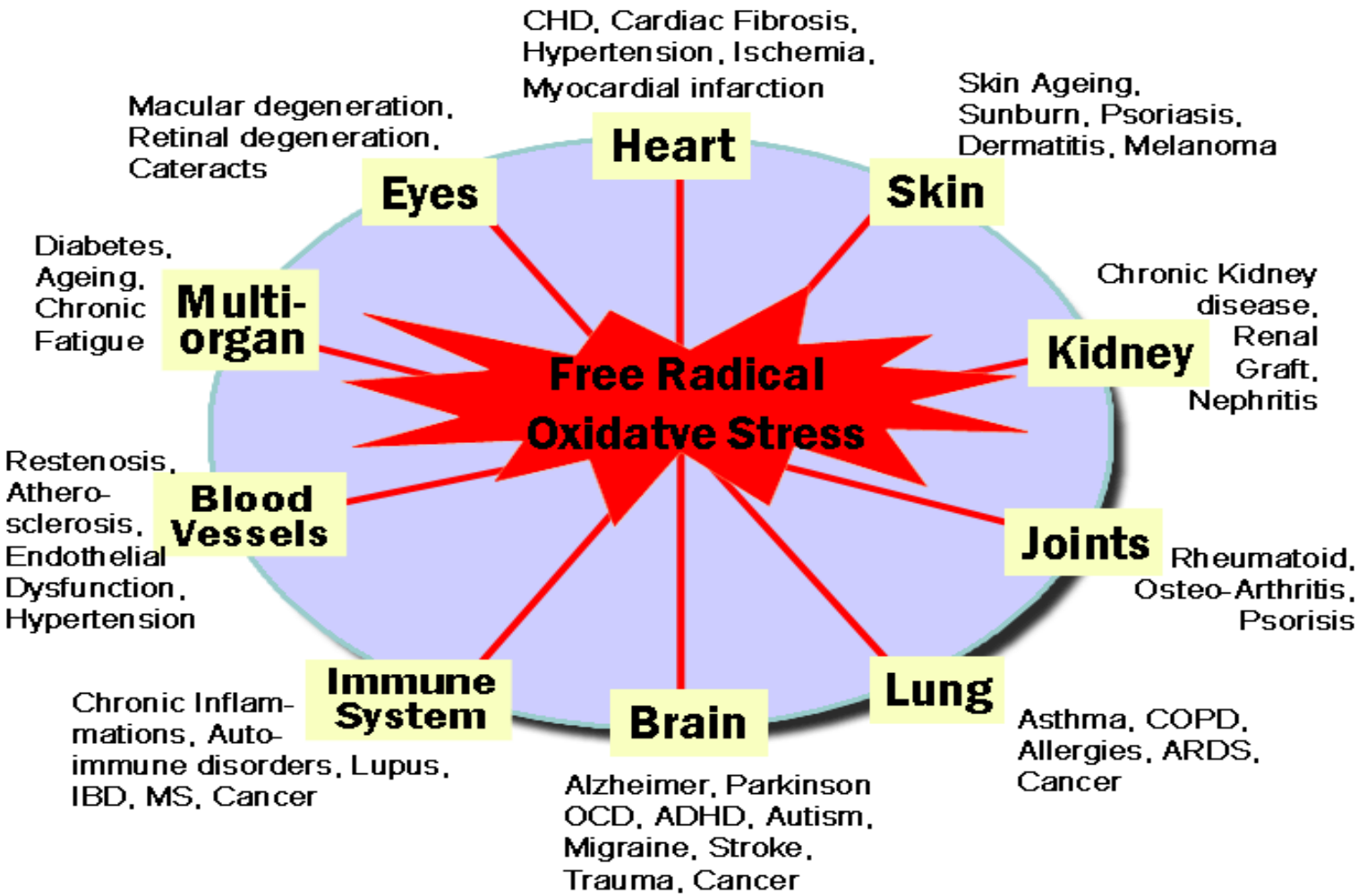
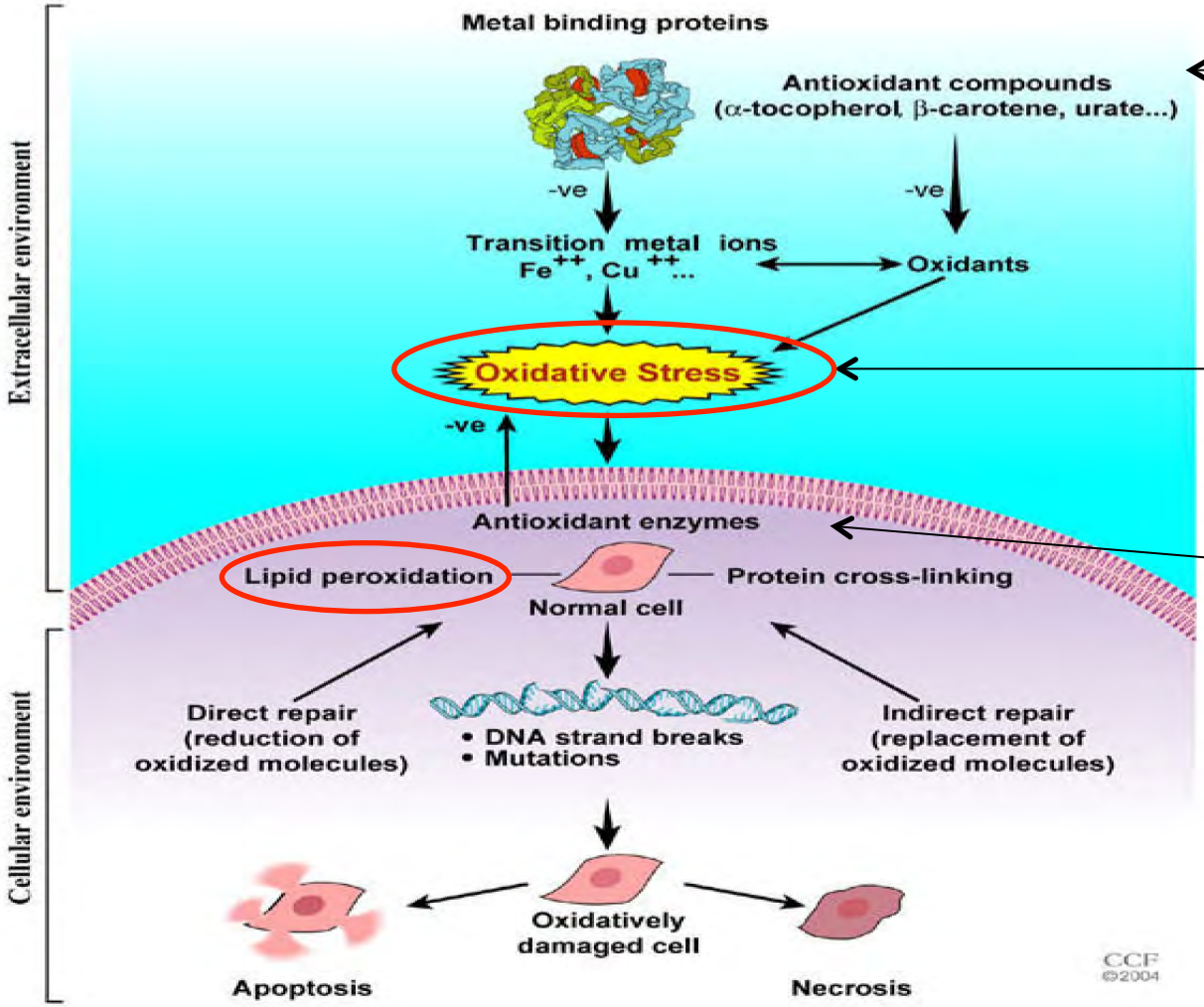
Oxidative stress exists in many diseases, including SLE



