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Intrarenal synthesis of complement C3 localized to distinct vascular compartments in ANCA-associated renal vasculitis

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ABSTRACT

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a small vessel vasculitis affecting multiple organ systems, including the kidney. The activation of the complement system contributes essentially to its pathogenesis by autoantibody-antigen recognition directed against host cells in ANCA-associated renal vasculitis. We herein provide evidence for intrarenal synthesis of complement C3 localized to distinct vascular compartments in ANCA-associated renal vasculitis that associated with distinct inflammatory signaling pathways. Therefore, a total number of 43 kidney biopsies with ANCA-associated renal vasculitis were retrospectively included and evaluated for presence/absence of C3 deposits localized to distinct vascular compartments in association with clinicopathological biopsy findings. In addition, intrarenal *C3* mRNA expression levels specifically from microdissected tubulointerstitial and glomerular compartments were extracted from transcriptome datasets. C3 deposits were present in the glomerular tuft, interlobular arteries, peritubular capillaries, and venules in ANCA-associated renal vasculitis. Most C3 deposits are localized to the glomerular tuft overlapping with peritubular capillaries. The presence of C3 deposits in the glomerular tuft correlated with impaired kidney function and overall short-term survival. Intrarenal complement C3 deposits were not associated with consumption of respective serum levels, supporting the concept of intrarenal C3 synthesis. Finally, intrarenal synthesis of complement C3 was linked to distinct inflammatory signaling pathways in the kidney that is especially relevant in ANCA-associated renal vasculitis. Considering recent advances in AAV therapy with the emergence of new therapeutics that inhibit complement activation, we here provide novel insights into intrarenal complement synthesis and associated inflammatory signaling pathways in ANCA-associated renal vasculitis.

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a small vessel vasculitis affecting multiple organ systems, including the kidney. Disease manifestations in the kidney are common and usually characterized by pauci-immune glomerulonephritis with only minor, if any, immunoglobulin and complement depositions in the vascular system. On a mechanistic level, pathogenic ANCA autoantibodies activate neutrophils, causing a release of inflammatory cytokines, reactive oxygen species, and lytic enzymes, resulting in inflammation and vascular injury [1]. The activation of the complement system contributes essentially to its pathogenesis by autoantibody-antigen recognition directed against host cells in ANCA-associated renal vasculitis [2]. Complement system activation induces neutrophil adhesion, and formation of neutrophil-platelet aggregates in vascular endothelial cells, implicating a direct mechanistic link between complement activation and vascular injury [2]. Previous studies described a mesangiocapillary pattern of glomerular complement C3 deposits present in the majority of ANCA-associated renal vasculitis, associated with worse renal outcome [3,4]. The measurement of serum complement C3 and C4 with immunoassays is routinely used in clinical practice to determine and monitor complement activation. Importantly, C3 hypocomplementemia is uncommon in ANCA-associated renal vasculitis and only observed in a minor fraction of cases [5]. These observations suggest a higher intrarenal complement synthesis particularly in ANCA-associated renal vasculitis. However, we

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have only limited knowledge about intrarenal complement synthesis and its functional importance in ANCA-associated renal vasculitis [5]. We herein describe the relevance of complement C3 deposits localized to distinct vascular compartments in a cohort of biopsy-proven ANCA-associated renal vasculitis. Furthermore, we provide evidence for intrarenal synthesis of complement C3 in ANCA-associated renal vasculitis that associated with distinct inflammatory signaling pathways.

2. Material and methods

2.1. Study approval

The use of parts of human specimens for research purposes was approved by the Ethics Committee of the University Medical Center Göttingen (28/9/17). All patients gave informed consent, and all samples were deidentified.

2.2. Study population

A total number of 43 kidney biopsies with ANCA-associated renal vasculitis at the University Medical Center Göttingen were retrospectively included between 2015 till 2020 (Supplementary Table 1), the patient cohort has previously been described [6]. At the time of kidney biopsy, all patients received glucocorticoids (GCs) and further remission induction therapy was initiated thereafter based on histopathological confirmation of ANCA-associated renal vasculitis. GCs were administered either as intravenous pulse therapy or orally with a tapering schedule. In addition, co-medication at the time of kidney biopsy including non-steroidal anti-inflammatory drug (NSAIDs), antibiotics, or proton-pump inhibitors (PPIs) were assessed.

