

Comparative analysis of SGLT-2 expression in renal vasculitis and lupus nephritis

The nephroprotective efficacy of sodium-glucose cotransporter-2 (SGLT-2) inhibitors (SGLT-2i) in patients with chronic kidney disease, with or without type 2 diabetes, has already been described.¹ Although patients with autoimmune diseases were excluded from large renal outcome trials, the use of SGLT-2i in antineutrophil cytoplasmic antibody-associated vasculitis (AAV) and systemic lupus erythematosus (SLE) for nephroprotection has increasingly been emphasised.²⁻⁴ While SGLT-2 was studied in diabetic nephropathy and IgA nephropathy (IgAN), the presence of SGLT-2 specifically in renal vasculitis and lupus nephritis has not been described yet.⁵

In renal vasculitis and lupus nephritis, SGLT-2 was detectable and predominantly localised to the tubulointerstitial as compared with the glomerular compartment (figure 1A). For comparative analysis, we next extracted transcriptome data sets for SGLT-2 expression (encoded by *SLC5A2*), specifically from microdissected tubulointerstitial (31 healthy controls, 17 with diabetic nephropathy, 25 with IgAN, 21 with renal vasculitis and 32 with lupus nephritis) and glomerular compartments (21 healthy controls, 12 with diabetic nephropathy, 27 with IgAN, 23 with renal vasculitis and 32 with lupus nephritis, www.nephroseq.org, January 2022, University of Michigan, Ann Arbor, Michigan, online supplemental tables 1 and 2).⁶ In renal vasculitis and lupus nephritis, tubulointerstitial *SLC5A2* mRNA expression was significantly higher as compared with the glomerular compartment ($p < 0.0001$, figure 1B), with no sex differences for tubulointerstitial ($p = 0.7$) or glomerular *SLC5A2* expression ($p = 0.4$, figure 1C). Interestingly, kidney function positively correlated with particularly tubulointerstitial *SLC5A2* mRNA expression in renal vasculitis and lupus nephritis (figure 1D and online supplemental figure 1A,B). Compared with healthy control kidneys, a significant reduction of tubulointerstitial *SLC5A2* mRNA expression levels was detectable in diabetic nephropathy ($p = 0.01$), while IgAN, renal vasculitis and lupus nephritis did not significantly differ ($p = 0.6$ for all comparisons, figure 1E and online supplemental figure 2A). In contrast, glomerular *SLC5A2* was significantly reduced in diabetic nephropathy ($p = 0.0005$), IgAN ($p = 0.0003$), renal vasculitis and lupus nephritis ($p < 0.0001$ for both comparisons, figure 1E). Interestingly, no association between kidney function and *SLC5A2* was observed in diabetic nephropathy and IgAN (online supplemental figure 3A,B). Gene set enrichment analysis in the whole data set (including 201 tubulointerstitial and 199 glomerular compartments) linking *SLC5A2* expression to potential signalling pathways revealed positive associations with lipid metabolism by peroxisome proliferator-activated receptor (PPAR)- α and the tricarboxylic acid (TCA) cycle (figure 1F and online supplemental table 3). Glomerular *SLC5A2* mRNA expression correlated

with protein and fatty acid metabolism (figure 1F and online supplemental table 4).

In summary, this comparative analysis revealed predominant tubulointerstitial expression of SGLT-2 in renal vasculitis and lupus nephritis. Moreover, worse kidney function correlated with loss of tubulointerstitial SGLT-2 expression particularly in renal vasculitis and lupus nephritis. Therefore, nephroprotection by SGLT-2i could be effective especially once the initial phase of remission induction in renal vasculitis and lupus nephritis is achieved and kidney function stabilised. Finally, this is the first report linking SGLT-2 to distinct metabolic signalling pathways in the kidney that could also be relevant for autoimmune diseases including AAV and SLE. In general, management of renal complications in AAV and SLE involves immunosuppressive and anti-inflammatory treatment, and also an approach towards nephroprotection and cardiovascular risk reduction.²⁻⁴ SGLT-2i exerts unequivocal nephroprotective effects by reducing glomerular hyperfiltration and albuminuria, tubular injury, loss of kidney function and incidence of acute kidney injury. These effects suggest that SGLT-2i is an ideal therapeutic approach also for patients with AAV and SLE, especially when renal and cardiac complications already manifested. Because of limited information about treatment at time of kidney biopsy or detailed histopathology in the current study, we emphasise future studies regarding SGLT-2, particularly in autoimmune diseases with renal involvement (including AAV and SLE).

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Contributors BT conceived the letter, analysed data and wrote the manuscript. SH and IAK performed histological analysis, PK provided samples of lupus nephritis. DT and EB performed gene set enrichment analysis. All authors reviewed and approved the manuscript's content before submission.