Free radicals/Reactive oxygen species (ROS)

----superoxide(O_2^-), hydroxyl radicals (OH)and hydrogen peroxide (H_2O_2)



Sulfhydryl-bearing compounds:
cysteamine(CYST)
N-acetylcysteine (NAC)
glutathione

NADPH oxidase ← Apocynin
myeloperoxidase
nitric oxide
synthase
xanthine oxidase
lipoxygenases

+

superoxide dismutase ← MnTBAP
Glutathione peroxidase
catalse

immune-cell dysfunction
autoantigen production
autoantibody reactivity

SLE

Projects:

1. Oxidative status in SLE patients
2. Oxidative status in lupus mice
3. Efficacy of antioxidants in SLE

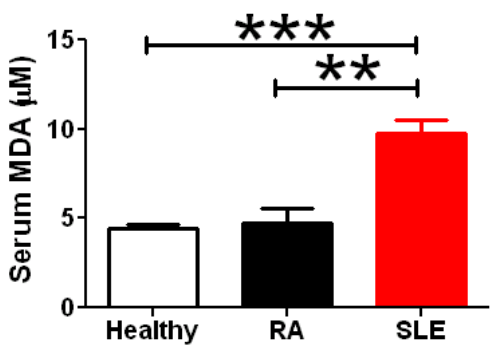
◆ Oxidative status in SLE patients---lipid peroxidation

1. Generation of ox-LDL is considered as a key event in the initiation and progression of atherosclerosis .Nature 1993,362:801-809, Lancet 1994; 344: 793

2. Ox-LDL and its major components--- 9-HODE and 13-HODE have been shown to stimulate a variety of cellular responses in renal diseases. Kidney Int 45:1628–1636,1994; Kidney Int 55:2192–2202,199; Exp Biol Med 229:1053–1060, 2004 (9-HODE: 9-hydroxy-10,12-octadecadienoic acid; 13-HODE: 13-hydroxy-9,11-octadecadienoic acid)

3. Previous works of our lab about metabolomic scan have showed: increased oxidized lipids (HODE,MDA)in the sera of SLE patients

Wu Plos one, 2012;7(6):e37210 (MDA: malondialdehyde)



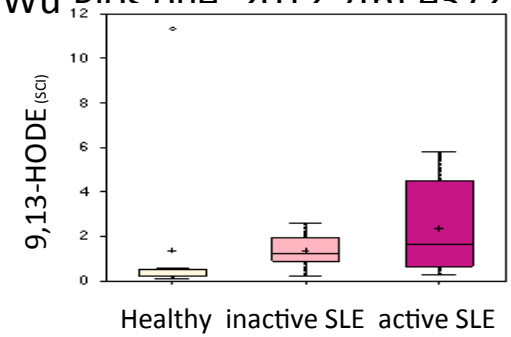


Figure 1. SLE patients exhibited increased serum levels of MDA and HODE

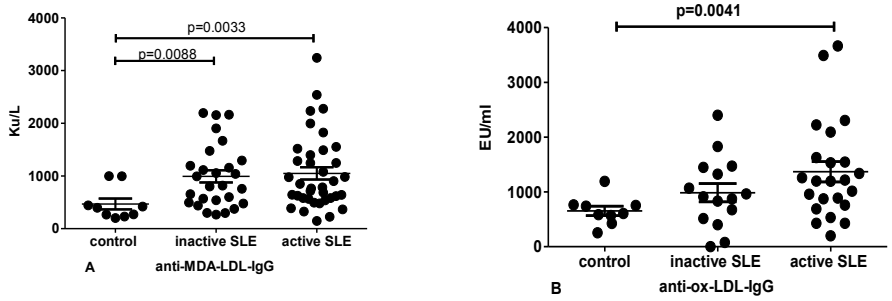


Figure 2. Active SLE patients exhibited increased serum levels of anti-MDA-LDL-IgG(A) and anti-LDL-IgG(B) compared to healthy controls

