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REVIEW PAPER/*PRACA POGLĄDOWA*

The immune response to SARS-CoV-2. Focus on severe COVID-19 pathogenesis

Odpowiedź immunologiczna na zakażenie SARS-CoV-2. Patogeneza ciężkiego przebiegu COVID-19

Rafal Pawliczak

Department of Immunopathology, Medical Faculty, Medical University of Lodz, Poland

ABSTRACT

SARS-CoV-2 pandemics increased research in the interaction of coronaviruses with human immune response. Moreover, a detailed analysis of SARS-CoV-2 immune response might be helpful in vaccine development and delivering some other therapeutic approaches. Several papers described SARS and MERS antiviral response. Unfortunately, not all data derived from SARS and MERS studies could be directly applied to the SARS-CoV-2 immune response, its clinical course and severe COVID-19 pathology. In this paper we are trying to summarize basic aspects of COVID-19 immunopathology focusing on immune response, pathogenesis of severe disease and the differences between SARS-CoV-2 and its predecessors. Moreover, we are trying to outline possible therapeutic approaches including but not limited to vaccines. All reviewed data have to be treated with caution. Next months and years will generate more results helping us to deal with SARS-CoV-2, which will confirm or disprove current information and the understanding of COVID-19.

KEY WORDS

SARS-CoV-2, COVID-19, immune response, immunopathology.

STRESZCZENIE

Pandemia SARS-CoV-2 spowodowała zainteresowanie badaczy interakcjami koronawirusów z układem immunologicznym człowieka. Analiza tych interakcji może być przydatna w zapobieganiu i leczeniu COVID-19. Literatura dotycząca zakażenia SARS i MERS jest stosunkowo bogata, ale niestety nie wszystkie dane pochodzące z badań mogą być przeniesione do patologii i kliniki COVID-19. W niniejszej pracy podsumowano aktualny stan wiedzy na temat immunopatologii, przyczyn ciężkiego przebiegu COVID-19 i różnic pomiędzy koronawirusami. Podjęto też próbę wskazania możliwych dróg terapii, w tym projektowania szczepionek. Wszystkie omawiane dane powinny być traktowane z dystansem. Następne miesiące i lata przyniosą obiektywną ocenę tego, co wiemy dzisiaj na temat COVID-19.

SŁOWA KLUCZOWE

SARS-CoV-2, COVID-19, odpowiedź immunologiczna, immunopatologia.

ADDRESS FOR CORRESPONDENCE

Prof. Rafal Pawliczak MD, PhD, Department of Immunopathology, Medical Faculty, Medical University of Lodz, 7/9 Żeligowskiego St, Lodz, Poland, e-mail: rafal.pawliczak@csk.umed.lodz.pl

INTRODUCTION

SARS-CoV-2 pandemic made researchers and general public interest focused on two major areas: 1) infection detection and 2) its treatment. It is of interest to understand the immune response in SARS-CoV-2 infection, because it implies the pathophysiology of COVID-19 disease and it may have some important impact on the treatment. Unfortunately, most of research data available today came from SARS and MERS coronavirus infection studies. These data, in most cases, cannot be directly translated to SARS-CoV-2, although the latter virus belongs to the same family – *Coronaviridae*, order *Nidovirales,* and realm *Riboviria*. Despite the wishful thinking reviews, the immune response to SARS-CoV-2 does not have be similar to its predecessors. There are a couple of facts supporting this opinion. SARS-CoV-2 is not seasonal (like SARS or other coronaviruses responsible for common cold) or endemically present like MERS [1–3]. The air temperature has low or no impact on its survival. The transmission rate and the contagiousness is much lower in SARS and MERS as compared to SARS-CoV-2. The disease characteristics are similar in the most severe cases to its predecessors and completely different in infected young adults and children. The most severe cases in all three coronaviruses are clinically present as an ARDS, which often requires ventilation support or mechanical ventilation. The mortality rate is different in all three coronaviruses. Moreover, the SARS-CoV-2 attacks almost all human body organs, not only the lungs, although their involvement is the most frequent and most severe. Interestingly, as in most mRNA viruses, the RNA of SARS-CoV-2 detection is the only reliable method of confirmation of the infection.

