Role of Microbiome and Host Response in Granulomatosis with Polyangiitis (PRO-GPA)

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Background and preliminary data

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) represent two major subtypes of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), characterized by necrotizing small vessel vasculitis (Kronbichler, Bajema et al. 2024). Specifically, GPA is associated with proteinase 3-specific ANCA (PR3-ANCA) and features a disease-defining histomorphologic pattern of necrotizing granulomatous inflammation that predominantly affects the respiratory tract (Falde, Fussner et al. 2024). However, approximately 50% of patients with 'localized GPA' (e.g., ear, nose, and throat [ENT]-limited disease) lack positive ANCA testing (Holle, Gross et al. 2010). ANCA-negative GPA can become ANCA-positive over time, which is usually associated with the development of a capillaritis phenotype (Falde, Fussner et al. 2024). In contrast to granulomatous inflammation, substantial overlap exists between GPA and MPA with respect to disease manifestations caused by capillaritis (e.g., pauci-immune glomerulonephritis) (Kronbichler, Bajema et al. 2024).The pathogenesis of AAV is poorly understood, however, disease manifestations are thought to result from intrinsic predispositions (e.g., human leukocyte antigen risk alleles) and extrinsic factors such as dysbiosis that result in chronic dysregulation of innate immune responses (e.g., neutrophil activation) (Arnold, Kitching et al. 2024, Falde, Fussner et al. 2024). In particular, **chronic nasal *S. aureus* carriage (CNSAC)** has been identified as an independent risk factor for relapse and occurs in up 70% of patients with GPA (Stegeman, Tervaert et al. 1994, Laudien, Gadola et al. 2010). CNSAC has been linked to higher endoscopically proven endonasal disease activity (Laudien, Gadola et al. 2010). Recently, a diminished humoral immune response to Vβ2-restricted superantigens along with reduced numbers of circulating toxic shock syndrome toxin-1 reactive $V\beta2^{+}$Th cells has been reported in patients with GPA (Liao, Rutgers et al. 2025). Notably, some studies suggest that treatment with trimethoprim-sulfamethoxazole reduces ENT-disease relapses in GPA (Stegeman, Tervaert et al. 1996), possibly through restoration of the nasal microbiome. In MPA, certain immunogenic *S. aureus* plasmids can induce loss of tolerance to myeloperoxidase (MPO) and experimental MPO-AAV (Ooi, Jiang et al. 2019).

German and European expert panels emphasize the urgent need for reliable biomarkers **for the prediction of clinical phenotype, disease course, and therapeutic response** (Hellmich, Sanchez-Alamo et al. 2024, Holle, Kubacki et al. 2025). In this context, proteomic analysis of the peripheral blood offers a novel, non-invasive approach to identify disease-specific protein signatures. Previous studies on GPA pathogenesis provided significant insights derived from microbiome and proteome analysis (Ishizaki, Takemori et al. 2017, Salmela, Rasmussen et al. 2017, Rhee, Sreih et al. 2018, Everts-Graber, Martin et al. 2019, Lamprecht, Fischer et al. 2019, Hellbacher, van Hoef et al. 2025). However, an in-depth analysis with respect to clinical subgroups (localized vs. systemic), histomorphologic phenotype (granulomatous vs. capillaritis), and disease status (remission vs. relapse vs. refractory disease) has not yet been performed but remains of considerable clinical interest. Most importantly, disease pathogenesis and the role of mucosal or bacterial antigens in autoimmunity remain an exciting possibility to derive novel biomarkers.

Hypotheses

1. The serum proteome profile and nasal microbiome of patients with GPA differs between clinical subgroups, histomorphologic phenotypes and disease status.

a. ‘Localized GPA’ and systemic PR3-AAV without granulomatous inflammation (isolated capillaritis) differ with respect to serum proteome profile and nasal microbiome.
b. Systemic GPA with granulomatous inflammation represents a transitional disease phenotype within the GPA/PR3-AAV disease spectrum.

2. The serum proteome profile and nasal microbiome in GPA patients is distinct compared to MPA patients. Remission and active disease can be differentiated by serum proteome analysis.
3. Molecular subtyping of circulating immunoglobulins in terms of their molecular antigen will be different in GPA (including all subtypes) and MPA.

Aims and Work Program

- Aim #1: To establish and comprehensively characterize a clinical cohort of patients with GPA (and MPA for comparative analysis) with detailed clinical and molecular phenotyping (mucosal microbiome in the ENT area by 16S RNA or shotgun sequencing).
- Aim #2: To identify shared and distinct molecular profiles based on serum proteomics in different GPA subgroups (and MPA for comparative analysis).
- Aim #3: To characterize the microbial and tissue proteins bound by IgA and IgG from patients with GPA (and MPA for comparative analysis).
- Aim #4: To integrate obtained data patterns and to develop a clinical tool for the prediction of clinical subgroups, histomorphologic phenotypes and disease status in GPA.

