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CONCEPT OF THE INFLUENCE OF SARS-COV-2 VIRUSES ON CELL MALIGNANCY

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ABSTRACT — To date, in the context of the COVID 19 pandemic, there are rumors and speculations about the consequences of the infection, as well as a concern on growing cancer risk due to vaccines and vaccination. In this study we reviewed the concepts of the viral action on cancer development and analyzed the data on the possibility of the malignant effect of the SARS-CoV-2 virus on cells. Analysis of the literature data showed that SARS-CoV-2 damages cells, like other viruses, but does not lead to their mutations. There are no changes in DNA, there is only misregulation of repression and expression of the genome, a perversion of signaling intercellular interactions that disrupt the mechanisms of differentiation and specialization of cells. The need of viruses to multiply in cambial cells of tissues contributes to the induction of their proliferation and the lack of specialization. Thus, the available information on the cytopathic effects caused by viruses in cells infected with COVID-19 does not yet provide information on the malignant effect of SARS-CoV-2. Our study is aimed at collecting and analyzing data that are necessary for planning effective treatment of patients with COVID 19 and predicting outcomes in the long term after the disease.

KEYWORDS — viral concept of cancer; COVID 19; SARS-CoV-2; malignancy; apoptosis; immunity; vaccination; differentiation and specialization; genome; ischemia; hypoxia; carcinogens; cancer risk.

RELEVANCE

One of concerns COVID 19 infection impacts caused by SARS-CoV-2 is a possible induction of malignant transformation of cells. Machitani M., Yasukawa M., Nakashima J. et al. (2020) showed that the critical genetic driver of many cancers is the catalytic subunit of telomerase: human telomerase reverse transcriptase (hTERT), originally identified as an RNA-dependent DNA polymerase. However, although hTERT is a DNA polymerase, it has phylogenetic and structural similarities to viral RdRPs, and hTERT has RdRP activity, playing an important role in tumor formation. Having considered the enzymatic function of RdRP in viral proliferation and tumor development, the authors of this study came to an unexpected intersection between cancer research and RNA virus investigations [1].

The idea of microbial induction of carcinogenesis is not new; it was suggested by French scientist Bosc (1903), who found similarity in epithelial damage caused by smallpox in sheep with carcinomatous epithelioma characterized by a significant growth and which is disoriented, atypical and aggressive [2]. Bosc does not find in this, however, the final distinction between the process of parasitic epithelioma and cancer. In the latter, he believes that the corresponding parasite is limited to existence in the epithelial cell, incapable of metastasis, and concludes that viral and microbial damage belongs to the group of *sporozoan diseases*. Burye and Veno (1903) supported the concept of microbial induction of oncogenesis and suggested that *cancer microbes can migrate into tissues adjacent to the tumor* [3]. The infectious concept of carcinogenesis was supported by I.I. Mechnikov and proved by Shoup (1932-1933), Bittner (1936). And only L.A. Zilber (1936), was the first to develop the concept of viral–genetic origin of tumors and the theory of serum antibodies against the background of cancer [4]. Sadhukhan P., Ugurlu M.T., Hoque M.O. (2020) consider the problem of paramount whether survivors of COVID-19 infection are at high risk of developing cancer and whether there are any clinical features in survivors after COVID-19 that may be associated with carcinogenesis [5]. But the presence of more than 150 types of substances that are carcinogens used to obtain tumor growth in an experiment do not fit into the viral concept of cancer. At the present stage, all assumptions about the oncogenicity of SARS-COV-2 are still hypothetical, despite the fact that according to the data of the International Committee on Taxonomy of Viruses (ICTV) (2021), groups of viruses leading to the

development of tumors are indicated. The concepts of the introduction of DNA viruses into the genome of cells are untenable due to the immediate activation of the protective mechanism — apoptosis, which was shown by the morphological analysis of biopsies obtained against the background of the developed multiple organ failure as a result of infection of the organism with SARS-CoV-2. The concept of ischemia and hypoxia due to the death of only alveolocytes is not supported by the facts of the presence of shortness of breath after normalization of the parameters of the study of the respiratory system. These data are explainable in the framework of the concept of damage to SARS-COV-2 erythrocytes, as one of the main targets of viruses, at the earliest stages of erythropoiesis. In this case, the infection is accompanied by the death of cells of organs involved in erythropoiesis. Due to the fact that the mechanism of direct oncogenicity of the pathogen COVID-19, SARS-COV-2, is extremely unlikely, an analysis of the indirect effect of DNA and RNA containing viruses on cell malignancy is required. The huge number of COVID-19 cases around the world, the severity of clinical manifestations, the lack of knowledge of complications and the high genetic variability of SARS-COV-2 indicate the high relevance of studies on the condition of patients after a COVID-19 infection in the long-term period, as well as data on the consequences of vaccination. Of particular importance is the prediction of possible post-infectious carcinogenesis induced by coronavirus as a long-term complication.

