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Fund “Nauka” Project № 25011 Resume – Competition-based Session 2025:
“Markers of necroptosis and pyroptosis in patients with pneumonia”
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Pneumonia continues to be one of the major challenges facing modern medicine, representing an infectious disease of high socio-economic importance and global prevalence. It affects all age groups, with the most vulnerable being children under the age of 1, adults over 65 years, and immunocompromised patients. The recent pandemic caused by the SARS-CoV-2 virus highlighted deficiencies in our understanding of the pathophysiological processes occurring in lung tissue during pneumonia and emphasized the need for more in-depth molecular and clinical studies to reveal new therapeutic approaches and strategies for more precise treatment monitoring.

One of the fundamental problems associated with the treatment of pneumonia is the increasing antibiotic resistance. The irrational empirical use of antibiotics leads to the selection of multidrug-resistant bacterial strains, which significantly complicates therapeutic management and increases mortality. In addition, the side effects of prolonged antibiotic therapy may often outweigh its potential benefits. Infectious diseases of the lower respiratory tract remain a leading cause of hospitalization and antibiotic use, underscoring the need for alternative diagnostic and therapeutic methods based on a deeper understanding of pathogenetic mechanisms.

In recent years, scientific attention has been directed toward necroptosis – a specific form of programmed cell death characterized by morphological features of necrosis but regulated by genetic mechanisms. Unlike apoptosis, necroptosis initiates an inflammatory response within the cell and surrounding tissue, making it particularly significant in infectious and inflammatory diseases, including pneumonia.

A key molecule in the necroptosis cascade is receptor-interacting protein kinase 3 (RIPK3). RIPK3 is involved in the activation of MLKL (mixed lineage kinase domain-like protein), leading to disruption of the cell membrane and the release of inflammatory mediators. Recent studies in murine models, primates, and humans have shown that bacteria producing pore-forming toxins (PFTs) can induce necroptosis in the respiratory epithelium independently of endogenous signals. Models using genetically modified mice lacking RIPK3 (Ripk3−/−) demonstrate significantly increased lung parenchymal damage in experimentally induced pneumonia, illustrating the dual role of necroptosis – as both a mechanism for infection control and a

contributor to tissue injury. In a clinical context, elevated serum levels of RIPK3 have been observed in patients with severe COVID-19 pneumonia, suggesting that RIPK3-mediated signaling contributes to the development of acute respiratory distress syndrome (ARDS).

Although there is substantial evidence for the involvement of RIPK3 in the pathogenesis of pneumonia, there is currently a lack of comprehensive studies tracking the dynamics of its levels in patients with varying disease severity, as well as its correlation with mortality, biomarkers such as CRP, procalcitonin, leukocytosis, and other clinical parameters. This represents a significant gap in knowledge that the present study aims to address.

Another important mediator in the immune response in pneumonia is interleukin-1 beta (IL-1β). This proinflammatory cytokine plays a central role in the early phase of the inflammatory response and is key to another type of cell death – pyroptosis – by stimulating neutrophil chemotaxis and the secretion of other cytokines. IL-1β levels correlate with disease severity and are believed to have both protective and potentially harmful effects. In bacterial pneumonia, high concentrations of IL-1β in bronchoalveolar lavage (BAL) have been associated with increased bacterial load, and in patients with ventilator-associated pneumonia (VAP), IL-1β, together with IL-8, has been established as a reliable diagnostic marker.

Of particular importance is the fact that IL-1β can be activated as a result of necroptosis independently of the classical inflammasome pathway, highlighting the close functional relationship between RIPK3 and IL-1β. This provides an opportunity to use these molecules not only as biomarkers for diagnosis and prognosis but also as potential therapeutic targets. RIPK3 inhibitors are already being investigated in the context of autoimmune and inflammatory diseases, and positive results from such studies could also find application in pneumonia.

In conclusion, RIPK3-mediated necroptosis and the inflammatory activity of IL-1β play a significant role in the pathogenesis of pneumonia. Investigating their levels, correlations with other indicators, and clinical significance may provide valuable information about disease severity, prognosis, and treatment response. This opens a new perspective for the development of precision medicine in the treatment of pneumonia, based on molecular targets and an individualized patient-orientated approach.

Expected results:

1. To establish a significant correlation between the levels of RIPK-3 and IL-1β and the other biomarkers investigated in the study (WBC, procalcitonin);

2. To establish a significant correlation between the levels of RIPK-3 and IL-1β and the severity of CAP;
3. To establish a significant correlation between the levels of RIPK-3 and IL-1β and 30-day patient mortality;
4. RIPK-3 may be used as a marker for monitoring response to therapy.