Aim #1: Clinical characterization of patients with GPA

- Patient enrollment of four different groups, each comprising n=15 patients is planned: (1) localized GPA, (2) systemic GPA with granulomatous manifestations, (3) PR3-AAV without granulomatous manifestations and (4) systemic MPA (comparison group).
- Clinical data of two study visits (baseline, after 6 months) obtained during routine clinical practice will be included. Definitions of symptoms or signs will be based on the Birmingham Vasculitis Activity Score (BVAS) and the current EULAR guidelines.
- Nasal swabs will be obtained at two study visits (baseline, after 6 months).
- Microbiota profiling using 16S RNA sequencing will be carried out to characterize the nasal microbial composition in different GPA subgroups.

Aim #2: Serum proteome profiling in GPA

- The combination of global serum proteomics with targeted N-terminomics captures quantitative differences in protein expression and enables the identification of functionally relevant proteoforms. This enables the description of disease processes both at the systemic level (expression profiles) and at the molecular-mechanistic level (proteoforms).

Aim #3: Characterization of the microbial and tissue protein repertoire recognized by circulating IgG and IgA from GPA patients

- Circulating IgG and IgA will be isolated from patients and incubated with mucosal protein lysates and bacterial lysates, starting with S. aureus ssp lysates.
- Metaproteomics workflow will be used to identify bacterial proteins recognized by the antibodies.
- Workflow will be applied to top bacterial species identified in 1 and 2.

Aim #4: Integrative analysis towards GPA pathogenesis

- We will perform a bioinformatic-based integration of data patterns derived from clinical, proteomic and microbial studies to elucidate GPA pathogenesis and to define the clinical and histomorphologic spectrum associated with GPA.
- The development of a clinical tool for the prediction of clinical subgroups, histomorphologic phenotypes and disease status in GPA is planned.

Project-related publications

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Supplement

Summary

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) represent a heterogenous autoimmune disease affecting multiple organs. AAV present in different histopathological forms, among these chiefly a granulomatous form (Granulomatous polyangiitis, GPA), frequently localized in the ear nose throat area, as well as a vasculitic syndromes, frequently localized in parenchymous organs like the kidney. The pathogenesis of this autoimmune disease is unknown, but an infectious trigger has been suspected for decades, without success in pinpointing the microbial organism. The closest and best candidate is *S. aureus*, which has been shown to colonize the mucosa of these patients and associates with poor disease prognosis. However, a causal relationship between *S. aureus* colonization and disease pathogenesis has not been established. While several autoantibodies have been suggested to serve as markers, none of them are sufficient to guide therapies which still consists mostly of very harsh immunosuppression involving glucocorticoids and cyclophosphamide or rituximab in severe cases. In this project, we hypothesize that the pathophysiology of GPA involves atypical immunoglobulins, present in both tissue and circulation, GPA patients that recognize currently unknown microbial antigens, and that are part of a distinct circulating proteome in GPA compared to other vasculitides. To identify these microbial targets, we will use a combination of detailed clinical phenotyping and sample collection at the bedside, as well as search for disease mechanisms and markers on the bench. Multilayered clinical and molecular phenotyping will be carried out using mass spectrometry-based profiling of gut microbiome, characterization of immunoglobulins directed against microbes and host tissue and monitoring of host response of circulating molecules. Together, this approach can potentially give rise to an actionable diagnostic test that can be used to monitor treatment response and allow for drug target discovery.

Work Programme

The outlined research project is planned within the translational research framework of the III. Department of Medicine and is intended to provide the foundation for a research group dedicated to proteome analysis in systemic inflammatory diseases.

1. Preparation (4 months): At the beginning of the project, the necessary prerequisites for its implementation must be established. These steps include the development of a study protocol (including informed consent sheet for study participants) with subsequent review of this study by the local Ethics Committee. In addition, a systematic literature review is planned to provide the conceptual framework. Parallel to this, training in fundamental laboratory procedures is envisaged.
2. Establishment of the Clinical Cohort (30 months): Once the project has been approved by the local Ethics Committee, patients will be enrolled and examined according to the defined criteria.
3. Serum Proteomics (30 months): Proteomic analyses of serum will begin following an initial training phase in the methodology and once serum samples from patients have been collected.
4. Data Analysis, Preparation of Figures and Tables (4 months).
5. Manuscript Preparation and Submission for Publication (3 months).