IMMUNE RESPONSE TO SARS AND MERS: LESSONS LEARNED

The SARS and MERS have different origin, epidemiology and entry receptors [4]. Interestingly, patients with severe disease in both aforementioned coronaviruses have an impaired IFN response and synthesis [5–11]. This deterioration, in connection with proinflammatory cytokine overproduction and complement activation in small vessels, results in severe ARDS and multiorgan failure [12]. SARS and MERS developed several escape mechanisms avoiding the immune response actions [8–11]. These may also apply to SARS-CoV-2, although the precise description and role of these processes in virus survival are to be elucidated. The persistence of the immune memory cells and antibodies presence is discussed later on.

THE ROLE OF THE SARS-COV-2 STRUCTURAL PROTEINS IN IMMUNE RESPONSE

The virus has four structural proteins. S (spike protein) mediated virus entry thru ACE-2 receptors. It is recognized by the majority of neutralizing antibodies and by T cell receptors. N (nucleocapsid protein) forms the complexes with viral RNA, which is the major target of the antibody, contains also T cells receptor epitopes, activates the complement through the alternative pathway. M (matrix protein) contains T cells receptor epitopes. E (Envelope protein) interacts with M protein. No data suggesting a role in an immune response available so far [12].

IMMUNE RESPONSE TO SARS-COV-2

INNATE IMMUNE RESPONSE

Exposure to SARS-CoV-2 takes places thru small droplets present in exhaled air and virus particles are present in the air in the form of aerosol. Then, virus particles bind to ACE-2 positive cells of the upper respiratory tract, bronchial epithelial cells and alveoli. Moreover, S protein of SARS-CoV-2 may bind to the CD26 (dipeptidyl peptidase-4 (DPP4), also known as adenosine deaminase complexing protein 2; the major binding receptor for MERS) facilitating the invasion [13]. This may influence negatively the activation of T lymphocytes and result in T cell infection. Similarly, the spike protein binds to CD147 (basigin (BSG) also known as extracellular matrix metalloproteinase inducer (EMMPRIN), a member of the immunoglobulin superfamily) [14–16]. This may help SARS-CoV-2 to enter cells which do not express the ACE-2 or CD26 receptors. As of today, there are no data indicating that any polymorphism in ACE-2, CD26 or CD147 receptors may influence the entrance of the virus or the course or the severity of the disease. Upon infection, viral antigens are recognized by several PRRs (pattern recognition receptors), such as Toll-like receptors (TLR) -7, -8, NOD-like receptors (NRL) and RIG-I-like receptors (RLR) molecules. PRRs-viral proteins interactions lead to several types adaptor proteins recruitment,

facilitating downstream signal transduction. Finally, NF-κB and AP-1 transcription factors are activated, they connect to the binding sites present in the IFN type I and III promoters as well as other proinflammatory genes. Infected cells start to produce mainly type I and III interferons as well as several chemokines. The latter attract dendritic cells, neutrophils, macrophages, and NK cells. The influx cells produce chemokines such as MCP-1, MIG and IP-10. This leads to activation of dendritic cells and lymphocytes. Coronaviruses are sensitive to IFN, but they are also able to shut down the IFN synthesis. No data to support this mechanism have been available regarding SARS-CoV-2 so far. Comparing to SARS-CoV, SARS-CoV-2 causes a release of a smaller amount of IFN type I and III, but higher levels of IL-6, IL-1β, TNF and IL-1RA were detected. This is a major difference contributing to the clinical course of the infection. SARS-CoV induces the expression of at least 11 cytokine genes and generates much higher levels of interferons [17]. In SARS-CoV-2 infection, infected cells produce and release the virions, which are able to infect almost every cell in human organism, because ACE-2 receptor expression is pretty abundant. The battery of cytokines generated during SARS-CoV-2 infection could be much broader. In summary, the innate response to SARS-CoV-2 seems to be inefficient and may lead to failure in viral clearings, but generates relatively high concentrations of pro-inflammatory cytokines, somewhat seen in other coronaviral infections (Figure 1). Whether it is related to the initial viral exposure, early viral load, age, sex or other confounders, remains to be elucidated.