2.3. ANCA autoantibody and complement measurements

MPO-ANCA (reference range: <3.5 IU/mL) and PR3-ANCA autoantibodies (reference range: <2 IU/mL) were measured by immunoassay (ImmunoCAP 250, Thermo Fisher Scientific, Waltham, USA). Plasma concentrations of human complement components C3c (9D9621, Abbott, Chicago, USA) and C4 (9D9721, Abbott, Chicago, USA) were determined by turbidimetric measurements on the ARCHITECT-C module. Reference range plasma concentrations for circulating C3c is defined between 0.82 and 1.93 g/L and C4 between 0.15 and 0.57 g/L.

2.4. Renal histopathology

Two pathologists (SH and PS) evaluated the kidney biopsies and were blinded to clinical data. Within a kidney biopsy, each glomerulus was scored separately for the presence of necrosis, crescents, and global sclerosis. Based on these scorings, histopathological subgrouping according to Berden et al. into focal, crescentic, mixed, or sclerotic classes was performed [7]. Furthermore, the ANCA renal risk score (ARRS), according to Brix et al. into low, medium, or high risk, was calculated [8]. Kidney biopsies were also evaluated analogously to the Banff scoring system for allograft pathology, as described previously [9]. In brief, Banff score lesions include interstitial inflammation (*i*), tubulitis (*t*), arteritis (*v*), glomerulitis (*g*), interstitial fibrosis (*ci*), tubular atrophy (*ct*), arteriolar hyalinosis (*ah*), peritubular capillaritis (*ptc*), total inflammation (*ti*), inflammation in areas of IFTA (*i-IFTA*) and tubulitis in areas of IFTA (*t-IFTA*) [9]. Systematic histological scoring of tubular injury lesions was evaluated as previously described [10]. In brief, epithelial simplification and tubular dilation, non-isometric cell vacuolization, cellular, red blood cell (RBC), and hyaline casts were given a score ranging from 0 to 4 as a percentage of the total affected cortical area of the biopsy (score 0: <1%, 1: ≥1–10%, 2: ≥10–25%, 3: ≥25–50%, 4: >50%). In addition, infiltrates of neutrophils, eosinophils, plasma cells, and mononucleated cells (macrophages, lymphocytes) were quantified as a fraction of the area of total cortical inflammation. The total cortical inflammation including areas of interstitial fibrosis and tubular atrophy, subcapsular and perivascular cortex including nodular infiltrates were considered.

2.5. C3 immunohistochemistry

Formalin-fixed, paraffin-embedded kidney sections were deparaffinized in xylene and rehydrated in ethanol containing distilled water. Tissue sections were stained using antibodies against C3c (1:10,000, A0062, Agilent Dako, Santa Clara, USA), labeling was performed using Novolink™ Polymer Detection System (Leica Biosystems, Wetzlar, Germany) according to the manufacturer's protocol. Nuclear counterstain was performed by using Mayer's Hematoxylin Solution (Sigma, St. Louis, USA). Kidney biopsies were evaluated for presence/absence of C3 deposits in the glomerular tuft, interlobular arteries, peritubular capillaries, and venules.

