CELL BIOLOGY

Cancer as a potential sequela of COVID-19 — should we modify 3D cell culture models accordingly?

Elena Petersen[1], Daria Chudakova[1], Daiana Erdyneeva[1], Zorigt Dulamsuren[1], Evgeniya Shabalina[1], Pavel Karalkin[2,3], and Igor Reshetov[2]

[1]Moscow Institute of Physics and Technology, Institutskiy per., 9, Dolgoprudny, 141701, Russian Federation
[2]I. M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), ul. Trubetskaya, 8–2, Moscow, 119991, Russian Federation
[3]P. A. Herzen Moscow Research Institute of Oncology, 2-oy Botkinskiy pr., 3, Moscow, 125284, Russian Federation

Address correspondence and requests for materials to Evgeniya Shabalina, evgenyashb@mail.ru

Citation: Petersen, E., Chudakova, D., Erdyneeva, D., Zorigt, D., Shabalina, E., Karalkin, P., and Reshetov, I. 2023. Cancer as a potential sequela of COVID-19 — should we modify 3D cell culture models accordingly? Bio. Comm. 68(3): 190–198. https://doi.org/10.21638/spbu03.2023.307

Authors' information: Elena Petersen, PhD, Senior Researcher, orcid.org/0000-0002-8150-7553; Darya Chudakova, PhD, Researcher, orcid.org/0000-0002-9354-6824; Daiana Erdyneeva, Junior Researcher, orcid.org/0000-0003-2279-0157; Dulamsuren Zorigt, Junior Researcher, orcid.org/0000-0001-8133-689X; Evgeniya Shabalina, MSc., PhD Student, orcid.org/0000-0002-8184-7363; Pavel Karalkin, PhD, Researcher, orcid.org/0000-0002-2838-0776; Igor Reshetov, Dr. of Sci. in Medicine, Senior Researcher, orcid.org/0000-0002-0909-6278

Manuscript Editor: Anna Malashicheva, Laboratory of Regenerative Biomedicine, Institute of Cytology, Russian Academy of Sciences, Saint Petersburg, Russia; Laboratory of Molecular Cardiology, Almazov National Medical Research Centre, Saint Petersburg, Russia

Received: December 9, 2022;

Revised: March 9, 2023;

Accepted: April 17, 2023.

Funding: This study was supported by grants No. 21-15-00411 and No. 18-15-00391 from the Russian Science Foundation. This study was made possible through the support of the Applied Genetics Resource Facility of Moscow Institute of Physics and Technology (support grant No. 075-15-2021-684).

Ethics statement: This paper does not contain any studies involving human participants or animals performed by any of the authors.

Competing interests: The authors have declared that no competing interests exist.

Abstract

COVID-19 pandemic was caused by SARS-CoV-2, a novel virus from the family *Coronaviridae*, firstly identified in Wuhan, China in 2019. COVID-19 remains one of the main challenges of healthcare, given growing numbers of people with COVID-19 in anamnesis, and given the long-lasting consequences and complications of this disease. Cancer is one of the most common diseases in the world, thus a big part of the population is affected by both COVID-19 and cancer. In this succinct review we refer to several recent works expressing a view that COVID-19 might be oncogenic, and describe molecular mechanisms of such phenomena. Next, we describe several tumorigenic changes in the tissue microenvironment as COVID-19 sequelae, which can potentially affect cancer pathogenesis and response of a tumor to therapy. 3D cell culture models are a "golden standard" of *in vitro* studies in translational oncology. To the best of our knowledge, 3D cell culture systems to study tumor behavior in the tissue microenvironment affected by COVID-19 have not been developed yet. We propose several actionable steps which can be taken to modify existing 3D cell culture models accordingly, to address the needs of translational oncology in the COVID-19 post-pandemic times.

Keywords: COVID-19, SARS-CoV-2, 3D cell culture models, tumor microenvironment, malignant tumors, translational medicine, personalized medicine, drug development, oncology.