THE ADAPTIVE IMMUNE RESPONSE

The adaptive immune response to SARS-CoV-2 is typical, relies on HLA class I and II antigens presenting the viral proteins. So far, based on bioinformatics studies, we know that there are 628 viral epitopes binding with any of HLA I alleles and 241 epitopes binding HLA II with similar possibilities [18–22].

The adaptive immune response to SARS-CoV-2 generates a high number of $CD8^+$ T lymphocytes and a relatively small amount of $CD4^+$ T lymphocytes. In some

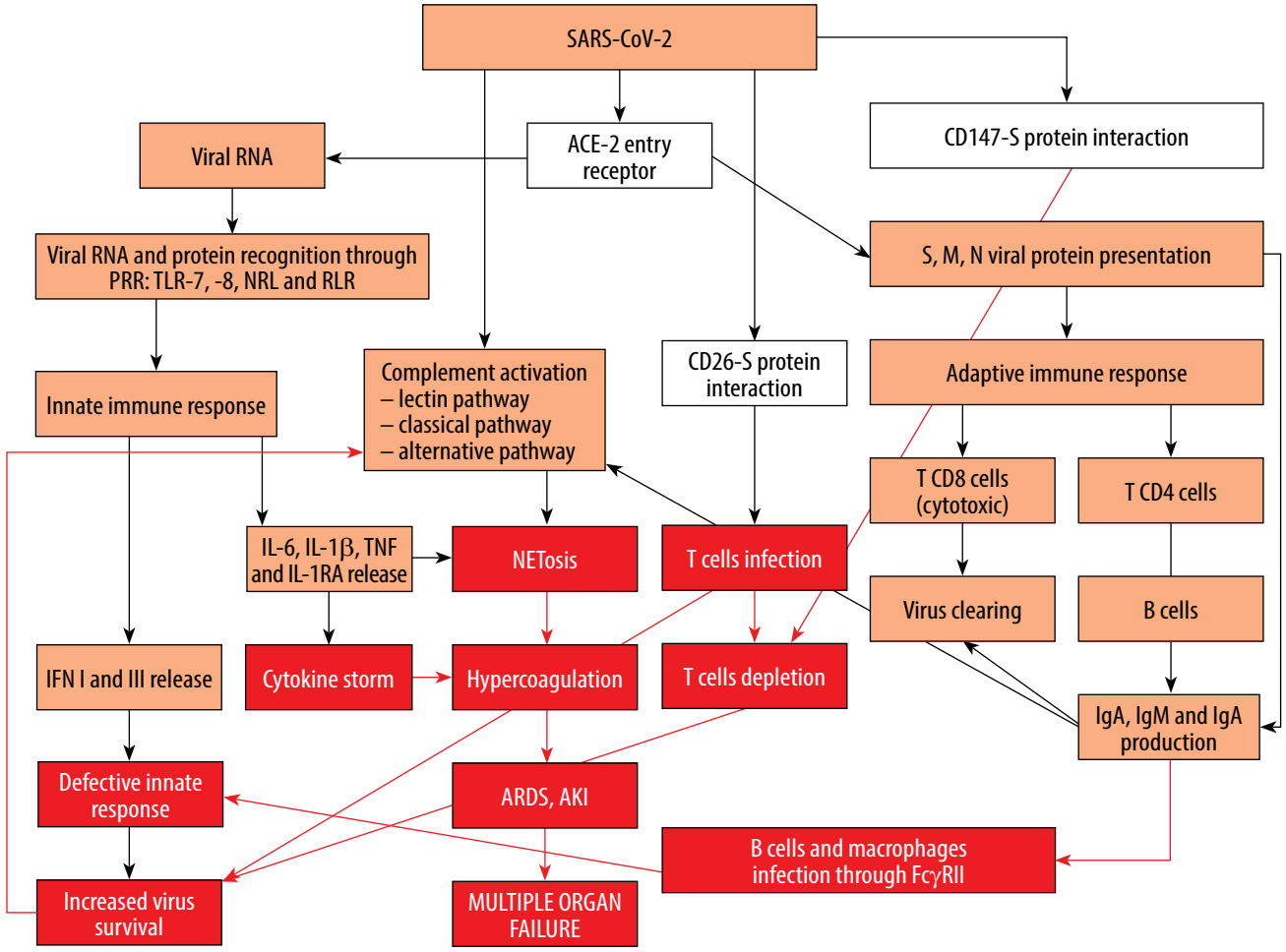

FIGURE 1. Immunopathology and immune response in SARS-CoV-2 infection. Defective immune response leading to virus survival and severe COVID-19 is depicted in red