MATERIAL AND METHODS

The study group included 35 patients of older age groups, of which 7 were not sick or vaccinated during the study and served as control; 12 were vaccinated a year after being discharged from the infectious diseases hospital for COVID-19, while 3 of them got sick again after contact with symptomatically infected COVID patients with carriers of the Indian delta strain; 16 were not sick and vaccinated, of which 3 were asymptomatic due to contacts 2 days before vaccination with COVID patients of SARS-COV-2 delta — a strain of etiology. The criterion for excluding patients from the study groups was the presence of cancer in the anamnesis before the disease and before vaccination. The distribution of patients is shown in Table 1.

RESULTS AND DISCUSSION

It was established that COVID-19 patients after vaccination had contact with asymptomatic infected patients who, within a week after contact, were admitted with a severe form of COVID-19 to infectious diseases hospitals. It was found that in 2 patients the clinical signs of COVID-19 were characterized as mildly symptomatic, and one developed a critical life-threatening condition that required non-invasive mechanical ventilation. Symptoms include shortness of breath, chills and fever, dry cough and weakness, fatigue, and headache. Liver damage, acute kidney injury, vasculitis and myocarditis were not observed in our studies. A concomitant disease in a seriously ill patient belonging to the older age group was arterial hypertension, obesity of the 1st level, a history of respiratory system diseases, and undergone surgical operations. Analysis of the data showed that the severity of the clinical manifestations of COVID-19 infection depends only on the initial state of the patient, his anamnesis of diseases transferred to the time of infection and against which infection with the SARS-COV-2 virus arose. Therefore, the key role in the pathogenesis of the disease is played exclusively by the interaction of the virus and the host. The high contagiousness and pathogenic properties of SARS-COV-2 viruses can cause significant tissue damage against the background of a weak, depleted and inhibited immune response, initially impaired in patients of older age groups with a burdened history. In such patients, the prognosis may not initially be entirely favorable and measures should be taken to prevent further damage to organ systems and multiple organ failure.

Current knowledge about the virological and immunological characteristics of SARS-CoV-2, the biology of the virus, the life cycle, tropism to many organs and cells, suggests how it will ultimately affect some biological and physiological functions of the host, in particular, the immune response.

Turnquist C., Ryan B.M., Horikawa I., Harris B.T., Harris C.C. (2020) suggest that analyzes of cytokine storm studies in patients during the COVID-19 pandemic will be of particular relevance to cancer research. Interleukin-6 (IL-6) has become a key component of the immune response to SARS-CoV-2, and the repurposing of anti-IL-6 therapeutic agents for COVID-19 is currently one of the main lines of research ongoing in clinical trials [6]. A framework needs to be defined to understand the role of IL-6 in the context of cancer research and the potential consequences of COVID-19. It is also necessary to use from the obtained results on immunity studies, how to induce protective reactions of cancer patients infected with SARS-CoV-2.

Van de Haar J., Hoes L.R., Coles C.E. et al. (2020) propose taking into account many common features and characteristics for prioritization to reconstruct evidence-based cancer treatment during the COVID-19 pandemic [7]. The critically necessary analysis will allow the development of an optimal anticancer

Table 1. *Distribution of vaccinated patients*

Age (years old)	Control	Vaccinated, recovered from COVID 19		Vaccinated, without a history of COVID 19	
		COVID negative (not infected after vaccination)	COVID positive (got ill after vaccination)	COVID negative	COVID positive
(20–39)		5	0	5	0
(40–59)		4	0	9	1
(60 >)		3	1	2	2
Total	7	12	1	16	3

treatment strategy that can accelerate the use of better and less toxic therapies based as a target on the immune system of patients.