Introduction

As of December 2022, COVID-19 caused ~6.6 million cumulative deaths around the world (https://covid19.who.int). The number of people who recovered from acute SARS-CoV-2 or were asymptomatic is significantly higher. Additionally, apart from the initial acute form of SARS-CoV-2, there are reports about reinfections (Bowe, Xie, and Al-Aly, 2022), prolonged duration of SARS-CoV-2 infection in immunocompromised individuals (Jacobs, 2021), and persistent infection in asymptomatic carriers (Ma et al., 2022). Many survivors of COVID-19 are also affected by so-called Long COVID or post-COVID-19 syndrome (PCS), a pathological condition affecting multiple organs and tissues long time after the initial infection, and significantly changing molecular and biomechanical characteristics of the affected tissue. Thus, the health toll of COVID-19 does not end after the virus is eliminated from the body of the patient. It is estimated that up to 40 % of people infected with SARS-CoV-2 suffer from PCS for weeks to months after the

acute phase (Bornstein et al., 2022). As cancer is one of the most common diseases worldwide, especially in the elderly (the group most susceptible to COVID-19), it is expected that a substantial part of the population will be affected by both COVID-19 and cancer. Compromised Tumor Microenvironment (TME) is one of the key factors affecting cancer pathogenesis in patients with history of COVID-19 (Malkani and Rashid, 2021). Therefore, it is of significant importance for translational oncology to develop human cell culture models closely resembling characteristics of the TME affected by COVID-19, as it is expected that pathogenesis of many diseases including cancer might be different among COVID-19 survivors, and only such models will have high level of precision in *in vitro* development of specific therapeutic and diagnostic approaches to cancer consequent to SARS-CoV-2 infection, or cancer as a comorbidity of COVID-19.

Cancer as a potential risk factor for COVID-19

It has been demonstrated in multiple studies that cancer patients are more susceptible to COVID-19 (Sun, Ched, and Viboud, 2020). The key host cell proteins used by SARS-CoV-2 to enter the cell are Angiotensin-converting enzyme 2 (ACE2) and Transmembrane serine protease 2 (TMPRSS2), although other biomolecules such as Cathepsin L, furin, CD26 and others can contribute to its entry, and ACE2-independent mechanisms of entry also exist (Shen et al., 2022). As one of ACE2-independent mechanisms of infection, it has been demonstrated recently that SARS-CoV-2 can bind to Receptor of Advanced Glycation End Products (RAGE) on monocytes, thus interfering with immunity and inflammation signaling cascades (Angioni et al., 2022).

Levels of ACE2 are elevated in some cancers, for example in lung cancer (Ahmad et al., 2021; Xiao et al., 2022) and Glioblastoma Multiforme (Chen et al., 2022), but it is also worth recalling that ACE-2 levels are extremely high in normal lung tissue as well (Hikmet et al., 2020), so the significance of the role of elevated ACE-2 is not entirely clear. Its level of expression can be elevated by inflammation, for example via interferon-dependent mechanisms (Scagnolari et al., 2021), and inflammation is one of the *bona fide* cancer hallmarks. Interestingly, ACE2 is upregulated both in lungs of lung cancer patients (and also in some other types of cancer), as well as in case of COVID-19 infection (Gottschalk, Knox, and Roy, 2021). This might be one of the factors contributing to higher susceptibility of cancer patients to COVID-19. Although, given that several isoforms of ACE2 exist, with different functions and abilities to bind SARS-CoV-2, including truncated isoform dACE2 which is elevated in many cancers and capable of inhibiting SARS-CoV-2 infection (Onabajo, 2021), levels of ACE2 in cancer tissues should be investigated more thoroughly. Also, changes in ACE2 and TMPRSS2 levels on the surface of the cells might be translation-independent and, for example, executed through the endosomal trafficking (Yao et al., 2022), thus changes in mRNA levels of ACE2 and TMPRSS2 (or absence of such changes) do not necessarily correspond to functional alterations of their levels on the cell membrane, thus complicating the assessment of their role and COVID-19 and cancer comorbidity pathogenesis. Moreover, binding to SARS-CoV-2 leads to ACE2 endocytosis, thus eventually leading to its reduced cell surface expression (Bartolome et al., 2021). Nevertheless, altered levels of the biomolecules used by SARS-CoV2 to enter the host cell may render cancer patients more susceptible to COVID-19.

Additionally, common pathology shared between cancer patients and COVID-19 patients is the alteration in immune response. Thus, another possible explanation of higher susceptibility of cancer patients to infection with SARS-CoV-2 is their "weakened immune system". Overall, in many cases and for a variety of reasons patients with cancers of different types of etiology may be more susceptible to COVID-19. It is also suggested that COVID-19 may contribute to cancer susceptibility, progression, tumor recurrence, and resistance to chemotherapy (Zalpoor et al., 2022). However, it still remains rather an open question whether COVID-19 makes an individual more susceptible to cancer, or if the history of having recovered from COVID-19 can affect tumor growth and response to the therapy.