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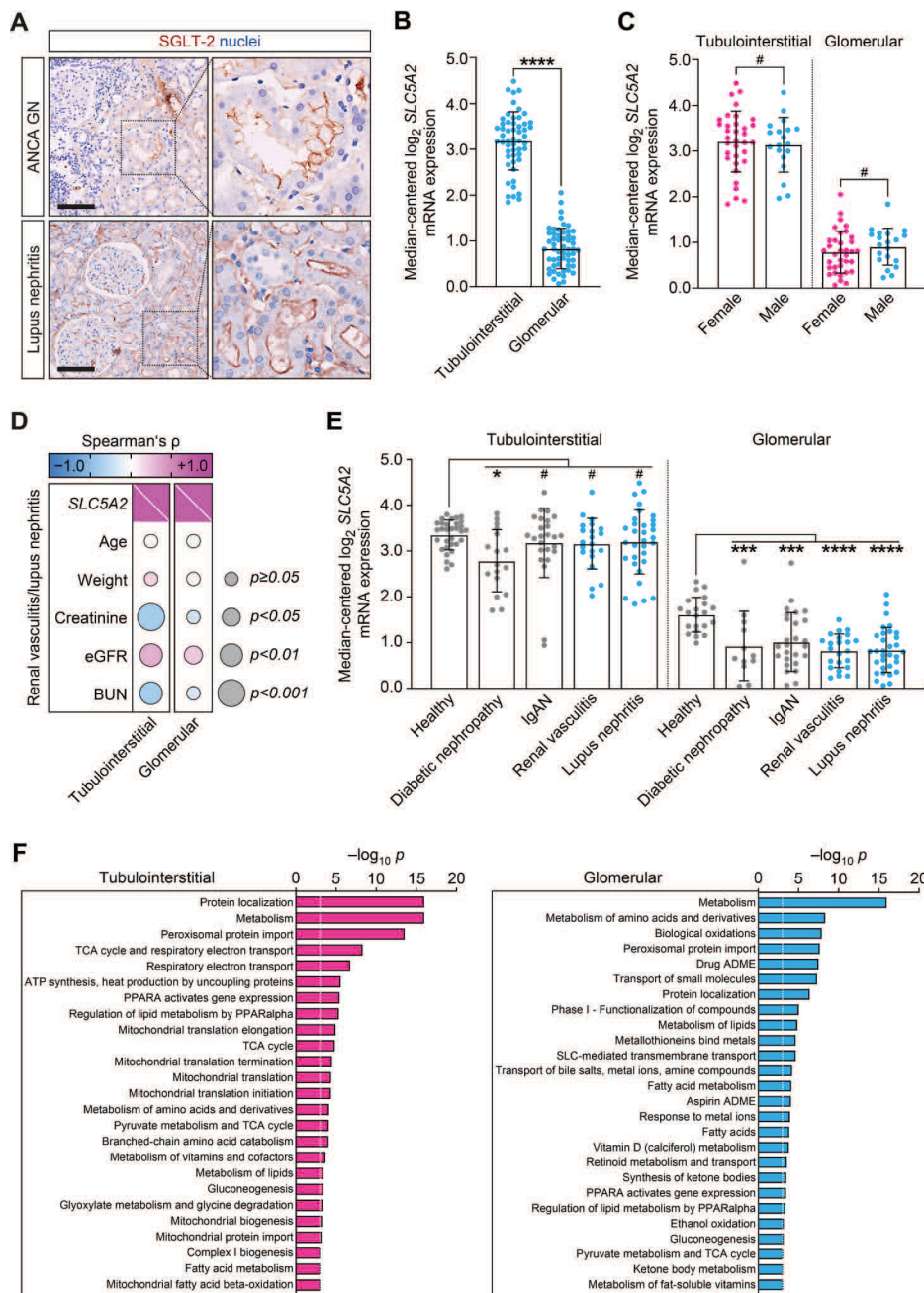


Figure 1 Comparative analysis of SGLT-2 expression in renal vasculitis and lupus nephritis. (A) Immunostaining for SGLT-2 in renal vasculitis (ANCA GN) and lupus nephritis, counterstaining was performed by using hematoxylin (scale bars 100 μ m). SGLT-2 was detectable and predominantly localised to the luminal brush border of the proximal tubule of the renal cortex in renal vasculitis and lupus nephritis. (B) Direct comparison between tubulointerstitial and glomerular *SLC5A2* mRNA expression in renal vasculitis (tubulointerstitial: n=21, glomerular: n=23) and lupus nephritis (tubulointerstitial: n=32, glomerular: n=32). In renal vasculitis and lupus nephritis, tubulointerstitial *SLC5A2* mRNA expression was significantly higher as compared with the glomerular compartment. Median centred \log_2 mRNA expression levels are shown, comparison of groups was performed using unpaired t test (****p<0.0001). (C) No significant sex differences in *SLC5A2* mRNA expression in microdissected tubulointerstitial (female: n=34, male: n=19) and glomerular compartments (female: n=35, male: n=20) of renal vasculitis and lupus nephritis. Median centred \log_2 mRNA expression levels are shown, comparison of groups was performed using unpaired t test (#not significant). (D) Correlations between tubulointerstitial and glomerular *SLC5A2* mRNA expression levels, clinical and laboratory markers of kidney function in renal vasculitis and lupus nephritis are shown by heatmap reflecting mean values of Spearman's ρ , circle size represents significance level. (E) Median centred \log_2 mRNA expression levels of *SLC5A2* in microdissected tubulointerstitial (healthy controls: n=31, diabetic nephropathy: n=17, IgAN: n=25, renal vasculitis: n=21, lupus nephritis: n=32) and glomerular compartments (healthy controls: n=21, diabetic nephropathy: n=12, IgAN: n=27, renal vasculitis: n=23, lupus nephritis: n=32) are shown. Comparisons of groups were performed using one-way analysis of variance (ANOVA) and correction for multiple comparisons by Holm-Šidák test (*p<0.05, **p<0.01, ***p<0.001, #not significant). (F) Entities $-\log_{10} p$ values of signalling pathways separated for gene enrichment associated with either tubulointerstitial or glomerular *SLC5A2* mRNA expression are shown (the dotted lines correspond to the predefined threshold value of p<0.001). Tubulointerstitial *SLC5A2* mRNA expression levels are associated with enrichment of genes predominantly involved in lipid metabolism by peroxisome proliferator-activated receptor (PPAR)- α and the tricarboxylic acid (TCA) cycle, glomerular *SLC5A2* correlated with protein and fatty acid metabolism .



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