Cortese M., Lee J. Y., Tserik B. et al. (2020), believes that the cause of carcinogenesis may be cell death as a consequence of inflammation and cytokine storm, showing morphological changes in organelles induced in epithelial cells of human lungs infected with SARS-CoV-2. On three-dimensional electron microscopy, ultrastructural pathological changes were characterized by reconstructions of whole cells and subcellular compartments, revealing extensive fragmentation of the Golgi complex, altered mitochondrial network and peroxisome recruitment to viral replication organelles formed by clusters of two-membrane vesicles (DMVs), as well as deep remodeling [8].

Thus, the available information on the cytopathic effects caused by viruses in cells infected with COVID-19 does not yet provide information on the malignant effect of SARS-CoV-2. At the same time, it is known that a number of pathogenic microorganisms that cause cell death do not lead to impaired restitution, and further regeneration is realized as a full-fledged one. The outcome of lung damage in patients in some cases is accompanied by complete regeneration of lung tissue, in other cases it ends in fibrosis, with filling of the defect with connective tissue, but not malignancy (Fig. 1).

Stanifer M. L., Kee C., Cortese M. et al. (2020) showed that enteric cells (hIEC), like alveolocytes, are only a productive site of replication of SARS-CoV-2, and suggested that the enteric phase of SARS-CoV-2 may be involved in the pathologies observed in patients with COVID-19 , contributing to an increase in the patient's viremia [9]. Mollica V., Rizzo A., Massari F. (2020) and Konrad H. S., Lorelei A. M., Emmanuel S. A., et al. (2020) pointed out TMPRSS2 not only as the most frequently modified gene in primary prostate cancer, but as a critical factor contributing to the infection of cells with coronaviruses, including SARS-CoV-2 [10, 11]. Hays P. (2020) believes that cancer patients are more prone to COVID-19 infection, he raises the additional question of whether COVID-19 infection induces the development of cancer [12].

CONCLUSION

Our analysis and reference literature on the mechanisms of action of SARS-CoV-2, the molecular responses that it induces upon infection in order to establish a connection between the consequences of the new coronavirus and malignancy showed that the virus is able to activate the main signaling pathways involved in aberrant cell growth, when This cytokine storm weakens the immune system's response to tumors. However, patients can develop cancer as a result not only from direct exposure to viruses, including SARS-CoV-2, but also from exposure to other carcinogenic factors present as malignant agents. We agree with Hays P. (2020) that this hypothesis should be tested in in vitro models as well as in preclinical studies. We plan to further monitor our group of patients who have been ill and vaccinated, who have

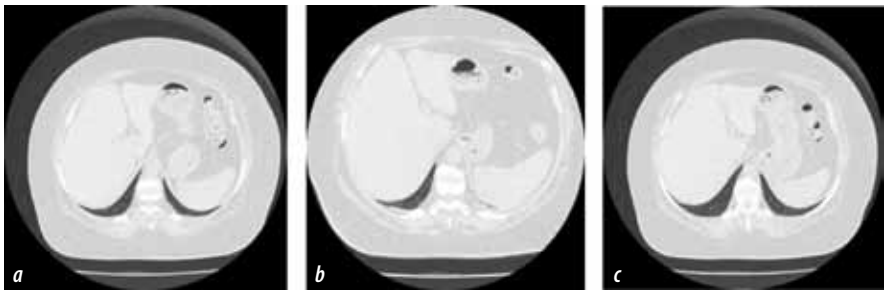

Fig. 1. *CT scan of a 67-year-old patient upon admission to the hospital with a PCR-confirmed diagnosis of COVID-19 SARS-COV-2 etiology.*
a), b) — upon admission 1.12.2020;
c) six months after recovery and discharge — 06/28/2021. Fibrous processes in lungs of patients undergoing COVID-19 are identified.

had and have not had COVID-19 for the development of cancer.

Thus, we can state that cells of various organs are the site of viral replication, leading to damage and cell death, but not to their malignancy. The recovery of patients and the restoration of lung tissue in the majority of patients indicate that the epithelium retains the ability to restitution and close defects with the performance of function. Damage to a significant part of cambial cells and ischemia, an uncontrolled inflammatory process have a detrimental effect, and the release of cytokines plays a leading role in respiratory fibrosis and multiple organ failure.

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