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COVID-19-ASSOCIATED IMMUNOPATHOLOGY MECHANISMS

Resume: *At the time being, identification of COVID-19 progression mainly relies on clinical manifestation as no biomarker was found to be reliable. Some research shows that a cytokine storm might trigger further severe disease progression. A cytokine storm can lead to multisystem organ failure and death. For instance, retrospective studies demonstrated a strong association between an elevated level of interleukin-6 (IL-6) and high mortality from COVID-19. Latest research showed that cytokines not only play a key role in driving the appearance of these clinical features but also represent the core of the development of inflammation. In particular, patients with severe COVID-19 showed profound increases in cytokines such as IL-2, IL-7, IL-10, GSCF, IP10, MCP-1, MIP1A and TNF-α, with the characteristics of a cytokine storm, which in turn correlates with the severity of COVID-19 clinical course. Therefore, the aim was to outline briefly the key player in cytokine storm, the role of T-lymphocytes and neutrophils in COVID-19 clinical course.*
Materials and Methods: *literature review.*
Discussion: *Solid body of research on circulating immune cells by flow and mass cytometry and/or single-cell RNA sequencing showed that SARS-CoV-2 induces activation of the innate immune system resulting in aggressive pro-inflammatory response, especially in severe COVID-19 clinical cases, nonetheless specific and non-specific immunity is suppressed follwoing acute immune reponse, therefore further research should be done to investigate the role of NK cells and cytotoxic proteins in order to understand the pathophysiology behind the COVID-19 severe clinical cases.*
Conclusion. *One of the main challenges in this battle with COVID-19 is to develop prognostic immunological criteria for the rapid progression of organ and system damage in post-COVID19 syndromes (macrophage hyperactivation syndrome, thrombosis and thromboembolism) for the rightest choice of therapeutic tactics and prevention of complications and unfavorable outcomes of patients based on the analysis of the data obtained. Solid body of research on circulating immune cells by flow and mass cytometry and/or single-cell RNA sequencing showed that SARS-CoV-2 induces activation of the innate immune system resulting in aggressive pro-inflammatory response, especially in severe COVID-19 clinical cases, nonetheless specific and non-specific immunity is suppressed follwoing acute immune reponse, therefore further research should be done to investigate the role of NK cells and cytotoxic proteins in order to understand the pathophysiology behind the COVID-19 severe clinical cases.*
Keywords: *cytokine storm, prognostic criteria, immunopathology, severity of COVID-2019*

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COVID-19 БІРЛЕСКЕН ИММУНОПАТОЛОГИЯЛЫҚ МЕХАНИЗМДЕР

Түйін: SARS-CoV-2 вирусымен шақырылған жұқпалы ауру ағзада түрлі аутоиммунды және аутоқабыну синдромдардың дамуына ықпал келтіреді. Солардың ішінде балалардың мульти жүйелі қабыну синдромы (PIMS) немесе мульти жүйелі қабыну синдромы (MIS-C) бар.Бұл асқынулар дәстүрлі емес сипатқа

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COVID-19 АССОЦИИРОВАННЫЕ ИММУНОПАТОЛОГИЧЕСКИЕ МЕХАНИЗМЫ

Резюме: Инфекция, вызванная SARS-CoV-2 запускает развитие различных аутоиммунных и аутовоспалительных синдромов, включая детский воспалительный мультисистемный синдром (PIMS) или мультисистемный воспалительный синдром

ие. Олар басқа вирусты және аутоиммунды аурулардан жоғары жиілікпен, клиникалық ағымы мен нәтижелерімен ерекшеленеді. Кейде осындай салдар COVID-19 ағымынан да ауыр болады. SARSCov2 вирусына иммунды жауаптың даму ерекшеліктерін және иммунды девиациялардың даму себептерін түсіну жеке адамда асқынулар мени кері салдардың дамуың болжамдауға көмектеседі. Оларды алдын-алу мақсатында диагностикалық және емдік шараларды ұйымдастыруға мүмкіндік береді. Қазір COVID-19-дың клиникалық ағымын идентификациялау көбіне клиникалық белгілерге сүйеніп жасалынады. Себебі бірде-бір биомаркер сенімді болмады. Кейбір зерттеулерге сүйенсек, цитокинді дауыл аурудың ауыр өршуіне әкелу мүмкін. Мысалы, цитокинді дауыл полиорганды жетіспеушілік пен өлімге әкеп соқтыру мүмкін. Жаңа ретроспективті зерттеулерде интерлейкин-6 (ИЛ-6) дәрежесінің жоғарылауы мен COVID-19 салдарынан қайтыс болу арасында корреляция бар екендігі анықталды. Соңғы зерттеулер бойынша, цитокиндер қабынудың патологиялық үрдістерінде маңызды орын алады. Мысалы, COVID-19 ауыр дәрежесі бар науқастарда IL-2, IL-7, IL-10, GSCF, IP10, MCP-1, MIP1A и TNF-α секілді цитокиндердің жоғарылауы, яғни цитокинді дауыл анықталды. Ол COVID-19-дың ауыр клиникалық дәрежесімен корреляция жасайды. Осы шолудың мақсаты цитокинді дауылдың негізгі триггерлерін сипаттау, COVID-19-дың клиникалық ағымындағы Т-лимфоциттер мен нейтрофилдердің маңызын анықтау.