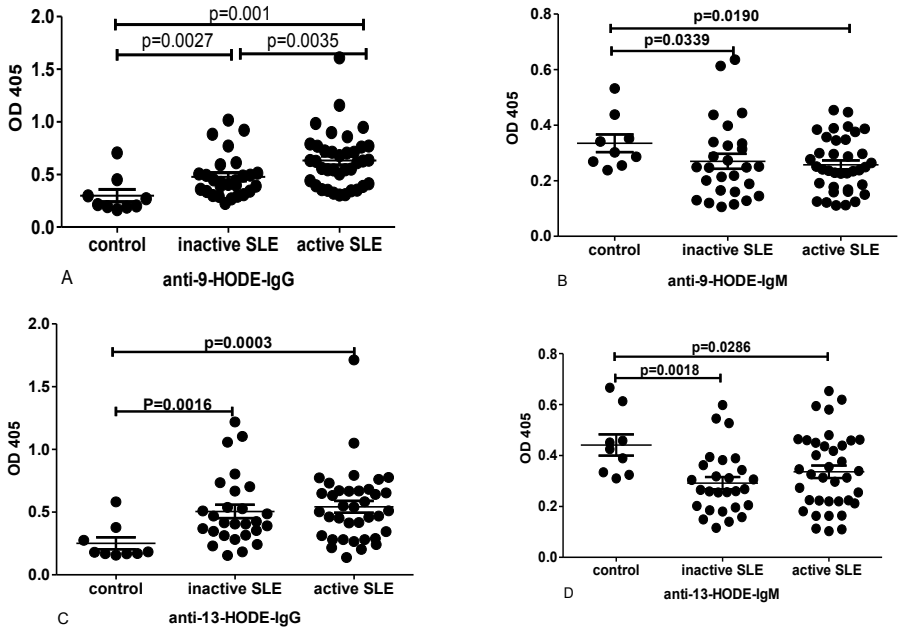


Figure 3. Active SLE patients exhibited increased serum levels of anti-9,13-HODE-IgG (A and B) but decreased anti-9,13-HODE-IgM (C and D) compared to healthy controls

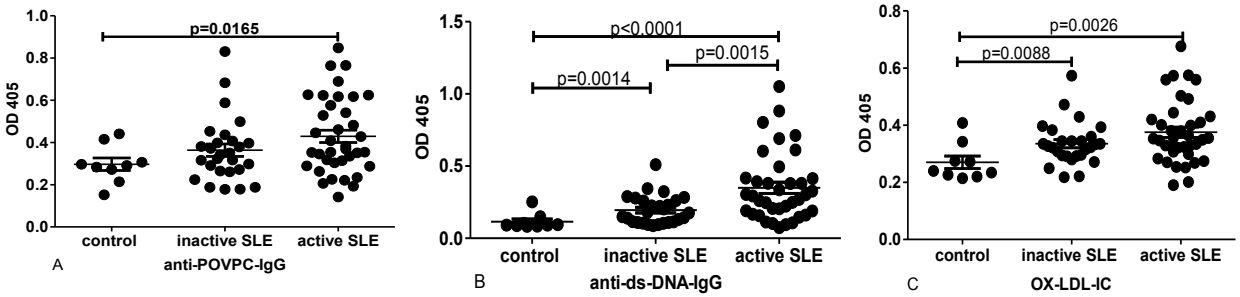


Figure 4. Active SLE patients exhibited increased serum levels of anti-POVPC-IgG (A),anti-ds-DNA-IgG(B) and ox-LDL-IC(C) compared to healthy controls

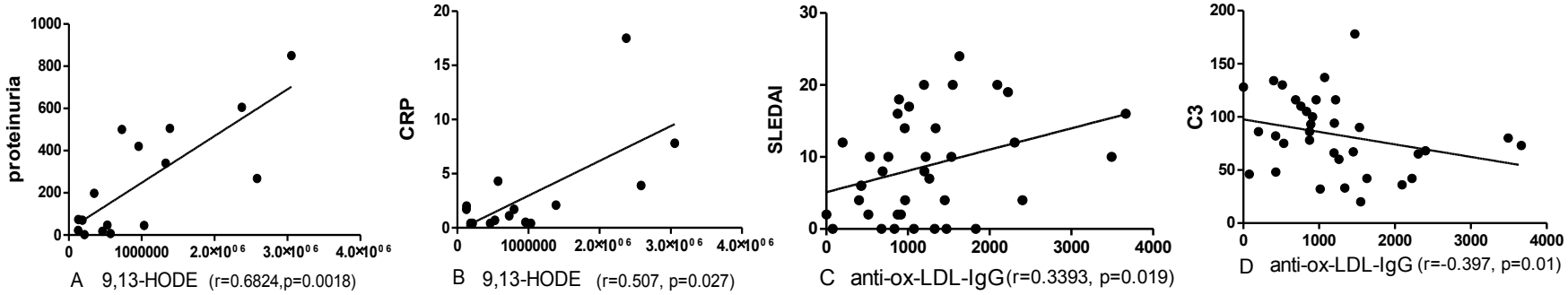


Figure 5. Serum HODE levels were positively correlated with proteinuria and CRP(A and B). Serum anti-ox-LDL-IgG was positively correlated with SLEDAI, and negatively with C3(C and D)