			2026				2027				2028			
Work Programme	**Start**	**End**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
(1) Preparation	Jan 26	Apr 26												
Development of the study protocol	Jan 26	Jan 26												
Submission of the study protocol to the local Ethics Committee	Jan 26	Jan 26												
Review by the local Ethics Committee	Feb 26	Apr 26												
Systematic Review of the Literature	Jan 26	Feb 26												
Formal training in laboratory techniques	Jan 26	Feb 26												
(2) Setup of Clinical Cohort	Apr 26	Sep 28												
Patient enrollement (baseline)	Apr 26	Mär 28												
Follow-up (nach 6 Monaten)	Okt 26	Sep 28												
(3) Serum-Proteomics	Apr 26	Sep 28												
Formal training in laboratory techniques	Apr 26	Jun 26												
Analysis of obtained samples	Jul 26	Sep 28												
Data analysis, preparation of figures/tables	Jul 28	Okt 28												
(5) Manuscript writing & Submission	Okt 28	Dez 28												

Methods

Aim 1: Establish and comprehensively characterize a clinical cohort of patients with GPA

A multicentric cohort study of patients with AAV (GPA and MPA) will be carried out. Clinical assessment of AAV patients in addition to serum proteome analysis will be performed at two study visits (baseline and after 6 months).

Clinical data will include instrumental and histopathological findings obtained during routine clinical practice. Definitions of symptoms or signs indicating new onset, worsening, or persistent disease activity will be based on the Birmingham Vasculitis Activity Score (BVAS) and the current EULAR guidelines (Hellmich, Sanchez-Alamo et al. 2024).

Recruitment is planned for four different groups, each comprising n=15 patients: (1) localized GPA, (2) systemic GPA with granulomatous manifestations, (3) systemic GPA without granulomatous manifestations, and (4) systemic MPA (comparison group).

In addition to the University Medical Center Hamburg-Eppendorf, patients will also be recruited at the Bad Bramstedt site (Auenlandklinik), where a larger cohort of patients with localized GPA is available. A retrospective analysis of AAV patients treated at the III. Department of Medicine revealed 61 patients with GPA and 49 patients with MPA, indicating that the planned recruitment is feasible. At the Bad Bramstedt site, a total of 101 GPA patients and 21 MPA patients were treated between 2023 and 2024. In case of insufficient recruitment at the two mentioned sites, additional recruitment through external cooperation partners is possible.

Microbial analysis of nasal, ear, nose and throat swabs obtained at the two study visits will be performed in cooperation with the Section of Rheumatology and Clinical Immunology at the University Hospital Münster (Prof. Kriegel).

Inclusion Criteria

- Patients with GPA or MPA (newly diagnosed or relapsing)
- ACR/EULAR classification criteria of 2022 for GPA or MPA
- Confirmation of AAV diagnosis by at least two specialists in rheumatology or nephrology

Exclusion Criteria

- Active infection
- Active malignancy
- Age < 18 years
- Lack of written informed consent
- Lack of willingness or capacity to provide consent for participation

Aim 2: Analysis of the Serum Proteome (bottom-up mass spectrometry-based proteomics)

The aim of the research project is to identify and characterize biomarkers from serum samples that have diagnostic and prognostic value. By combining global serum proteomics with targeted N-terminomics, not only quantitative differences in protein expression but also functionally relevant proteoforms will be captured. This enables the description of disease processes both at the systemic level (expression profiles) and at the molecular-mechanistic level (proteoforms).

In the first step, dimethyl labeling of N-termini and lysine residues is performed, followed by proteolytic digestion into peptides. The peptide mixture is then fractionated using C18 cleanup and nano-liquid chromatography before being introduced into the mass spectrometer. Peptides are analyzed on a high-resolution Orbitrap analyzer (Exploris480) using a data-independent acquisition (DIA) strategy combined with high-field asymmetric waveform ion mobility spectrometry (FAIMS). Finally, peptides are identified and quantified using a bioinformatics pipeline (FragPipe/DiaNN). In parallel, OLINK affinity-based proteomics will be performed.

Aim 3: Immunoglobulin purification and profile binding (Mechanistic Profiling of Autoantigens)

Within the research group, the analysis of binding affinity of purified immunoglobulin (IgG) from serum samples to tissue lysates has already been established in autoantibody-mediated diseases such as lupus nephritis. In this context, a clear binding of autoantibodies from serum samples to lupus-specific autoantigens could be demonstrated. Within the framework of the present research project, this approach is planned to be transferred to GPA.

In the first step, IgG will be purified from the serum of GPA patients and healthy controls, applied to a microcentrifugation column, and incubated. After binding, the column is washed to remove unbound proteins. The IgG fraction is eluted using an IgG elution buffer.

The binding of IgG from serum samples to human proteins (autoantigens) will be carried out by immunoprecipitation. For this purpose, patient serum is mixed with microbial lysate from the 10 most regulated bacterial taxa and incubated. Subsequently, an IgG affinity matrix is added to capture IgG from the serum sample. Following washes, the autoantigen will be identified by mass spectrometry. Sample processing is carried out according to a modified SP3 protocol for protein purification. Finally, proteome analysis is performed using mass spectrometry.

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