Әдістер: әдебиетті шолу. Талқылау. Ағымды және масс-цитометрия және/немесе жеке жасушалардың РНК секвенирлеу арқылы айналымдағы иммунды жасушаларды жүйелі зерттеу барысында, SARS-CoV-2 туа пайда болған иммунды жүйені белсендіретіні анықталды. Бұл, әсіресе COVID-19 ауыр дәрежесінде, агрессивті қабыну жауабына әкеледі. 19 клиникалық жағдайлар бар. Арнайы және арнайы емес иммунитет жедел иммунды жауап әсерінен бәсеңдейді. Сондықтан COVID-19-дың ауыр клиникалық жағдайлардың патофизиологиясың зерттеу үшін, NK-жасушалар мен цитокинді ақуыздардың маңызын анықтау үшін терең молекулярлы зерттеулер қажет.

Қорытынды. COVID-19 жеңудегі негізгі мақсаттардың бірі - COVID-19 кейіңгі синдромдардағы (макрофаттар гиперактивация синдромы, тромбоз бен тромбоэмболия) ағзалар мен жүйелер зақымдалуының тез үдеуінің болжамды иммунологиялық қағидаларын ойлап табу. Алынған мәліметтерге сүйеніп, науқастарды емдеу мен асқынуларды алдын алудың дұрыс жолын табуға болады. Арнайы және арнайы емес иммунитет жедел иммунды жауаптан соң төмендейді. Сондықтан COVID-19 ауыр клиникалық жағдайлардың патофизиологиясын түсіну үшін NK-жасушалар мен цитотоксикалық ақуыздардың маңызын анықтауға арналған зерттеулер жүргізу керек.

Түйінді сөздер: цитокинді дауыл, иммунопатология, COVID-2019 асқынулары.

(MIS-C). Эти осложнения носят необычный характер, резко отличаясь относительно высокой частотой и целым рядом особенностей в клиническом течении и исходах, от описанных при других вирусных и аутоиммунных заболеваниях. В ряде случаях такие последствия носят более тяжелый характер, чем течение самого COVID-19.

Понимание особенностей развития иммунного ответа на SARSCov2 и причин развития иммунных девиаций позволят прогнозировать не только вероятность развития осложнений и неблагоприятных последствий для каждого отдельного индивидуума, но и выстраивать диагностическую и лечебную стратегию в целом для их предупреждения.

В настоящее время идентификация клинического течения COVID-19 в основном основывается на клинических проявлениях, поскольку ни один биомаркер не оказался надежным. Некоторые исследования показывают, что цитокиновый шторм может привести к более тяжелому прогрессированию заболевания, к примеру, цитокиновый шторм может привести к полиорганной недостаточности и смерти. Недавние ретроспективные исследования показали, что существует корреляция между повышенным уровнем интерлейкина-6 (ИЛ-6) и высокой смертностью от COVID-19. Последние исследования показали, что цитокины играют ключевую роль в патологических процессах воспаления, к примеру, у пациентов с тяжелой формой COVID-19 наблюдалось значительное повышение уровня цитокинов, таких как IL-2, IL-7, IL-10, GSCF, IP10, MCP-1, MIP1A и TNF-α, с характеристиками цитокинового шторма. что, в свою очередь, коррелирует с тяжестью клинического течения COVID-19. Целью данного обзора является описание ключевых триггеров цитокинового шторма, роль Т-лимфоцитов и нейтрофилов в клиническом течении COVID-19.

Материалы и Методы: обзор литературы.