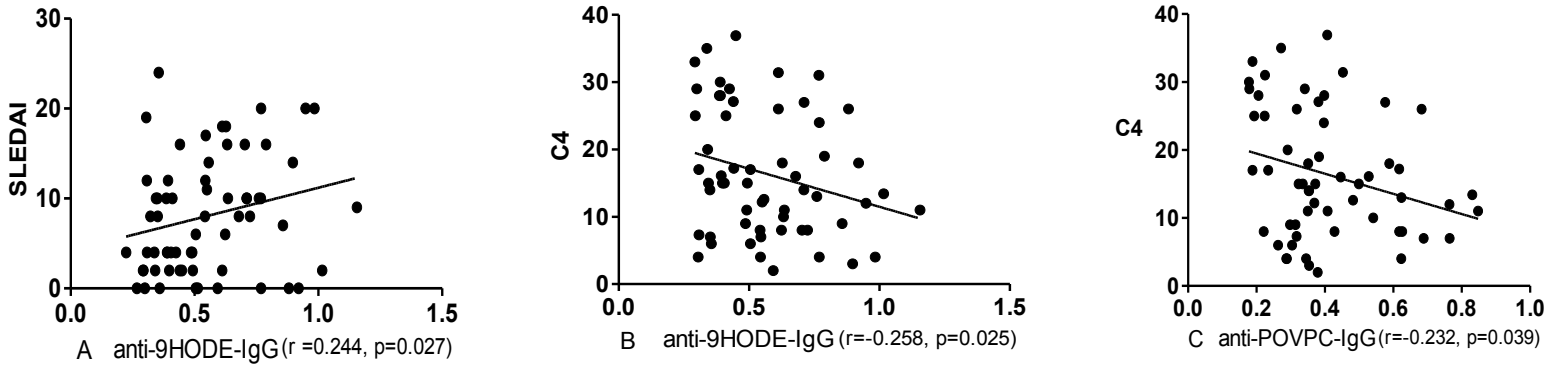


Figure 6. Anti-9-HODE-IgG was positively correlated with SLEDAI (A), and negatively with C4 (B). Anti-POVPC-IgG was negatively correlated with C4 (C).

◆ Oxidative status in lupus mice

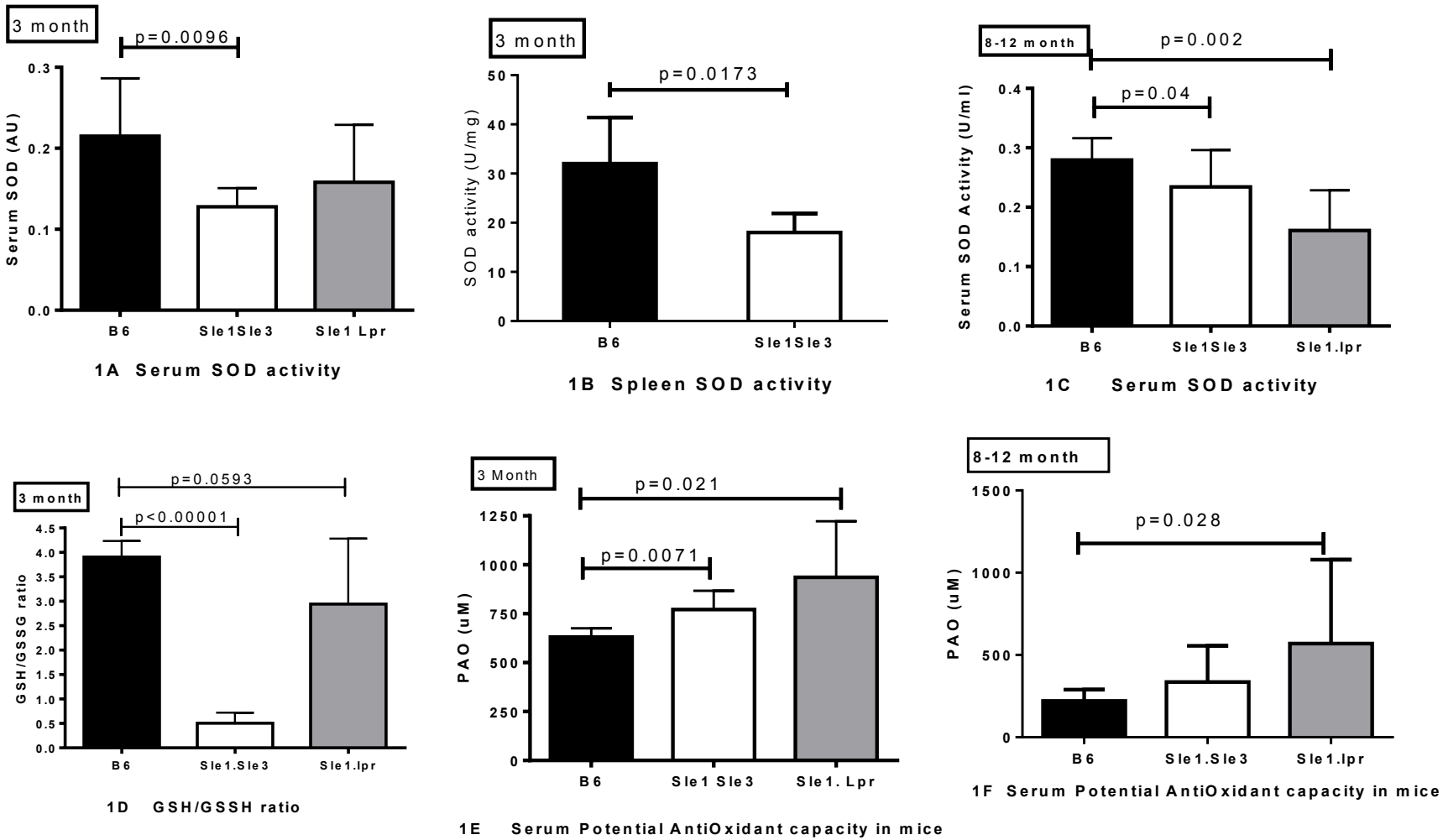


Figure 1 – lupus mice exhibited significantly lower serum superoxide dismutase (SOD) activity and reduced glutathione (GSH) levels versus healthy B6 controls. Serum potential antioxidant capacity (PAO), in contrast, was significantly increased in disease-prone mice.