2.6. Analyses of transcriptome array datasets

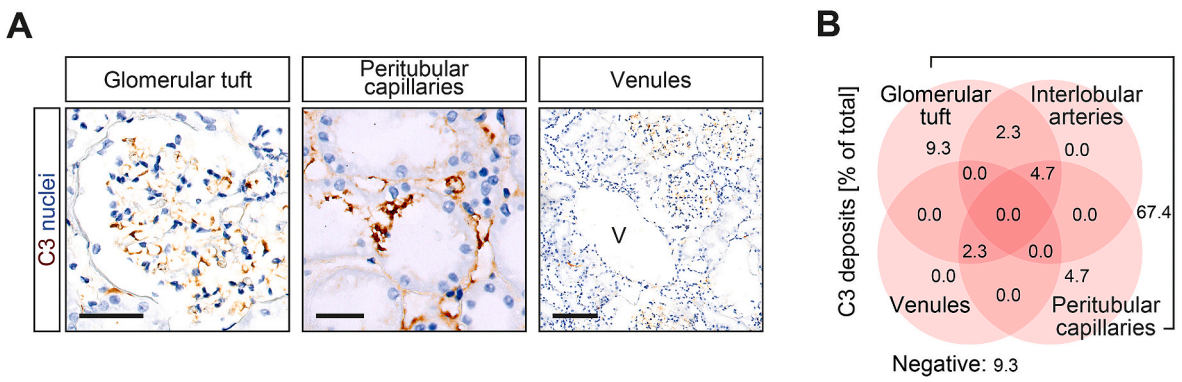
Publicly available transcriptome array datasets for *C3* mRNA expression (encoded by *C3*) from Nephroseq (www.nephroseq.org, May 2022, University of Michigan, Ann Arbor, MI). Particularly, median-centered $\log_2$ mRNA expression levels (reporter ID: 718, platform: Affymetrix Human Genome U133 Plus 2.0 Array, altCDF v10) were extracted specifically from microdissected tubulointerstitial (31 healthy controls, 32 with lupus nephritis, and 21 with renal vasculitis) and glomerular compartments (21 healthy controls, 32 with lupus nephritis, and 23 with renal vasculitis, Supplementary Tables 4 and 5) [11]. Furthermore, clinical (age, weight) and laboratory parameters (serum creatinine, estimated glomerular filtration rate/eGFR, blood urea nitrogen/BUN) were available for this cohort [11]. For gene set enrichment analysis, genes coexpressed with *C3* were extracted from the whole dataset (including 201 tubulointerstitial and 199 glomerular compartments) from Nephroseq (www.nephroseq.org, February 2022, University of Michigan, Ann Arbor, MI) [11]. Pathway analysis was performed separately for gene enrichment associated with either tubulointerstitial or glomerular *C3* mRNA expression with a correlation threshold of ≥0.5 by using reactome (http://reactome.org), the top 20 pathways with a predefined entities value of $p \leq 0.05$ were included and shown in Supplementary Tables 6 and 7 [12].

2.7. Statistical methods

Variables were tested for normal distribution using the Shapiro-Wilk test. Statistical comparisons were not formally powered or prespecified. Continuous and ordinal variables were presented as mean ± SD, categorical variables as percentages of total. Spearman's correlation was performed to assess the correlation between clinical, laboratory, and histopathological parameters, and heatmaps reflecting the mean values of Spearman's ρ are shown, the asterisks indicating statistically significant correlations. Data analyses were performed with GraphPad Prism (version 8.4.3 for macOS, GraphPad Software, San Diego, California, USA). Stepwise multiple regression analyses were performed using IBM SPSS Statistics (version 27 for MacOS, IBM Corporation, Armonk, NY, USA), rectangle boxes indicate statistically significant correlations. We retained covariates significantly associated with C3deposits in a multivariable regression model, limiting the model covariates to avoid model over-fit. A probability (p) value of <0.05 was considered statistically significant.

3. Results

Immunostaining confirmed presence of C3 deposits in 39/43 (90.7%) of cases localized to the glomerular tuft, interlobular arteries, peritubular capillaries, or venules in ANCA-associated renal vasculitis (Fig. 1A and B and Supplementary Tables 1 and 2). Most C3 deposits