Обсуждение. Глубокие исследования циркулирующих иммунных клеток с помощью проточной и масс-цитометрии и/или секвенирования РНК отдельных клеток показали, что SARS-CoV-2 индуцирует активацию врожденной иммунной системы, что приводит к агрессивному провоспалительному ответу, особенно при тяжелой форме COVID-19. 19 клинических случаев, тем не менее, специфический и неспецифический иммунитет подавляется вследствие острого иммунного ответа, поэтому требуются глубокие молекулярные исследования для изучения роли NK-клеток и цитотоксических белков для изучения патофизиологии тяжелых клинических случаев COVID-19.

Заключение. Одной из основных задач в этой битве с COVID-19 является разработка прогностических иммунологических критериев быстрого прогрессирования поражения органов и систем при пост-COVID19-синдромах (синдром гиперактивации макрофагов, тромбозы и тромбоэмболии) для наиболее правильного выбора лечебной тактики и профилактики. осложнений и неблагоприятных исходов у больных на основе анализа полученных данных. Тем не менее, специфический и неспецифический иммунитет подавляется после острого иммунного ответа, поэтому необходимо провести дальнейшие исследования для изучения роли NK-клеток и цитотоксических белков, чтобы понять патофизиологию тяжелых клинических случаев COVID-19

Ключевые слова: цитокиновый шторм, иммунопатология, осложнения COVID-2019

Introduction. The Severe Acute Respiratory Syndrome Coronavirus has introduced global changes into the healthcare system worldwide. At the time being, identification of COVID-19 progression mainly relies on clinical manifestation as no biomarker was found to be reliable. Some research shows that a cytokine storm might trigger further severe disease progression [1]. A cytokine storm also called hypercytokinemia is a physiological reaction leading to excessive release of pro-inflammatory signaling molecules called cytokines; and thus leading to multisystem organ failure and death. For instance, retrospective studies demonstrated a strong association between an elevated level of interleukin-6 (IL-6) and high mortality from COVID-19 [2]. SARS-CoV-infected patients demonstrated acute lung injury, systemic inflammatory response syndrome and acute respiratory distress syndrome [3]. Latest research showed that cytokines not only play a key role in driving the appearance of these clinical features but also represent the core of the development of inflammation [4]. In particular, patients with severe COVID-19 showed profound increases in cytokines such as IL-2, IL-7, IL-10, GSCF, IP10, MCP-1, MIP1A and TNF-α, with the characteristics of a cytokine storm, which in turn correlates with the severity of COVID-19 clinical course [4]. Therefore, the immune system can be a double-edged sword, so at the beginning it plays pro-inflammatory, so to say, antiviral role, but following strong cytokine storm can be damaging to the organism. Thus, using effective therapeutic strategies to manage effectively the response of immune system can help to alleviate the damaging outcomes and reduce the mortality rate. This review aims to investigate most recent research on COVID-19 immunopathology and underlying ones associated pathologies such as cytokine storm and lymphopenia.

Discussion. Clinical features of COVID-19 infection. COVID-19 belongs to the family of RNA viruses with the diameter of 60-140 nm [5]. The transmission appears trough respiratory droplets during coughing or sneezing followed by entry into the nasal system after inhaling [6]. The symptoms of COVID-19 include fever, fatigue and respiratory symptoms such as cough, sore throat, and shortness of breath [7]. The patients develop lymphopenia and pneumonia with the pulmonary ground-glass opacity on chest computed tomography scan [7]. Nonetheless, approximately 20% of the infected patients developed pulmonary infiltrates leading to moderate and severe clinical outcomes [8].