◆Efficacy of antioxidants in SLE

1.Effects of Apocynin (a specific inhibitor of NADPH-oxidase)

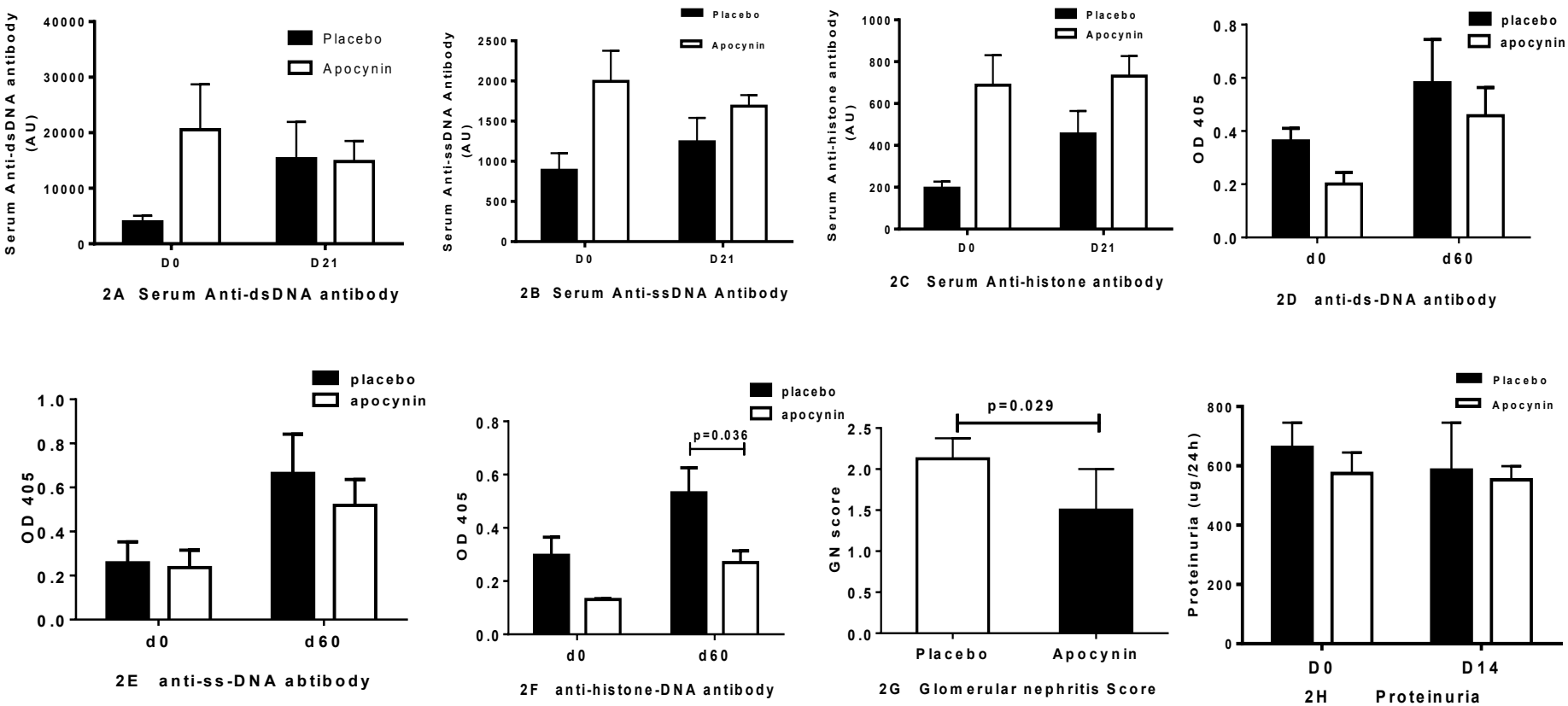


Figure 2 – Autoantibodies in vehicle- and apocyanin-treated (p.o.). Apocyanin-treated mice trended toward less disease from D0 to D21 and D60 versus vehicle-treated controls.

