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THE NEUTROPHIL AND CLINICAL CHARACTERISTICS OF POST-COVID PNEUMONIA

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Abstract. Unusually for a viral infection, the immunological phenotype of post-COVID-19 patients is characterised by a depleted lymphocyte and elevated neutrophil count, with the neutrophil-to-lymphocyte ratio correlating with disease severity. Neutrophils are the most abundant immune cell in the bloodstream and comprise different subpopulations with pleiotropic actions that are vital for host immunity. Neutrophils also contribute to complications of post- COVID-19 such as thrombosis, acute respiratory distress syndrome and multisystem inflammatory disease in children. In this Progress review, we discuss the anti-viral and pathological roles of neutrophils in SARS-COVID-19 infection.

Key words: viral infection, immune cell, neutrophil, SARS-COVID-19 infection

Neutrophils contribute to hypersensitivity pneumonitis in SARS-CoV-19 infection and altered neutrophil immunometabolism, with accumulation of succinate correlating with disease severity . A coronavirus demonstrated that neutrophils produce cytokines and chemokines in response to alveolar epithelial cell infection with SARS-CoV-19, resulting in an inflammatory response which contributes to lung injury .

Neutrophils are the first responders to infection and extravasate rapidly from the blood vessels into tissue. They are the most abundant leukocyte in blood, with about 10^{11} neutrophils produced by the bone marrow each day, representing 40-60% of circulating immune cells in healthy adults (1). Neutrophils kill pathogens using oxidative burst, degranulation, phagocytosis and the release of neutrophil extracellular traps (NETs) (2). Their role is most prominent in bacterial infection but they can also contribute to antiviral immunity. Disease in COVID-19 patients is associated to increased neutrophil-to-lymphocyte ratio and high expression of neutrophil-related cytokines IL-8 and IL-6 in serum, and neutrophilia has been described as a predictor of poor outcome (3). Peripheral blood neutrophil counts in patients with COVID-19, although not as elevated as bacterial pneumonia, are higher in severe COVID-19 compared with mild cases and most other viral infections (4). Neutrophils are associated with the development of thrombosis and pulmonary infiltrates found in post-mortem samples following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-19) (5). In this Progress review, we focus on emerging data on the roles of neutrophils in the pathogenesis and response to SARS-CoV-2.

An altered neutrophil-to-lymphocyte ratio occurs in many conditions such as cancer, cardiovascular disease, sepsis and inflammatory disorders, including Systemic lupus erythematosus (SLE) and psoriasis . Patients with COVID-19 with chronic disease had significantly higher absolute neutrophil counts (8) similar to the neutrophilia in both Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) (6). The limited antiviral response in COVID-19 may exacerbate neutrophil infiltration, resulting in exuberant inflammation (10). COVID-19 is characterised by a cytokine storm and the Pyrin domain containing 3 (NLRP3) inflammasome has been implicated. The inflammasomes are molecular mechanism involving multiprotein complexes which regulate the production of pro-inflammatory cytokines. NLRP3, a member of the nucleotide oligomerization domain (NOD)-like receptor (NLR) family, is present in neutrophils (1). After NLRP3 activation, pro-caspase 1 is cleaved to the active form caspase 1, leading to the cleavage of

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pro-inflammatory pro-IL-1β and pro-IL-18 into the active forms (5). Single-stranded ribonucleic acid (ssRNA) viruses, such as SARS-CoV-19, induce Nuclear factor kappa B (NF-κB) activation and the further production of pro-IL-1β and pro-IL-18 (4). Simultaneously, ROS and Adenosine 5'-triphosphate (ATP) produced by mitochondria trigger NLRP3 inflammasome assembly (9). Active NLRP3 inflammasome is present in peripheral blood mononuclear cells (PBMCs) and post-mortem tissues of post-COVID-19 patients, and high expression of its derived products such as Casp1p20 and IL-18 were seen to correlate with disease severity and poor clinical outcome (6). NLRP3 inflammasome activation has also been described in neutrophils of post- COVID-19 patients (3). Aymonnier et al. found that neutrophils from post-COVID-19 patients with respiratory failure demonstrated NLRP3 inflammasome molecule Apoptosis-associated speck-like protein containing a CARD (ASC) specks, and their early formation in NETosis. In patients with post- COVID-19 neutrophils with intact multilobulated nuclei, ASC specks formation and histone H3 citrullination was elevated (4). Coagulation cascade activation is a common finding in patients with COVID-19 and is associated with disease severity (7). Elevated levels of fibrin D-dimer degradation products, a marker of fibrin degradation indicating overactive coagula

tion, correlates with a worse clinical outcome (9). High plasma levels of plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) in hospitalised COVID-19 patients had strong correlations with neutrophil counts and activation, and extremely high levels of tPA increasing fibrinolysis (7). Plasmatic matrix metalloproteinase-9 (MMP-9) was likewise increased in post-COVID-19 patients which induced platelet and neutrophil activation, and NETs formation *in vitro* (8). Post-mortem studies have consistently shown that micro-thrombi are present throughout the pulmonary vasculature (8). Collectively, these data suggest that coagulation activation and vasculopathy within the lungs (pulmonary intravascular coagulopathy [PIC]) plays a role in modulating COVID-19 pathogenesis (10).

The clinical syndrome of severe COVID-19 has several unique features, including, unusually for a viral infection, an increased neutrophil-lymphocyte ratio. Neutrophils play a role in viral clearance in terms of NETs and the production of IFN. However, neutrophils can have detrimental effects by aiding the pathogenesis of SARS-CoV-19 and exacerbating complications of post- COVID-19 such as ARDS, thrombosis and MIS-C. Understanding the role of neutrophils in the pathogenesis of post-COVID-19 may lead to identification of key therapeutic targets and/or biomarkers for early identification of patients who may benefit from immunomodulatory agents to control hyperinflammation and reduce mortality rates.

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