The deadliest player in cytokine storm. There are heterogeneous immune responses against viruses, but intervention of innate immunity with its cellular and soluble components is critical in early phases of a primary infection by cytopathic viruses [9]. Recent research indicated that several cytokines might play an important role in the development of cytokine storm. For instance, significantly high levels of pro-inflammatory cytokines are characteristic to the majority of the patients, in particular, a recent study showed that 19 of 30 analyzed cytokines/chemokines or immune-related molecules were significantly increased in blood of patients with COVID-19 compared to the controls (all p adjusted = 0.05 to < 0.001 [10]. Moreover, meta-analysis by Lui et al. showed that according to a total of 149 distinct studies serum levels of Interleukins (IL)-2, IL-2R, IL-4, IL-6, IL-8, IL-10 and tumor necrosis factor α were significantly upregulated in severe COVID-19 patients; strikingly that IL-6 and IL-10 were of the greatest difference in non-severe and severe COVID-19 cases. On the other hand, the levels of IL-5, IL-1β and Interferon (IFN)-γ showed no difference to a statistical significance. Thereby suggesting that the combination of cytokines, especially IL-6 and IL-10, as well as T cell related immune signatures might represent potential biomarkers as prognostic criteria for the severity of SARS-CoV-2 clinical course [11]. Furthermore, according to meta-analysis by Ulhag et al, IL-6 levels were significantly increased in COVID-19-infected patients with severe condition compared with those with non-severe condition (SMD = 0.71, 95%CI −0.31–1.12, P = 0.0005). However, one should note that meta-analysis was limited only to nine studies and there was high heterogenecity (I2 = 89%; P < 0.00001) [12]. In addition, systematic and meta-analysis by Khinda and colleagues on COVID-19 disease severity and mortality in association with laboratory markers indicated that in acute phase reactants, IL-6 levels were increased and were higher for fatal than for severe; moreover, IL-10 levels were also found to be increased [13]. In addition, some papers suggest that IL-10 could also be regarded as a critical driver of cytokine storms during COVID-19 [14] A recent meta-analysis by Mojtanabi et al indicated markedly higher serum levels of IL-6 in the severe group compared to the non-severe group with a mean difference of +23.1 pg/mL (95% CI: 12.42-33.79) and the overall effect of 4.24 (P-value < 0.001). Moreover, meta-regressions the mean difference was independent on neither age nor sex [15]. Therefore, this study suggests that IL-6 can be a trigger in the development of cytokine storm.

One the other hand, another systematic review and meta-analyses on comparison IL-6 in COVID-19 and other inflammatory conditions showed that IL-6 might not represent a key player in COVID-19 severe clinical course. So, in particular, mean IL-6 concentrations were almost 100 times higher in patients with cytokine release syndrome (3110·5 pg/mL, 632·3–15302·9 pg/mL; p<0·0001) [16]. Nonetheless, FDA approved two monoclonal antibodies targeting the IL-6 receptor, tocilizumab and sarilumab, as well as an investigative antibody targeting IL-6 directly (clazakizumab) [17].

One should note, that there are limitations in meta-analyses. In particular, meta-analyses assessing the impact of COVID-19 on laboratory markers have difficulties with various methodological issues such as potential datasets overlapping, imprecise estimation of study means and error. Moreover, general mortality rate estimation studies often neglect other comorbidities that can affect the study results. Although, the body of COVID-19 research is increasing exponentially therefore there will be changes further as deeper we investigate the virus and the body's immune system mechanisms. For example, some single-cell transcriptome and flow-cytometry-based studies showed that nasopharyngeal viral load correlates with plasma levels of interferons and cytokines IFNα, IFNγ and TNF, suggesting that viral load might be critical trigger for the cytokine storm. Although, one should note that investigating the levels of cytokines in the blood serum exclusively without studying the levels of their production within cells and receptors in integrated way cannot ex-

plain all the clinical and immunological phenomena observed in COVID-19.

The role of T-lymphocytes in COVID-19 clinical course

A recent study by He et al. showed that the decrease of CD3+, CD4+ and CD8+ T lymphocyte correlated with the course of patients with COVID-19 pneumonia, especially in severe cases. Moreover, the study results also suggest that the level of T lymphocyte might be used as a prognostic indicator for the severity of COVID-19 pneumonia [18]. Flow cytometry study of 52 confirmed hospitalized patients with COVID-19 at the day of admission and after 7 days of care showed that there was an increase in CD4+ T cells (p = 0.019), CD8+ T cells (p = 0.001) compared to "nonresponders", who were the patients who died [19]. Huang et al. showed that T lymphocytes (total, CD4+, and CD8+ cells) demonstrated a downward trend until the fourteenth day following gradual return to the normal levels, therefore, it was suggested that irreversible damage of cellular immunity occurs in the early stages of COVID-19 [20]. In addition, another similar study also showed that measured lymphocyte levels counts weekly, in particular, there is a decline during the first week, following stable trend within the second week after the onset of symptoms [21]. Moreover, meta-analysis by Mulchandani et al, on cytokine storm showed that severe COVID-19 is characterized by significantly increased levels of pro-inflammatory cytokines and reduced T lymphocytes. The study included 23 studies, mean cytokine levels were significantly higher (IL-6: MD, 19.55 pg/mL; CI, 14.80, 24.30; IL-8: MD, 19.18 pg/mL; CI, 2.94, 35.43; IL-10: MD, 3.66 pg/mL; CI, 2.41, 4.92; IL-2R: MD, 521.36 U/mL; CI, 87.15, 955.57; and TNF-alpha: MD, 1.11 pg/mL; CI, 0.07, 2.15) and T-lymphocyte levels were significantly lower (CD4+ T cells: MD, −165.28 cells/μL; CI, −207.58, −122.97; CD8+ T cells: MD, −106.51 cells/μL; CI, −128.59, −84.43) among severe cases as compared to non-severe ones [22]