2. The effects of MnTABP---SOD2 mimetic

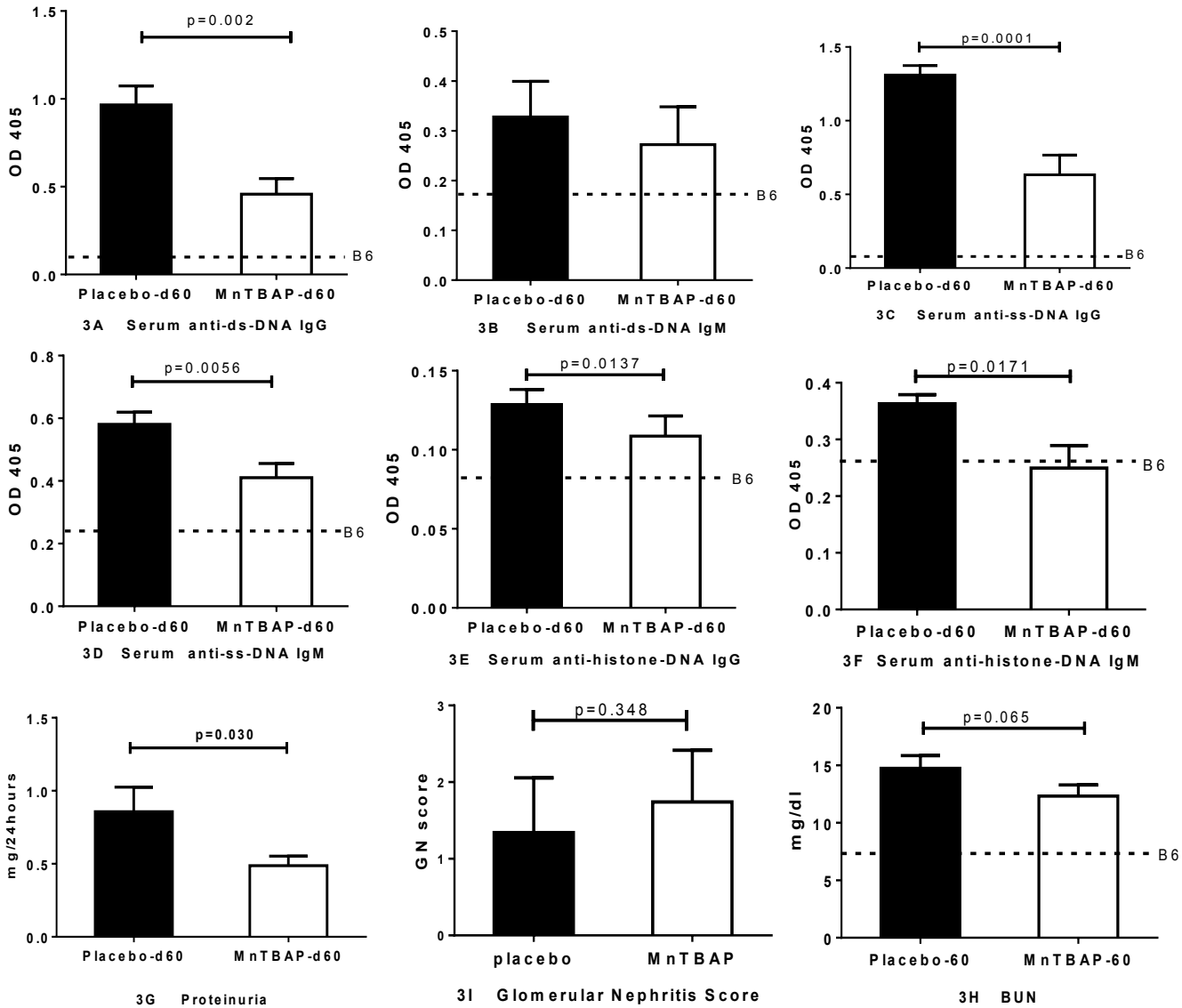
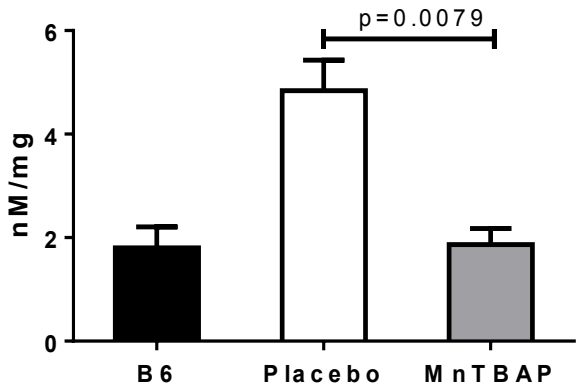
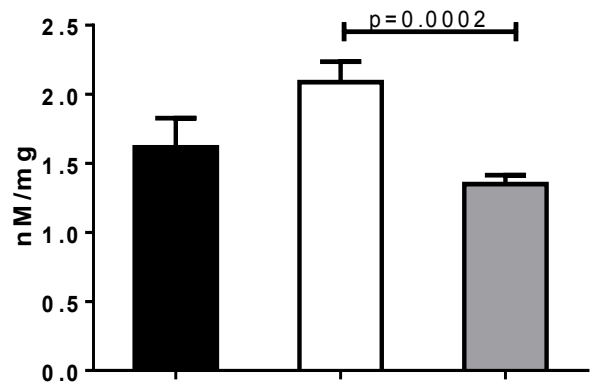


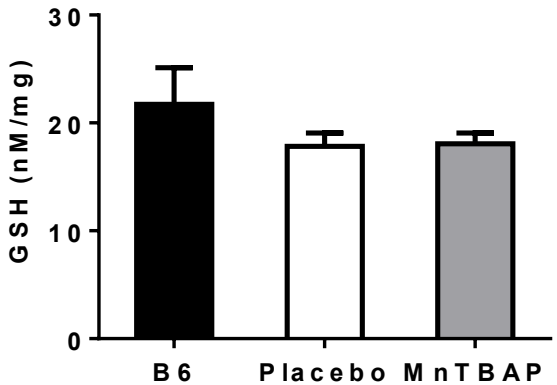
Figure 3 – After 60 days of MnTBAP or vehicle control, NZM2410 mice exhibit significantly lower pathogenic autoantibody levels, proteinuria and BUN, although glomerulonephritis scores were not significantly different.



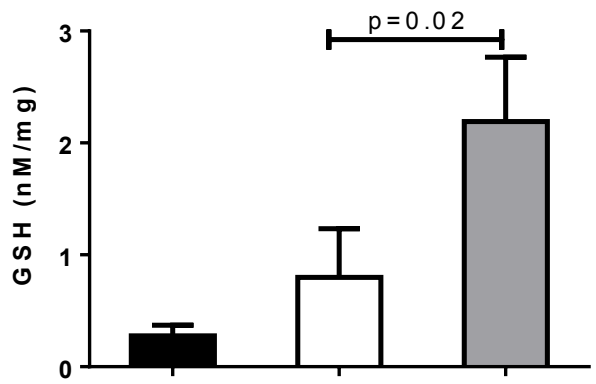
4A MDA levels in spleen



4B MDA levels in kidney



4C GSH activity in Spleen



4D GSH activity in kidney

Figure 4--Splenic and renal MDA were reduced in MnTBAP-treated mice versus vehicle controls. Renal GSH levels were significantly elevated in MnTBAP controls.