postmortem studies, 80% of lung infiltrating cells are cytotoxic CD8$^+$ T lymphocytes. This cellular adaptive response is somehow dysfunctional and may cause severe tissue damage. Interestingly, in most cases, virus is cleared in about 10–12 days post infection, whereas cellular infiltrates and tissue damage is more prominent between day 14 and 28. In most cases the highest levels of tissue damage appear after the virus stops replicating, around the 14th day of infection. These data came from primates experiment and have not been confirmed in humans so far, although the clinical course of severe COVID-19 might confirm the above scenario. Several explanations of severe tissue damage are possible. One is the decrease in expression of ACE-2 receptors as a consequence of viral infection, second is an autoimmune reaction due to epitope spreading in prolonged cells destruction, third is the prolonged influx cells survival in the tissues related to a high number of virions and/or viral proteins and the presence of the pro-inflammatory cytokines/chemokines, locally at high concentrations, fourth is the multilateral complement activation, fifth is the combination of all aforementioned mechanisms. The failure in activation of T cells (through CD147 and CD25) may also result in T cell death in activation, induce the death mechanism leading to T cell depletion. Lymphopenia is a typical finding in MERS, SARS and COVID-19, in contrast to typical viral infections [23]. There are some data suggesting that lasting T cells in severe COVID-19 are energetically depleted [24]. Antibodies (IgM and predominantly IgG) against S protein have some blocking effects on virus adherence to the ACE-2$^+$ cells. IgM and IgA could be detected in human sera and fluids on or after the 7th day from the infection. The IgG levels are increasing at 14 days from the infection. Some data from China, Italy and the USA revealed that elderly patients have lower IgM titers [25–27]. Interestingly, sIgA against SARS-CoV-2 are an important immune barrier preventing SARS-CoV-2 from entering the body *via* mucosal membranes. Therefore, some efforts were done in manufacturing nasal or inhaled vaccines. Some papers show that the sIgA might be blocking the SARS-CoV-2 entrance activity.

EARLY AND HIGH ANTI-SARS-COV-2 IGG LEVEL: A PATIENTS' FRIEND OR A FOE?

In very few studies devoted to severe COVID-19 authors have found that the early presence of IgG and its persistence in the high titer correlates positively with the severe course of COVID-19. The data coming from MERS infections suggest that IgG may bind to S protein of coronaviruses and enhance its ability to infect B cell and macrophages through the FcγRII receptor [13]. Whether it is a case for SARS-CoV-2 remains to be elucidated in further studies. This interplay may have an important influence on the excess of proinflammatory cytokines produced in severe cases of COVID-19. It may also have an impact on vaccine designing and clinical efficacy.

CYTOKINE STORM

SARS-CoV-2 infection results in synthesis of various pro-inflammatory cytokines. The typical signature consists of IL-1β, IL-6 and IL-10. Interestingly, IL-1β and IL-6 are typical for any infection, mostly bacterial. IL-10 is a gold standard immunosuppression cytokine. The source of IL-10 remains unknown. Additionally, patients with severe COVID-19 reveal high levels of IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, granulocyte-colony stimulating factor (G-CSF), granulocyte monocyte chemotactic protein 1 (MCP-1), macrophage inflammation protein-1α, IFN-γ, and TNF [23]. The author speculates that most of the cytokine storm is secondary to the high IL-6 levels [28]. Upon infection, Th1 cells with high levels of GM-CSF, which might activate CD14$^+$CD16$^+$ macrophages, start and accelerate IL-1β and IL-6 production [29–32]. On the other hand, activation of Th17 cells might lead to macrophages activation, potentiating IL-6 synthesis [23]. Taken together, these pathways might lead to an extremely high level of IL-6 resulting in a cascade activation of other cytokine synthesis. Some data from anti-cancer studies suggest that this effect might be related to CAR-T activation [23]. So far, there have been no experimental or clinical data to support this hypothesis.