Nonetheless, the kinetics of T cell responses following COVID-19 infection and how cellular immunity is developed at the time being, is poorly understood. For example, a recent cohort of 2043 health care workers and longitudinally collected serum samples in the spring and summer of 2020 during the first wave of COVID-19 activity in Pennsylvania, USA showed that recent additional infections potentially limit the duration of symptoms following COVID-19 infections through mechanisms that do not involve cross-reactive antibodies. Moreover, cellular immune responses elicited by recent common infections transiently reduce symptom duration following SARS-CoV-2 infections. In addition, this study showed that antibody responses elicited by SARS-CoV-2 are long lived and detectable up to 140 days following infection in the majority of individuals [23]. Moreover, some studies suggest that there are autoantibodies can also trigger severe COVID-19 clinical outcomes.

Neutrophils as hidden players in covid-2019 clinical course

Most recent studies showed that activated neutrophils and neutrophil extracellular traps (NETs) could be the key players in COVID-19 mediated fatal cases. NETs represent extracellular webs of DNA, histones, and microbicidal proteins released from activated neutrophils in order to trap and kill pathogens [24]; however, NETs may also be key players in the pathophysiology of thromboinflammation in COVID-19 [25]. In particular, a recent Elisa study on measurement of anti-NET antibodies in 328 individuals hospitalized with COVID-19 showed that the patients who required mechanical ventilation demonstrated a greater burden of anti-NET antibodies compared to those not requiring oxygen supplementation. Levels of anti–NET IgG and anti–NET IgM had an inverse correlation with the efficiency of NET degradation by COVID-19 sera [25]. Descriptive cross-sectional study showed that high neutrophil count was found to be predictive of severe clinical course and death in the patient. Therefore, research should be done further on neutrophils' role in COVID-19 pathology.

Conclusion. COVID-19 global pandemics showed that research on human immunology systems is still under its way. There are many potential key triggers in immunopathological processes, nonetheless, it should be noted the research should not only investigate cytokines separately, but the ratio of pro/anti-inflammatory cytokines can be the key in understanding the COVID-19 phenomenon. Therefore, in order to understand fundamentally the COVID-19 pathology further research on the process of restoring the function of the immune system (CD-profile and functional lymphocytes of peripheral blood) of patients who underwent COVID-19 in the dynamics of the infectious process in mild, moderate, severe and extremely severe courses (with the development of ARDS and acute damage to the myocardium, kidneys, central nervous system) should be performed. One of the main challenges in this battle with COVID-19 is to develop prognostic immunological criteria for the rapid progression of organ and system damage in post-COVID19 syndromes (macrophage hyperactivation syndrome, thrombosis and thromboembolism) for the rightest choice of therapeutic tactics and prevention of complications and unfavorable outcomes of patients based on the analysis of the data obtained. Solid body of research on circulating immune cells by flow and mass cytometry and/or single-cell RNA sequencing showed that SARS-CoV-2 induces activation of the innate immune system resulting in aggressive pro-inflammatory response, especially in severe COVID-19 clinical cases, nonetheless specific and non-specific immunity is suppressed follwoing acute immune reponse, therefore further research should be done to investigate the role of NK cells and cytotoxic proteins in order to understand the pathophysiology behind the COVID-19 severe clinical cases.

Abbreviations

COVID-19 Coronavirus disease 2019
SARS - Severe Acute Respiratory Syndrome
IL-2 - Interleukin 2
IL-6 -Interleukin 6
IL-4 - Interleukin 4
IL-8 - Interleukin 8
IL-10 Interleukin 10
NET - neutrophil extracellular traps
NK - natural killer cells
FDA - Food and Drug Administration
WHO - World Health Organization

Ethics approval and consent to participate

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