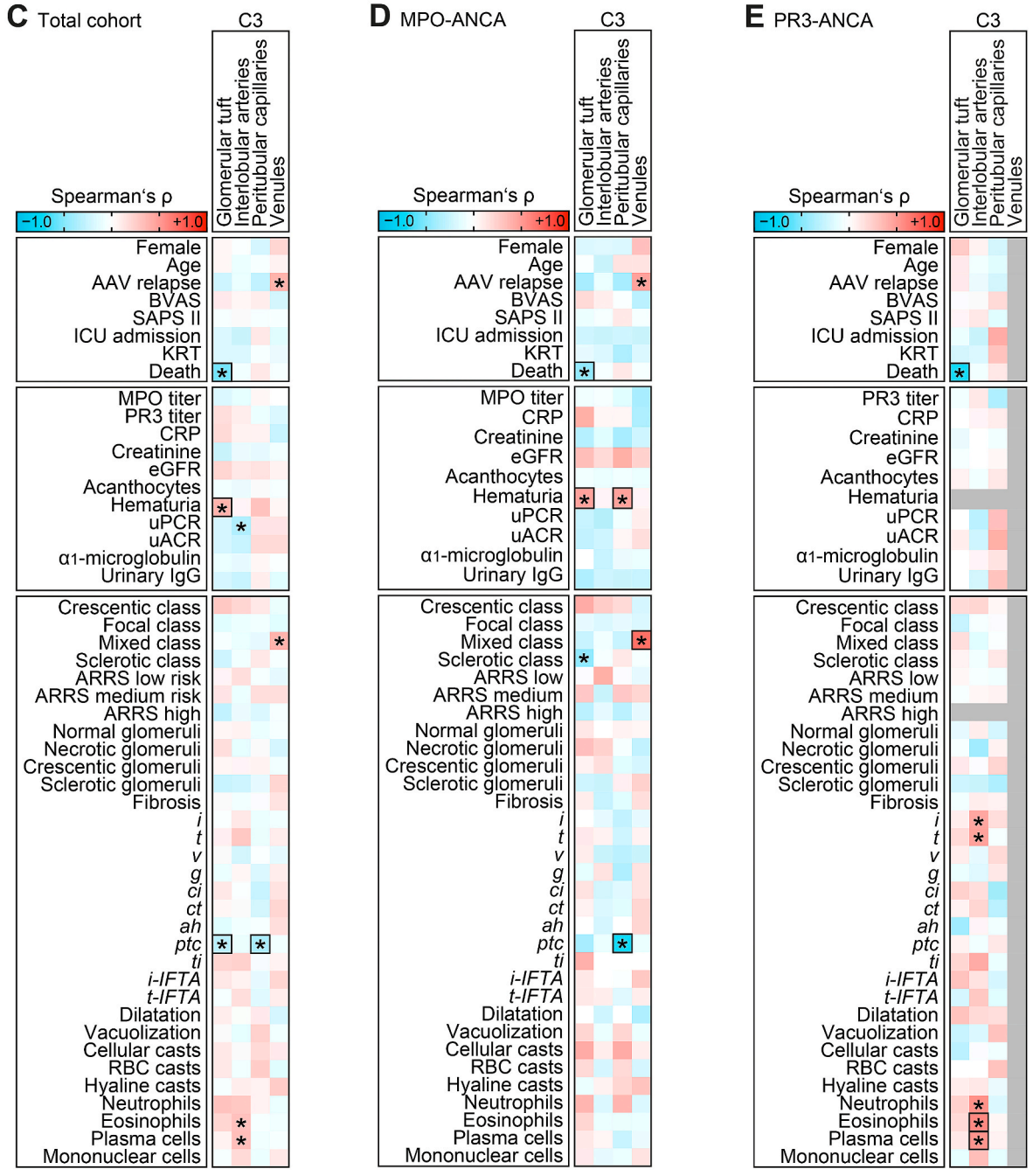


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Fig. 1. Complement C3 is present in distinct vascular compartments of ANCA-associated renal vasculitis. (A) Representative photomicrographs of C3 and hematoxylin counterstain in the glomerular tuft with typical mesangiocapillary pattern, peritubular capillaries, and venules (V), scale bars from the left to the right: 25 μm, 50 μm, and 100 μm. (B) The presence of C3 in the glomerular tuft, interlobular arteries, peritubular capillaries, and venules is presented as a fraction (%) of the total. (C-E) Association between C3 deposits localized to the glomerular tuft, interlobular arteries, peritubular capillaries, and venules and clinicopathological characteristics in the total cohort, in the MPO-ANCA and PR3-ANCA subgroups are shown by heatmap reflecting mean values of Spearman's ρ. Asterisks indicate significant associations in the univariate analysis ($p < 0.05$), rectangle boxes indicate significant associations in the stepwise multiple regression analysis ($p < 0.05$). The grey boxes for C3 in venules and ARRS high risk within the heatmap reflect no data analysis because the respective parameter was absent in all cases, for hematuria because the respective parameter was present in all cases. Abbreviations: AAV, ANCA-associated vasculitis; ah, arteriolar hyalinosis; ANCA, anti-neutrophil cytoplasmic antibody; ARRS, ANCA renal risk score; BVAS, Birmingham Vasculitis Activity Score; CRP, C-reactive protein; *ct*, tubular atrophy; eGFR, estimated glomerular filtration rate (CKD-EPI); *g*, glomerulitis; *i*, interstitial inflammation; ICU, intensive care unit; IgG, immunoglobulin G; *i-IFTA*, inflammation in IFTA; MPO, myeloperoxidase; PR3, proteinase 3; RBC, red blood cell; KRT, kidney replacement therapy; SAPS II, simplified acute physiology score II; *t*, tubulitis; *ptc*, peritubular capillaritis; *ti*, total inflammation; *t-IFTA*, tubulitis in IFTA; uACR, urinary albumin-to-creatinine ratio; uPCR, urinary protein-to-creatinine ratio; *v*, intimal arteritis.