IMMUNOPATHOLOGY OF SARS-COV-2 INFECTION

In contrast to most viral infections, SARS-CoV-2 leads to more or less prominent lymphopenia. It is more profound and could be equal or lower than 20% of hospital admission in severe cases. This directly affects the number of CD4$^+$, CD8$^+$, NK and B cells. The CD8$^+$ and memory T cell numbers are low in severe cases. Most studies have shown the high level of activation of CD8$^+$ T cells [30, 33]. At some point in the middle of the clinical course of severe COVID-19, T lymphocytes are revealing exhausting phenotypes with PD-1 (programmed cell death protein-1) and T cell immunoglobulin domain and mucin domain-3 (TIM-3), killer cell lectin-like receptor subfamily C member 1 (NKG2A) high expression levels on CD8$^+$ lymphocytes. This also is applied to B cells, which show an exhausting phenotype (Figure 2). The importance of these phenotypes in severe COVID-19 is still to be elucidated. The levels of eosinophils, monocytes and basophils are reduced in severe cases of COVID-19. More than 1/3 of patients admitted to the hospitals showed var-

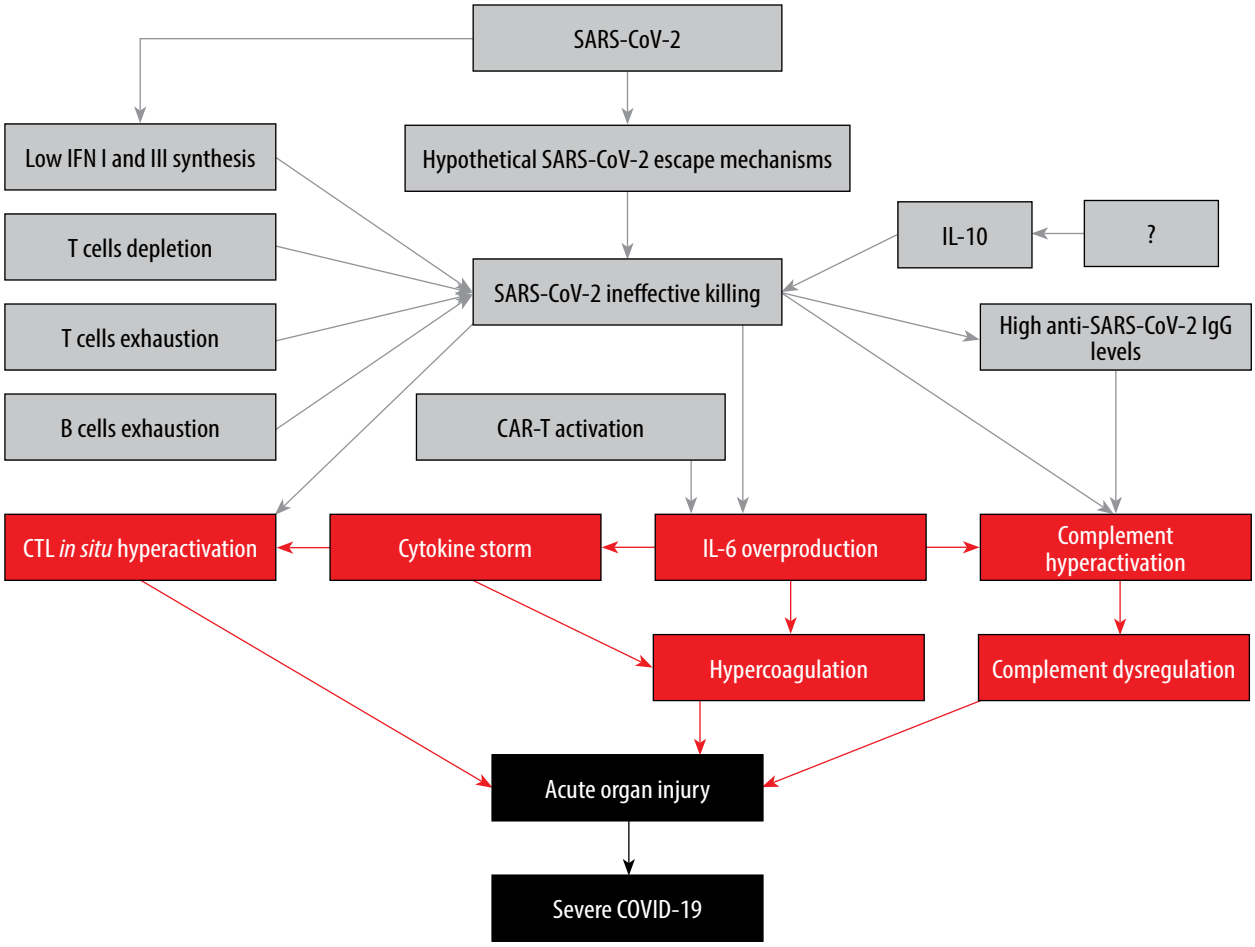

FIGURE 2. Summary of events leading to severe COVID-19. Direct SARS-CoV-2 related events are presented in gray, pathological consequences in red, clinical aftermath in black

ious levels of neutrophilia. It is difficult to predict if this is an effect of SARS-CoV-2 infection or bacterial co-infection [23].

COMPLEMENT ACTIVATION IN SARS-COV-2

Complement activation is a robust response in many virial infections. In most cases viruses are opsonized by C3b and C4b outside of the host cells. When the virus tagged by aforementioned proteins is present inside the cells, the IFN related pathways are activated causing an anti-viral state. Similarly, the tags are activating the AP-1 and NF-κB causing the transcription of genes leading to express proinflammatory cytokines. These mechanisms might be activated in most human cells.

Severe cases of COVID-19 share many similarities with congenital or acquired complementopathies. Therefore, complement activation in SARS-CoV-2 is of interest and might be a starting point in projecting the treatment strategies. The complement system lies between and integrates innate and acquired immunity response. It is also a *libero* connecting the humoral and cellular response. Human complement is activated in SARS-CoV-2 infection through interaction of N protein with mannan-binding lectin-associated serine protease 2 (MASP-2), the primary enzymatic initiator of the lectin complement pathway [34]. This activates the complement cascade leading to MAC formation, cell lysis and the presence of