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Sparsentan reversibly decreases mesangial IgA deposition in gddY mice: a possible role for mesangial-cell -surface autoantigen expression

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INTRODUCTION

In the sera of IgA nephropathy (IgAN) patients, we discovered IgA autoantibodies specific to mesangial cells (MCs) and identified their target cell-surface autoantigens (β2 spectrin and CBX3) [1,2]. However, regulation of their MC-surface expression have not been clarified. We previously reported that Sparsentan, a Dual Endothelin Angiotensin Receptor Antagonist (DEARA), achieved a rapid reduction in proteinuria of gddY mice (spontaneous IgAN model mice) [3]. This finding prompted us to investigate the mechanisms responsible for SP's efficacy specific to IgAN.

AIM

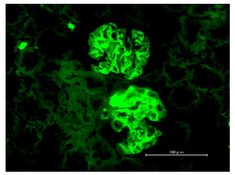
We aim to explore the effects of Sparsentan on mesangial IgA deposition in gddY mice and the role of endothelin-1 (ET-1) and angiotensin II (Ang II) in the mesangial cell (MC) surface expression of β2 spectrin and CBX3.

REFERENCES

1. Nihei Y et al. Identification of IgA autoantibodies targeting mesangial cells redefines the pathogenesis of IgA nephropathy. Sci Adv. 2023 9(12):eadd6734.
2. Higashiyama M et al. Oral bacteria induce IgA autoantibodies against a mesangial protein in IgA nephropathy model mice. Life Sci Alliance. 2024 Feb 8;7(4):e202402588.
3. Nagasawa H et al. Sparsentan is superior to losartan in the gddY mouse model of IgA nephropathy. Nephrol Dial Transplant. 2024 Aug 30;39(9):1494-1503.

RESULTS

Sparsentan reversibly decreases mesangial IgA deposition independently of serum IgA levels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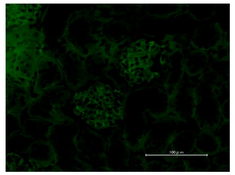
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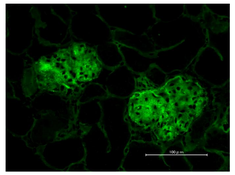
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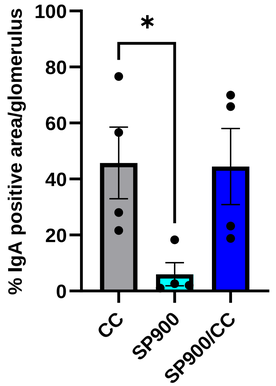
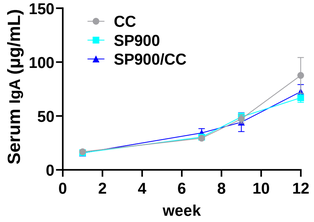
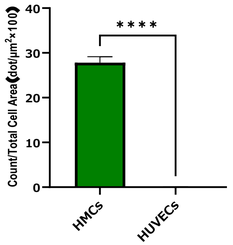
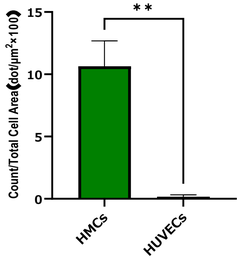




β2 spectrin and CBX3 selectively express on HMCs in vitro

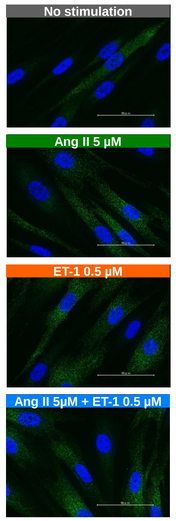


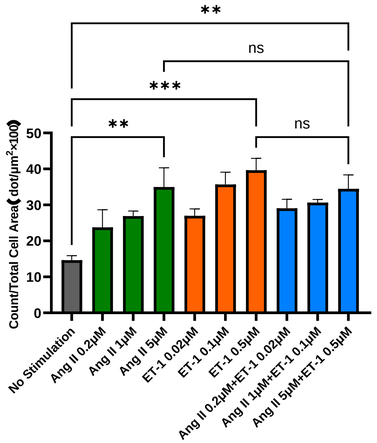
【β2 spectrin】



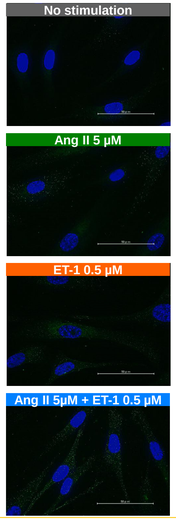
【CBX3】

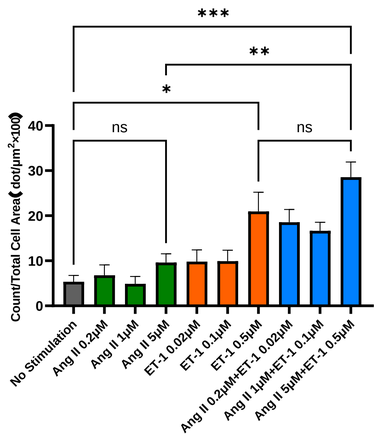
Ang II and/or ET-1 stimulation increases HMC-surface autoantigens expression in vitro





【β2 spectrin】





【CBX3】

CONCLUSIONS

Sparsentan reversibly protects from mesangial IgA deposition independently of serum IgA levels in gddY mice. This may result from the suppression of ET-1- and Ang II-induced surface expression of the autoantigens.
Further studies are required to elucidate the mechanisms behind these novel findings.

METHODS

In vivo:
gddY mice (4 wks old) were treated with:
(1) control chow for 12 wks (CC)
(2) chow with SP at 900 ppm for 12 wks (SP900)
(3) SP900 for 8 wks & CC for 4 wks (SP900/CC)
(n = 4/group; 1 outlier removed (CC),
1 death/group (SP900, SP900/CC).
Kidneys were collected at week 12 for IF staining.
Data are shown as mean ± SEM. Kruskal–Wallis test with Dunn's post hoc test. *P < 0.05.

In vitro:
Cell-surface β2 spectrin and CBX3 were analyzed by IF following fixation with 4% PFA.
Primary human MCs (HMCs) and HUVECs were cultured (48 hours).
HMCs were serum-starved (24 hours) and stimulated with ET-1, Ang II or both (48 hours).
Three IF images per group were quantified using the Hybrid Cell Count application, defined as the number of positive signals per total cell area.
Data are shown as mean ± SEM. One-way ANOVA. *P < 0.05, **P < 0.01, ***P < 0.001.

CONTACT INFORMATION

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