were localized to the glomerular tuft with a mesangiocapillary pattern overlapping with peritubular capillaries in 29/43 (67.4%), followed by an overlap with C3 deposits in interlobular arteries and venules (Fig. 1B and Supplementary Table 2). There was a strong association between C3 deposits in the glomerular tuft and peritubular capillaries ($p = 0.002$, Fig. 1B). Next, we analyzed the association of vascular complement deposits with clinical parameters and histopathological lesions in ANCA-associated renal vasculitis. By stepwise multiple regression, we identified that C3 deposits localized to the glomerular tuft were associated with a better short-term survival during the disease course particularly in MPO-ANCA-associated renal vasculitis ($p = 0.013$) and hematuria ($p = 0.013$, Fig. 1C and D). Interestingly, the presence of C3 in peritubular capillaries was also associated with less pronounced peritubular capillaritis (*ptc*), especially in the MPO-ANCA subgroup ($p = 0.014$, Fig. 1D). The only association of C3 deposits in venules was observed with mixed class ANCA-associated renal vasculitis in patients with MPO-ANCA autoantibodies ($p = 0.001$, Fig. 1D). Finally, C3 deposits in interlobular arteries were associated with eosinophilic ($p = 0.030$) and plasma cell infiltrates in the PR3-ANCA subgroup ($p < 0.001$, Fig. 1E). Notably, intrarenal C3 deposits were not associated with any co-medication, including NSAIDs, antibiotics, or PPIs (Supplementary Table 3). In summary, complement C3 is present in distinct vascular compartments of ANCA-associated renal vasculitis.

We next analyzed the association between intrarenal C3 deposits and systemic levels of complement components C3 and C4. The only association was observed between glomerular C3 deposits positively correlating with serum levels of complement C3 ($p = 0.011$, Fig. 2A), indicating that intrarenal complement deposition occurs independent of systemic activation of the complement system and supporting intrarenal synthesis of complement C3. To confirm transcriptional induction of intrarenal C3, we next extracted transcriptome datasets for *C3* mRNA expression specifically from microdissected tubulointerstitial (31 healthy controls, 32 with lupus nephritis, and 21 with renal vasculitis) and glomerular compartments (21 healthy controls, 32 with lupus nephritis, and 23 with renal vasculitis, Supplementary Tables 4 and 5) [11]. As compared to healthy controls, we observed a significant induction of *C3* mRNA transcripts in the tubulointerstitial ($p < 0.0001$) and glomerular compartments of renal vasculitis ($p < 0.0001$, Fig. 2B). Interestingly, intrarenal *C3* mRNA expression was significantly higher in renal vasculitis as compared to lupus nephritis for both compartments ($p < 0.0001$ and $p < 0.001$, respectively, Fig. 2B). Intrarenal *C3* mRNA expression correlated with impaired kidney function in the tubulointerstitial and glomerular compartments of renal vasculitis (Fig. 2C). Gene set enrichment analysis in the whole dataset (including 201 tubulointerstitial and 199 glomerular compartments) linking intrarenal *C3* mRNA expression to potential signaling pathways revealed associations with interferon signaling, antigen presentation and adaptive immune responses in the tubulointerstitial compartment (Fig. 2D and Supplementary Tables 6). Glomerular *C3* mRNA expression correlated with collagen metabolism, extracellular matrix organization and alternative complement system activation (Fig. 2E and Supplementary Tables 7). In summary, intrarenal synthesis of complement C3 is linked to distinct inflammatory signaling pathways in ANCA-associated renal vasculitis.