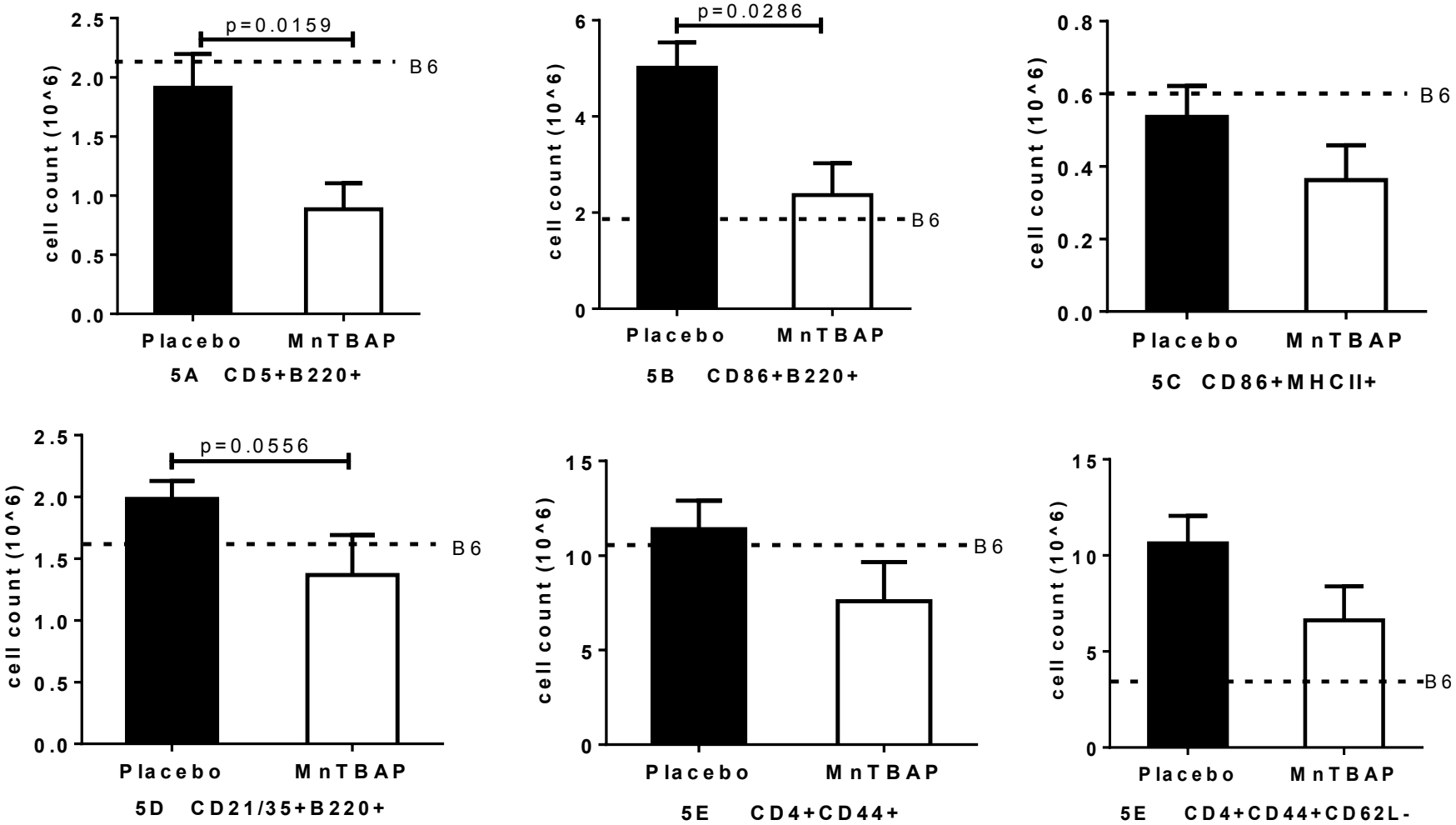


Figure 5 – MnTBAP treatment significantly reduced CD5+B220+ (B-1a B cells), CD86+B220+ (plasmacytoid dendritic cells), and CD21/35+B220+ (marginal zone B cells) cell counts in the spleen.