COVID-19 as a potential risk factor for cancer — molecular mechanisms of predisposition

Strong lines of evidence support the point of view that SARS-CoV-2 can act as an oncogene (comprehensively reviewed in several recent reviews (Gómez-Carballa, Martinón-Torres, and Salas, 2022; Goubran et al., 2022; Spirina et al., 2022; etc.)), although some works suggest it may also act as a tumor suppressor (Li Y.-S., 2022). Nevertheless, it is clear that the interplay between SARS-CoV-2 infection (including Long COVID and its molecular sequela) and malignancy exists, and it has been hypothesized that SARS-CoV-2 is a lung cancer risk factor (Khiali, Rezagholizadeh, and Entezari-Maleki, 2022)

There is a multitude of COVID-19-associated changes with oncogenic potential, such as metabolic changes, immunity changes, altered endocrine functions, and others (Umesh, Pranay, Pandey, and Gupta, 2022).

Notably, it is expected that some of the changes might be very long-lasting, similarly to the changes caused by SARS-CoV-1 (Wu Q. et al., 2017). Here, we will describe some of them in more detail, but concise-

ly, as a number of comprehensive reviews on this topic (referenced above) have been published recently. Firstly, COVID-19 causes elevation of pro-inflammatory cytokines (IL-6, TNF-α, IFN- γ, and others), hence creating "pro-inflammatory cytokine milieu", inflamed niche critical for tumorigenesis (Coussens and Werb, 2002; Mojic, Takeda, and Hayakawa, 2017). It should be noted that a cytokine storm is observed only in some cases of COVID-19 disease and is not mandatory in the progression of the disease. However, modifications of the three-dimensional cell model of solid tumors should take into account both the presence and absence of this symptom. Moreover, COVID-19 leads to a functional exhaustion of CD8+ T cell sub-population (such exhaustion is one of the characteristics of a chronic viral infection), thus compromising immune defense, including anticancer immune response. Secondly, SARS-CoV-2 causes DNA damage (Victor et al., 2021, 2022), affects chromatin organization (Iourov and Vorsanova, 2022), and compromises genome stability maintenance in the host cell (Pánico, Ostrovsky-Wegman, and Salazar, 2022; Victor et al., 2022), which may contribute to cancerogenesis, as genome instability is one of the hallmarks of cancer. Apart from DNA damage, COVID-19 leads to changes in DNA methylation, including altered DNA methylation profile of the several loci involved in oncogenesis, for example oncogenic gene *AHNAK2* (upregulated in lung cancer), and many gamma-delta T-lymphocyte genes involved in cancer immunity response (Wang et al., 2022). Although pathogenesis of the PCS remains unclear, it has been hypothesized that at least partially it might be caused by the presence of persisting SARS-CoV-2 virus (Jacobs, 2021), or by molecular changes similar to those caused by prolonged and persistent viral infections. It is estimated that malignant tumors induced by viral infection account for at least 10 % of all cases of cancer in humans (Gaglia and Munger, 2018). Hitherto, the list of tumor-associated viruses comprises Epstein-Barr Virus (EBV), Human Herpesvirus type 8 (HHV-8), Merkel Cell Polyomavirus (MCPV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), T-lymphotropic Virus type 1 (HTLV1), and others, as well as several potentially oncogenic viruses, and this list is expected to grow (Di Paolo, 2014; Morales-Sánchez and Fuentes-Panana, 2014). Their oncogenic potential is at least partially associated with their persistent nature (Di Paolo, 2014). There is an interplay between SARS-CoV-2 and several oncogenic viruses. SARS-CoV-2 proteins can trigger lytic reactivation of oncogenic viruses (Chen et al., 2021). For example, reactivation of Epstein — Barr virus (EBV), cytomegalovirus (CMV), or herpes simplex virus (HSV) has been reported in case of severe COVID-19 (Balc'h et al., 2020; Lehner et al., 2020; Naendrup et al., 2022). Notably, reactivation of such viruses can lead to immune dysregulation and elevated expression of IL-6 (as demonstrated for EBV, in particular), thus reinforcing COVID-19-induced "cytokine storm" and, at the same time, contributing to pro-inflammatory tumorigenic niche. Likewise, viruses known to be oncogenic can facilitate SARS-CoV-2 infection. For example, human CMV infection is associated with increased SARS-CoV-2 superinfection via upregulating levels of ACE2 (Perera et al., 2022). Moreover, some endogenous retroviruses (ERVs) are associated with cancer and can be induced by SARS-CoV-2, for example ERV type W (Charvet et al., 2022; Sahu, Singh, and Rai, 2022; Simula et al., 2022). Similarly to some oncogenic viruses, SARS-CoV-2 decreases antioxidant gene expression and induces aberrant oxidative stress in the host cell (Zhang et al., 2022). It has also been suggested that SARS-CoV-2 acts as a "molecular sponge" binding several microRNAs (miRNAs) in the host cell and thus disrupting their interaction with targets (Li C., 2022). Among these miRNAs two, hsa-miR-302c-5p and hsa-miR-16–5p, are involved in ACE2-regulating networks and also in cancerogenesis (Lin et al., 2008; Yang et al., 2022). SARS-CoV-2 can also affect cancer cell phenotype plasticity and stemness. Cancer cells can change their phenotype and obtain stem cell-like characteristics via the epithelial to mesenchymal transition (EMT), which in turn facilitates metastasis. It has been shown recently that M protein of SARS-CoV-2 triggers elevation of the genes regulating EMT in breast cancer cells (Nguyen, 2022).