4. Discussion

Intrarenal complement deposits are increasingly recognized as a potential marker of kidney injury in renal vasculitis [3]. This is especially relevant because clinical trials currently investigate inhibition of the complement system in ANCA-associated renal vasculitis [13]. We herein describe that C3 deposits were detectable in interlobular arteries, peritubular capillaries, and venules in a considerable subset of cases with ANCA-associated renal vasculitis. Most C3 deposits were localized to the glomerular tuft overlapping with peritubular capillaries. Moreover, C3 deposits in interlobular arteries were associated with eosinophilic and plasma cell infiltrates in the PR3-ANCA subgroup. This finding is in line with previous reports that eosinophils express receptors for various complement proteins, known to promote eosinophil recruitment, extravasation, and activation [14]. The presence of C3 deposits in the glomerular tuft correlated with overall short-term survival, implicating that this subgroup may have had a superior response to remission induction therapy.

The concept of intrarenal complement deposits resulting from systemic complement system activation with decreased serum levels of complement C3 have been found in about 75% of patients with focal lupus nephritis, and in 90% with diffuse nephritis [15]. In addition, the concept of intrarenal C3 synthesis has been described more than three decades ago in experimental lupus nephritis [16]. A comprehensive range of complement genes are expressed in lupus nephritis, including most components of the activation pathways [17]. Our observation that intrarenal complement C3 deposits are not associated with consumption of respective serum levels further supports the concept of intrarenal C3 synthesis contributing to complement deposition in ANCA-associated renal vasculitis. This is in line with independent reports that C3 hypocomplementemia is uncommon in ANCA-associated renal vasculitis and only observed in a minor fraction of cases [5]. We here provide evidence for intrarenal synthesis of complement C3 in ANCA-associated renal vasculitis, correlating with impaired kidney function. Although we have a detailed picture of the complement system, we have only a limited knowledge about the functional importance of intrarenal complement synthesis, particularly in ANCA-associated renal vasculitis. Here, we link intrarenal synthesis of complement C3 to distinct inflammatory signaling pathways in the kidney that is especially relevant in ANCA-associated renal vasculitis. Hence, intrarenal synthesis of complement C3 may significantly impact kidney injury in ANCA-associated renal vasculitis, correlating with impaired kidney function.

The limitations of this study include its retrospective single-center design and no independent validation of our findings. However, intrarenal complement deposits are increasingly recognized as a potential marker of autoantibody-mediated tissue damage in AAV [3]. Considering recent advances with the emergence of new therapeutics that inhibit complement activation in autoimmune diseases including ANCA-associated renal vasculitis and lupus nephritis, we here provide novel insights into intrarenal complement synthesis in ANCA-associated renal vasculitis. In addition, we herein describe distinct inflammatory

