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INVESTIGATING NEUTROPHIL SUBPOPULATION DYNAMICS IN A MOUSE MODEL OF SARS-COV-2 INFECTION

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Abstract

The project largely involved studying neutrophil dynamics or kinetics in a mouse model of SARS-CoV-2 infection. The study is carried out in a mouse model using transgenic mice expressing the human ACE-2 receptor, which allows the virus to enter cells.

Keywords: virus, mouse model, neutrophil population

INTRODUCTION

Since the first reports of an outbreak of a severe acute respiratory syndrome (ARDS) caused by coronavirus 2 (SARS-CoV-2) in China in December 2019 (*1*, *2*), the coronavirus disease 2019 (COVID- 19) have grown to be a global public health emergency. SARS-CoV-2 infection is characterized by a range of symptoms including fever, cough, fatigue and myalgia in the majority of cases and occasional headache and diarrhea (*1*, *3*). Among reported cases, approximatively 80% present mild conditions, 13% serious, and 6% developing critical case requiring intensive care associated, with fatality rate of 2-8% of reported cases (*4*). More severe cases of COVID-19 show development of ARDS and acute lung injury, leading to mortality caused by damage to the alveolar lumen. A high number of patients with ARDS secondary to COVID-19 developed life-threatening thrombotic complications (*5*). Coronavirus infections in the past have been characterized by the onset of a virus-induced inflammation associated with a cytokine storm that begins at the infection site and spreads throughout the body via the systemic circulation (*6*). It is therefore reasonable to postulate that the inflammatory response measured both at cellular and molecular levels would represent a main prognostic signature for the disease. Molecular assays have been the gold standard to directly detect for the presence of the virus as well to respond to the demand of clinicians to characterize the infection onset, notably cytokine storm, an uncontrolled inflammatory response, resulting in viral sepsis, ARDS, respiratory failure, shock, organ failure, and death (*7*, *8*). However, there is a lack of prognostic markers on complications onset in severe cases.

MATERIAL AND METHODS

A retrospective cohort of 201 patients with confirmed COVID-19 pneumonia revealed that older age, neutrophilia, and organ and coagulation dysfunction were the major risk factors associated with the development of ARDS and progression to death (*9*). ARDS and sepsis are among the most frequently observed common complications in deceased patients (*3*). In severe cases, bilateral lung involvement with ground-glass opacity is the most common chest computed tomography (CT) finding but more surprisingly, abnormal CT scans were also observed on asymptomatic COVID-19 patients (*10*). Immune transcriptome profiling from broncho-alveolar lavage fluid of COVID-19 patients showed hypercytokinemia (*6*). In addition, serum concentrations of both proinflammatory cytokines and anti- inflammatory cytokines, including IL-6, TNF-α, and IL-10 increased in the majority of severe cases and were markedly higher than those in moderate cases, suggesting cytokine storms might be associated with disease severity, providing insights into immune therapeutics (*3*, *11*). The cytokine storm has been associated with

massive influx of innate immune cells, namely neutrophils and monocytes, which may aggravate lung injury. However, little is known about the innate immune features and the molecular mechanisms involved in COVID-19 severity. Increasing clinical data indicated that the neutrophil-to-lymphocyte ratio (NLR) is a powerful predictive and prognostic indicator for severe COVID-19 (*12–14*). Lymphopenia, neutrophilia, and high NLR are commonly presented and associated with more severe viral infection (*12*, *15*). However, there are very few treatments (if none) specifically tackling neutrophil functions that could alleviate inflammation and facilitate infection resolution.

RESULTS AND DISCUSSION

The first comprehensive evaluation of whole blood circulating neutrophils in septic (*16*) and COVID-19 patients was made (16). High dimensional mass cytometry revealed a specific neutrophil signature of sepsis severity that does not overlap with other inflammatory biomarkers, and that distinguishes patients with sepsis from those with non-infectious inflammatory syndrome (*16*). Unsupervised analysis of 40-dimesional mass cytometry data characterized previously unappreciated heterogeneity within the CD64+ immature neutrophils and revealed two new subsets distinguished by CD123 and PD-L1 expression. These immature neutrophils exhibited diminished activation and phagocytosis functions. Critically, the proportion of CD123-expressing neutrophils correlated with clinical severity. To test the hypothesis of a virally-driven neutrophil profile that could be a good COVID patients' disease-state indicator, the multi-parametric neutrophil profiling strategy was applied. This strategy was based on known neutrophil markers to distinguish COVID-induced phenotypes in critical (in intensive care unit) compared to severe symptomatic patients (in infectious departments). After this strategy, two new CD10-CD64+ immature neutrophil subsets expressing either LOX-1 or CD123 that were specific to COVID-19 were identified. In addition, previous work showed that LOX-1 is important mediator of inflammation and neutrophils dysfunction in sepsis and cancers (*17, 18*).

CONCLUSIONS

Despite these very interesting results the functional characteristics of these neutrophil subsets and their role in COVID-19 pathogenesis is still unknown.

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