various complement activation products. Blocking MASP-2 attenuates lung injury in animal studies. Human bioinformatic data suggest that more than one pathway of complement activation is involved. Data from Italian severe COVID-19 patients suggested the activation of complement pathways [34]. In autopsy specimens, C4d and C5b-9 complement fragments were found in lungs, skin vasculature and in renal tubular epithelial cells. In many patients they were colocalized with S coronavirus proteins. Two genetic variants in complement regulators (decay-accelerating factor (DAF) and complement factor H (well known as causing complement regulation insufficiency, resulting in atypical hemolytic uremic syndrome, or age-related macular degeneration, respectively) were connected with SARS-CoV-2 severe cases [35–37]. Activation of

complements leads to generation of C5a and C3a [34]. These active complement components lead to accumulation of activated neutrophils. As an activation of neutrophils extracellular traps (NETs) containing C3, properdin, and factor B leads to activation of the alternative complement pathway. NETosis as a physiological mechanism is helpful in pathogen elimination. In SARS-CoV-2 infection, probably due to entry of abundant receptors (ACE-2 and FcγRII), viral proteins might initiate endothelial injury, related to complement activation (leading to intravascular coagulation) resulting in the multi-organ failure [38]. This is clinically present as ARDS or AKI [39]. Both diseases, when fully presented are difficult to control even in the ICU settings [40–43]. Therefore, many strategies focused on prevention of complement activation are proposed as important aspects of COVID-19 treatment.

PERSPECTIVE IN THE PERSISTENCE OF SARS-COV-2 IMMUNITY

So far, there have been just a few anecdotal case reports about COVID-19 survivors being re-infected. Available data on antibodies waning suggest that they may be absent after 30–80 days of the infection [44–47]. Data from SARS and MERS studies suggest that memory T cells are still present at least 2 years after the infection and much lower antibody levels are still present after surviving of a severe SARS or MERS disease. The levels of antibodies are undetectable in most mild SARS and MERS cases after half a year, similarly as in cases of common cold coronavirus infections [12]. Therefore one could speculate that at least natural immunity against SARS-CoV-2 is fading over the time. If this is the case in the immunity after vaccination, we will see based on data from ongoing clinical trials.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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