Recently, several publications, as well as reviews summarizing these publications, have suggested, supported by medical histories, that COVID-19 can cause hematologic malignancies in predisposed individuals. This is an important observation that requires close attention in the COVID-19 outbreak study (Costa et al., 2022), especially by practicing oncologists, but it is beyond the scope of this review, which focuses exclusively on three-dimensional cellular models of solid tumors.

COVID-19-associated changes in tissue microenvironment

There are several COVID-19-associated alterations not only within the host cell, as discussed above, but also in the tissue microenvironment, including tumor microenvironment (TME) (Malkani and Rashid, 2021). Briefly, TME comprises extracellular matrix (ECM) of particular architecture, molecular composition and mechanical characteristics (such as rigidity, porosity, density, etc.), various secreted signaling molecules (extracellular vesicles, cytokines, circulating cell-free non-coding RNAs, etc.), immune and stromal cells, as well as adjacent non-tumorous tissue, all contributing to cancer pathogenesis.

One of the very prominent long-term consequences of COVID-19 is pulmonary fibrosis (Amin et al., 2022; George, Wells, and Jenkins, 2020), a known risk factor

for lung cancer (Li et al., 2014), the pathological condition significantly changing lung tissue as a TME due to the excessive extracellular ECM accumulation in the lungs and alteration of its characteristics. Molecular and mechanical changes of ECM due to lung fibrosis are well studied (Burgstaller et al., 2017); speaking somewhat simplistically, ECM becomes stiffer, which in turn can affect the behavior of cancer cells in such a microenvironment.

Aforementioned, not only lungs TME, but also TME in other organs is expected to be modified by COVID-19, thus contributing to the tumorigenesis and metastasis of different nosological entities in various tissues and organs. For example, SARS-CoV-2 spike S1 subunit induces activation of the brain microglial cells (Frank et al., 2022) — tissue-resident non-migratory macrophages of CNS — the innate immunity cells of the brain, involved in the etiology and pathogenesis of primary brain tumors (PBTs), including glioma (Wu Q. et al., 2017) and accounting to approximately 30 % of PBTs mass (Graeber, Scheithauer, and Kreutzberg, 2002; Hohmann et al., 2022).

It should be noted that several key differences exist not only between non-cancerous tissue microenvironment and TME, but also between TME and premalignant microenvironment (PME). For example, there are significant differences in the immune cell cytokine secretome in PME and TME in head and neck cancer (Johnson, De Costa, and Young, 2014). Any changes in tissue microenvironment shifting it from "normal" to "pre-malignant" state, or from "pre-malignant" to "malignant" are considered tumorigenic here. There are persistent alterations in the profile of immune cells in the lung tissue microenvironment affected by SARS-CoV-2 infection (Cheon et al., 2021). A shift to the pro-inflammatory cytokine milieu during COVID-19 is a characteristic of a pre-malignant niche compared to non-cancerous tissue.

