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P-005

Complement activation and immune responses induced by Nuvaxovid and ChAdOx1 vaccines against Covid-19

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Abstract

The Nuvaxovid (NVX-CoV2373) and ChAdOx1 vaccines have been used during the COVID-19 pandemic. To test the potential role of complement in their immunogenicity and side effects, we analyzed whether they induce complement activation in human serum. Nuvaxovid and ChAdOx1 vaccines were incubated in pooled and individual serum samples from healthy donors with different vaccination statuses. The formation of C5a, C3a and the terminal complement complex (sC5b-9) was quantified using enzyme immunoassays. Both Nuvaxovid and ChAdOx1 activated the complement system primarily through the classical pathway in a concentration-dependent manner. Both vaccines induced significant C5a formation, with higher levels observed through the classical than the alternative pathway. Nuvaxovid increased both C3a and sC5b-9 levels. There was significant variability in complement activation between individual serum samples. Strongest responses were observed post-vaccination. For the S-protein containing Nuvaxovid the complement activation product levels correlated with anti-S IgG levels and for the adeno-vectored ChAdOx1 with the adenoviral anti-hexon antibodies. The results have potential implications for the immunogenicity and safety profiles of these vaccines.

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P-006

MicroRNA sequencing of plasma exosomes reveals complement dysregulation in COVID-19

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Abstract

COVID-19 pathogenesis primarily impairs lung function through pneumonia, diffuse alveolar damage, and acute respiratory distress syndrome (ARDS), with severe cases of ARDS advancing to non-resolving pulmonary fibrosis. Mechanical ventilation can exacerbate lung injury and promote the release of profibrotic mediators, including microRNAs (miRNAs). We hypothesized that miRNAs shuttled in plasma exosomes may serve as superior biomarkers of COVID-19 pathogenesis during severe ARDS and the convalescent stage of infection. Plasma samples were deactivated at 56 ˚C for 45 minutes to eliminate microbial contaminants and stored at –80 ˚C. Exosomes were isolated via polyethylene glycol-based precipitation after thrombin pre-treatment to remove fibrin, and their presence was confirmed by transmission electron microscopy. Small RNA libraries were prepared from exosomal RNA using adaptor ligation and cDNA synthesis, followed by sequencing on an Illumina platform. Differential miRNA expression was analyzed using DESeq2 and edgeR, with known and novel miRNAs identified through miRDeep2 and miREvo pipelines. MicroRNA sequencing analysis of plasma exosomes revealed a unique repertoire of circulating miRNAs in patients with severe ARDS and during convalescence, compared to healthy controls. Strikingly, several critical miRNA targets were identified as complement immune factors, responsible for bridging host innate and adaptive immunity. Circulating miR-26b-5p, which targets the 3'-UTRs of complement components C1S, C3, and C5, was significantly upregulated in both critical ARDS and convalescence, indicating complement dysfunction. In contrast, miR-27b-3p which targets C1S and C5, and miR-16-2-3p which targets the complement anaphylatoxin receptor C5aR1, were significantly downregulated with disease severity and remained low during convalescence, suggesting sustained inflammatory C5aR1 signaling. Furthermore, miR-532-5p, which targets the terminal pathway regulator C7, was significantly downregulated, while miR-146a-5p, targeting soluble regulatory complement factor H (FH), was significantly upregulated during convalescence. These miRNA alterations correlated with complement component expression in lung tissues from patients with fulminant COVID-19. Finally, SARS-CoV-2 spike-overexpressing HUVECs cultured with C7- and FH-depleted serum exhibited elevated production of IL-6, IL-8, and CXCL10—key mediators of the cytokine storm—along with significantly increased C5aR1 expression. Together, these findings suggest that persistent complement dysregulation may contribute to vascular inflammation and post-acute COVID-19 lung disease.

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P-007

Molecular epidemiology and comparative virulence patterns of *Acinetobacter baumannii* isolates from war-related injuries in Ukraine

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Abstract

Background: Multidrug-resistant Acinetobacter baumannii remains as a global concern with its ability to adhere, disperse and sustain on areas involving suboptimal infection control measures, especially war zones. We aimed to evaluate the molecular epidemiology and virulence factors of A. baumannii isolates from conflict zone in Ukraine.

Methods: In 2022, 46 A. baumannii wound isolates were received from war-related injuries in Ukraine. Antimicrobial susceptibility testing and whole genome sequencing were performed to all isolates (n = 46). The resistome, virulome, K- and O-types of isolates were detected using VFDB and Kaptive 2.0, respectively. Virulence traits of the isolates were tested in vitro and in vivo by phenotypic assays; capsule abundance, serum survival, biofilm formation, Galleria mellonella infection and mouse pneumonia.