Mechanism study

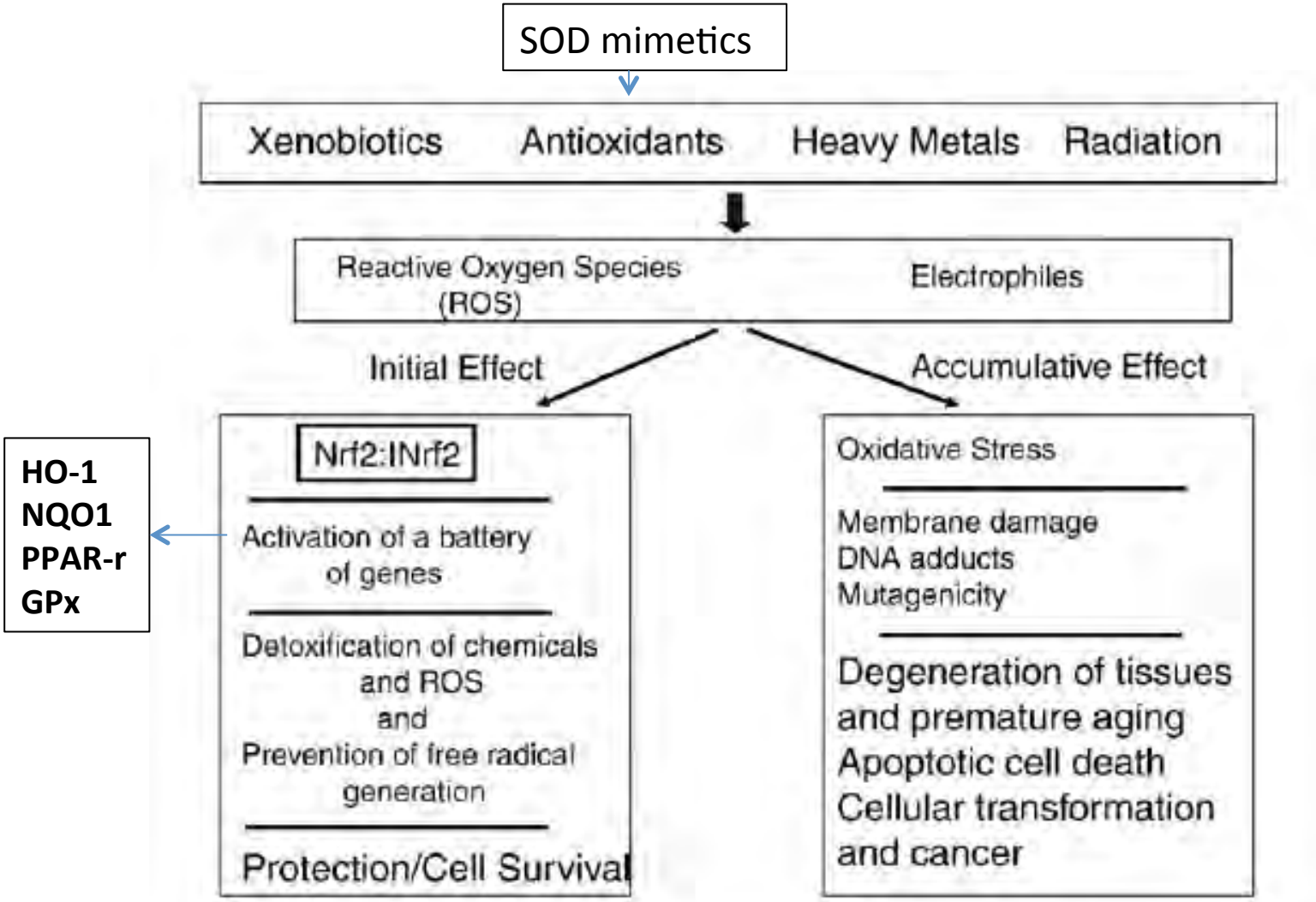


Fig. 1. Chemical and radiation exposure and coordinated induction of defensive genes.

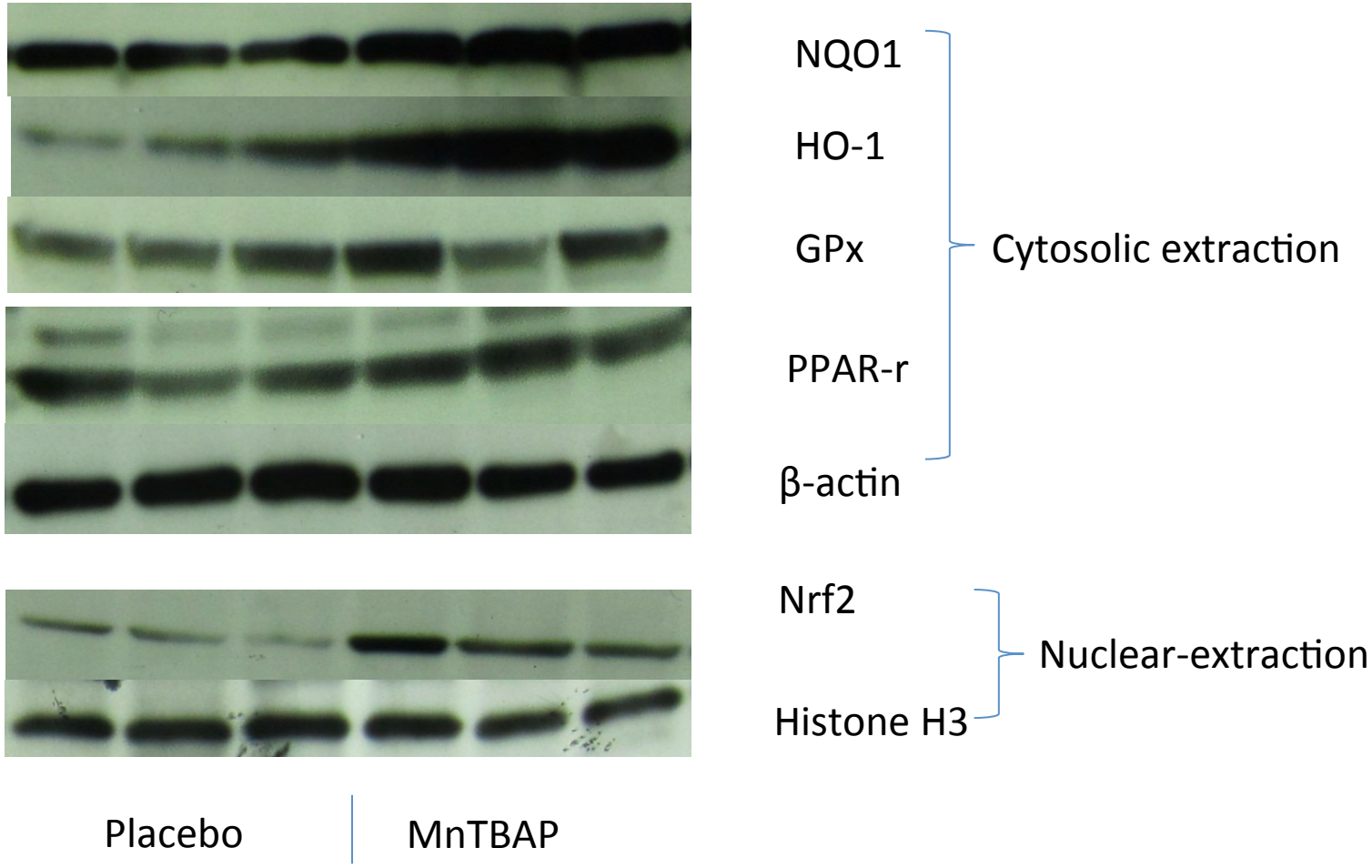


Figure 6 WB of mice Kidney

Summary

- Active SLE patients exhibit significantly increased serum levels of oxidized lipids and IgG anti-oxidized-lipid autoantibodies, the current findings suggest that coordinate elevation of oxidized lipids, autoantibodies to these lipids, and immune complexes of these antigen-antibody components could serve as potential serum markers of disease activity in SLE.
- Lupus mice exhibit increased oxidative status and antioxidant treatment might eliminate the renal injury by inducing activities of defensive genes.

Future Plans for Long term Research at Sun Yat Sen University

Future Directions:

1. To see if these oxidative-lipids markers can be used to predict disease activity in longitudinal cohorts of SLE patients.
2. Trial of anti-oxidants in SLE patients.

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