Apart from this, as for the impact of COVID-19 on the tissue microenvironment, there are several reports about the increased formation of advanced glycation end products (AGEs) within ECM (thus, altering levels of RAGE — receptor recognising AGEs and also capable of binding SARS-CoV-2 — and triggering pro-inflammatory state) (Allen et al., 2022), microvascular damage resulting in local hypoxia (Østergaard, 2021), alterations of immune checkpoint molecules axis, such as expression of Programmed Death-1 (PD-1) and Programmed Death-Ligand 1 (PD-L1) (Loretelli et al., 2021; Malkani and Rashid, 2021), and ECM remodeling (Breisnes, Leeming, Fazleen, and Sand, 2022; Guizani et al., 2021; Gutman et al., 2022; Ramírez-Martínez et al., 2022; Shirvaliloo, 2021). Another molecular characteristic of the tissue affected by COVID-19 is an increased production of AGEs. This may potentially lead to an increased level of cross-links within the ECM, thus resulting in its increased stiffness, similarly to the contribution of AGEs to ECM stiffness in diabetes (Sant et al., 2020).

The cell secretome (extracellular vesicles (EV's) and their molecular cargo, cytokines, and other regulatory biomolecules) within the tissue microenvironment changes during and, supposedly, long after the acute phase of SARS-CoV-2 infection (Mao et al., 2021). Alarmingly, there are reports about the involvement of SARS-CoV-2 S protein in amyloidogenesis and prion-like pathological processes (Nystrom and Hammarstrom, 2022), while amyloidosis is known to be oncogenic (Hemminki, Försti, Sundquist, and Sundquist, 2014).

Blood-gas barrier (BGB, also known as alveolar-capillary barrier, ACB) in the lungs might be compromised by COVID-19, thus leading to changes in microcirculation. Importantly for cancer metastasis to the brain, SARS-CoV-2 spike protein subunits also affect Blood-brain barrier (BBB) function, as has been demonstrated in two-dimensional (2D) static and tri-dimensional (3D) microfluidic in-vitro models (Buzhdygan et al., 2020), and it remains to be investigated whether these changes remain after virus is eliminated from the body. One should not also exclude a possibility that SARS-CoV-2 proteins, even partially degraded, may stay in the system for a longer period of time, although it is still just a speculative assumption, yet to be tested.

Lastly, not only cancer-associated alteration of microbiome can make cancer patients more susceptible to COVID-19, but, *vice versa*, SARS-CoV-2 can also contribute to oncogenesis via microbiome alteration in the tissue microenvironment, as has been demonstrated for gut microbiota and colorectal cancer (Mozaffari et al., 2022; Odun-Ayo and Reddy, 2022), and pancreatic cancer progression (Zhang, Liu, and Yang, 2022). COVID-19 also has an impact on the oral microbiome (Naqvi et al., 2022), therefore it is plausible to suggest that it may subsequently have an impact on malignant neoplasms of the oral cavity. For example, COVID-19-associated Fusobacterium nucleatum (F. nucleatum) bacteremia has been reported (Wolff et al., 2021), while it is known that F. nucleatum can be cancer-promoting (reviewed in (McIlvanna et al., 2021)). Not surprisingly, COVID-19 alters microbiomes of the respiratory tract too (Merenstein, Bushman, and Collman, 2022).

3D cell culture models resembling TME affected by COVID-19 — an unmet need in translational oncology

Mounting evidence demonstrates that 3D cell culture systems more closely mimic conditions *in vivo* compared to conventional adherent 2D systems (Kapałczyńska et al., 2018), and therefore they are a more appropriate

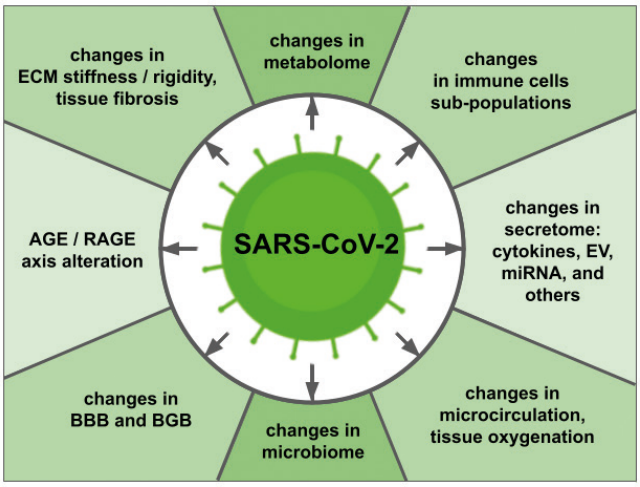

Figure. Impact of COVID-19 on tumor microenvironment. SARS-CoV-2 can lead to the tissue/tumor microenvironmental changes shown in the figure. Changes may be experienced by extracellular matrix (ECM) (stiffness), tissue fibrosis; AGE/RAGE; blood-brain and blood-gas barriers (BBB/BGB); microbiome; tissue microcirculation/oxygenation; secretome (cytokines, extracellular vesicles (EV), etc.); immune cell subpopulations; metabolome.