Results: Five out of 46 (10.8%) isolates tested extensively drug resistant (XDR) and 84.78% of the isolates tested multidrug-resistant (MDR). Distance matrix analysis based on SNPs generated 5 main clusters of 46 isolates. Dominating sequence types of the isolates were ST2 (19%), ST19 (19%), ST400 (19%) and ST78 (19%). Comparative assessment of virulence profiling revealed that, KL235 and K91 are highly encapsulated K types and are found in ST2 and ST19 isolates. Virulome analysis revealed missing T66S encoding genes, Omp33-36 and biofilm production related genes (*bap*, *blp1*) in ST19 isolates. High level of encapsulation was observed in ST19 isolates followed by lower serum survival compared to the rest of the study cohort. ST19 isolates expressed a higher survival and virulence score at 24 h in mice and G. mellonella viability assay, respectively. However, prolonged infection up to 120 h in G. mellonella larvae and 72 h in mice showed that ST19 isolates have lower ability to kill larvae followed by clearance in lung and BAL fluid while ST2 isolates managed to persist the infection and lethality ($p = 0.0001$).

Conclusion: Although *A. baumannii* is known for its strain specific behavioral pattern in terms of virulence, our study revealed that STs act parallel on genotypic and phenotypic basis. Instability and absence of TS66, OMP-33/36 and biofilm encoding genes and its effect on encapsulation should be studied further for possible antivirulent and immunization therapies.

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P-008

A novel complement-based drug candidate against fungal infections with promising results in a murine model of invasive pulmonary aspergillosis

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Abstract

Background: Upon inhalation, the opportunistic fungal pathogen Aspergillus fumigatus can cause invasive pulmonary aspergillosis (IPA), a potentially life-threatening disease. There is an urgent need for novel antifungal therapeutics due to an emergence of antifungal resistant isolates, severe side effects of antifungals, and the increase of patients with risk factors such as immune deficiencies and therefore an increase of IPA cases. Our solution is a novel antibody-like antifungal drug candidate, which is comprised of a human IgG1 Fc region, a hinge region, and a peptide derived from MASP-1 instead of the Fab region. This peptide has been demonstrated to bind to Aspergillus fumigatus, activate complement, and trigger phagocytosis. The aim of this study was to investigate the peptibody in a murine model of IPA.

Methods: Cyclophosphamide-treated mice were intranasally challenged with a clinical isolate of *Aspergillus fumigatus* and either treated with three different peptibody dosages (low, medium, high) or "mock-treated" with a vehicle control (PBS) or Fc fragments at 1 h, 8 h, and 24 h post-infection. To investigate adverse effects of this novel antifungal drug candidate unifected animals were included, which were either given PBS or the high peptibody dosage. After 14 days of survival monitoring, organs and bronchoalveolar lavage (BAL) fluid were obtained, and the fungus burden was assessed.

Results: The intranasal challenge with *Aspergillus fumigatus* resulted in a lethal outcome for the animals receiving PBS. While the intranasal administration of Fc fragments did not improve the outcome, the low peptibody dosage rescued 30% of the animals. When administered the medium dosage, the survival increased to 80% and the outcome was further improved to 100% with the high peptibody dosage. Peptibody-treated animals also showed a lower fungal burden in their lung tissue and BAL fluid compare to "mock-treated" mice. No adverse effects by the peptibody were detected in uninfected animals.

Conclusion: The study concludes that peptibody plays a critical role in the fungal clearance and survival of the treated animals, highlighting the remarkable potential of this novel antifungal drug candidate as a salvage treatment for IPA in patients with compromised immune systems.

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P-009

Evasion of complement and amyloid-beta by the neurotropic pathogen *Borrelia burgdorferi* in human 3D cultures

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Abstract

Background: Amyloid-beta is toxic to neurons and, in excess, can trigger Alzheimer's disease. Oligomers of the amyloid-beta peptide are known to activate the complement system. Previous findings suggest that amyloid-beta acts as an antimicrobial peptide and protects the brain from infectious agents. While evasion of the complement system is a common trait among pathogens, little is known about the role of amyloid-beta in host-pathogen interactions. The aim of this study was to determine whether, and how, amyloid-beta plays a role in the innate immune system, and whether a well-known neurotropic pathogen, *Borrelia burgdorferi*, has evolved strategies to evade amyloid-beta, a potential component of the innate immune system.

Methods: Human 3D neuronal tetracultures were used to model complement and amyloid-beta evasion by *B. burgdorferi* in a neuronal microenvironment. The effects of multiple interactions between amyloid-beta, bacteria, and complement molecules in infected 3D cultures were studied using ELISA, Western blot, transmission-electron