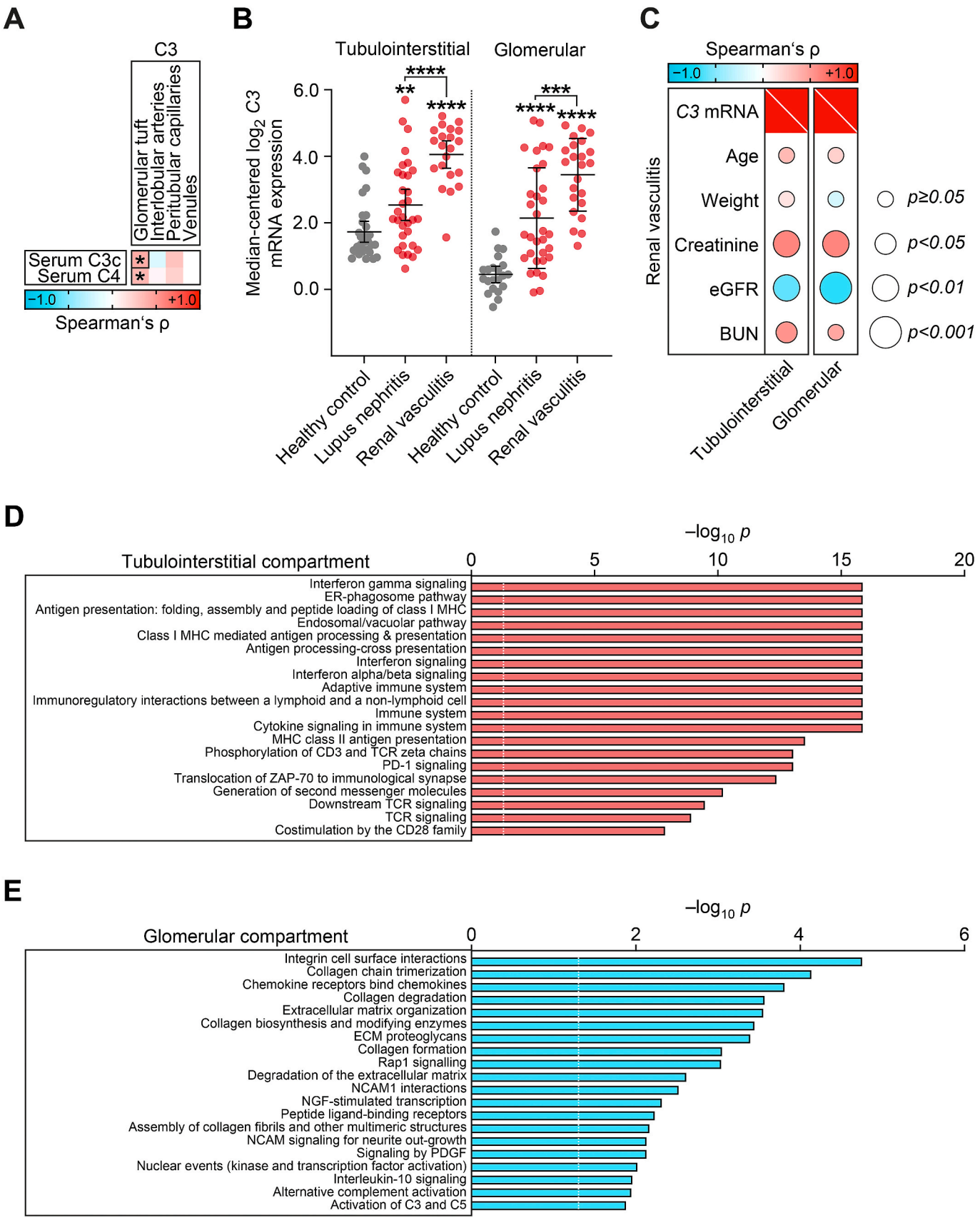

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Fig. 2. Intrarenal synthesis of complement C3 is linked to distinct inflammatory signaling pathways in ANCA-associated renal vasculitis. (A) Association between C3 deposits localized to the glomerular tuft, interlobular arteries, peritubular capillaries, and venules and serum levels of C3c and C4 in ANCA-associated renal vasculitis are shown by heatmap reflecting mean values of Spearman's ρ. Asterisks indicate significant associations in the univariate analysis ($p < 0.05$), rectangle boxes indicate significant associations in the stepwise multiple regression analysis ($p < 0.05$). (B) Median centered $\log_2$ *C3* mRNA expression levels in microdissected tubulointerstitial (healthy controls: n = 31, lupus nephritis: n = 32, renal vasculitis: n = 21) and glomerular compartments (healthy controls: n = 21, lupus nephritis: n = 32, renal vasculitis: n = 23) are shown. Comparisons of groups were performed using one-way ANOVA corrected for multiple comparisons by Holm-Šídák test (***$p < 0.001$, ****$p < 0.0001$). (C) Correlations between tubulointerstitial and glomerular *C3* mRNA expression levels, clinical and laboratory markers of kidney function in renal vasculitis are shown by heatmap reflecting mean values of Spearman's ρ, circle size represents significance level. (D,E) Entities -$\log_{10} p$ values of top 20 signaling pathways separated for gene enrichment positively associated with either tubulointerstitial or glomerular *C3* mRNA expression are shown (the dotted lines correspond to the predefined threshold value of $p \leq 0.05$). Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

signaling pathways associated with intrarenal C3 synthesis that might be affected by targeted therapy of the complement system in ANCA-associated renal vasculitis.

Author statement

Samy Hakroush: Conceptualization, Data curation, Writing - review & editing. **Désirée Tampe:** Data curation, Writing - review & editing. **Eva Baier:** Data curation, Writing - review & editing. **Ingmar Alexander Kluge:** Data curation, Writing - review & editing. **Philipp Ströbel:** Data curation, Writing - review & editing. **Björn Tampe:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft.

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Data availability

Deidentified data are available on reasonable request from the corresponding author.

Declaration of competing interest

SH, DT, EB, IAK, PS and BT have no conflicts of interest to report related to this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2022.102924.

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