tool to study cancer cell behavior in the "ecosystem" of the TME, especially in case of anti-cancer drug screening and selection of personalized anti-cancer therapies (comprehensively reviewed in (Law et al., 2021)).

There are many 3D cell culture models developed and applied as a tool to study SARS-CoV-2 infection, described in detail in several recent publications (Basu, Pamreddy, Singh, and Sharma, 2022; Chen et al., 2022; de Melo et al., 2021; Rosa et al., 2021; Zhang et al., 2021). There are also similar systems developed for the needs of translational oncology (Law et al., 2021). At the same time, there are no such models reflecting COVID-19-caused changes in the TME for the study of cancer as COVID-19 sequelae or COVID-19 comorbidity. Here we emphasize that, as highlighted previously, TME of individuals with COVID-19 in anamnesis, and especially individuals with PCS, is most likely different compared to TME of those who were not infected by SARS-CoV-2. These changes might affect cancer pathogenesis in individuals affected by COVID-19, in particular their response to the therapy, or, perhaps, a profile of disease biomarkers. This should be taken into consideration when selecting personalized anti-cancer therapy for such individuals or re-defining guidelines for therapy (chemo-, immuno-, radiotherapy) regimen in post-COVID-19 patients.

Below we briefly outline the COVID-19-induced changes in the characteristics of the TME (Figure), which might be tumorigenic or affect the response of the tumor to the therapy, and propose how these changes should be incorporated into 3D cell culture systems for the needs of translational oncology.

One of the most commonly used 3D cell culture models is multicellular tumor spheroids (MCTS), including those with elements of ECM. MCTS can be homotypic (composed of cells of one type) or heterotypic (composed of cells of different types, for example tumor and stromal cells), thus if SARS-CoV-2 infection leads to changes in immune system sub-populations in post-COVID-19 individuals, as has been demonstrated at least for peripheral immune system (Ryan et al., 2022), the corresponding changes should be reflected in the composition of heterotypic MCTS including cancer cells and immune cells.

Next, numerous studies, including studies utilizing MCTS systems, demonstrated that hypoxia can lead to resistance to chemotherapy (Däster et al., 2017). Cell culture models mimicking hypoxia and normoxia, including perfusion systems allowing to model intermittent hypoxia or tissue-specific O_2 levels (physioxia) are technically feasible and physiologically relevant (Pavlacky and Polak, 2020). There are several 3D culture cell models which recapitulate lung fibrosis (comprehensively reviewed in (Kiener et al., 2021)). In particular, there are animal models of COVID-19-induced lung fibrosis (Dinnon et al., 2022); they might be a valuable source of decellularized ECM for 3D cell culture models in translational oncology, given that such ECM will have many key features similar to those of ECM from post-COVID-19 human lungs. One of such features is the elevated levels of AGEs within ECM, reported for individuals recovered from COVID-19. This should not be ignored when developing 3D models for anti-cancer drug screening, as elevated AGEs may lead to resistance of the cancer cells to particular chemotherapeutic agents, as has been demonstrated for conditions other than COVID-19. Another approach to recapitulate formation of AGEs within the ECM is its *in vitro* chemical modification by glycating agents.

As previously stated, cell secretome, in particular EVs and their molecular cargo, changes during and after COVID-19. One of the possible approaches to examine their role in tumorigenesis would be addition of the EVs isolated from the individuals who recovered from COVID-19 to the aforementioned 3D cell culture systems.

Next, SARS-CoV-2 causes host's microbiome alteration in a variety of cancers, such as colorectal cancer (Mozaffari et al., 2022; Odun-Ayo and Reddy, 2022), and pancreatic cancer (Zhang, Liu, and Yang, 2022). Not surprisingly, there are also alterations of the lung microbiome caused by COVID-19 (Merenstein, Bushman, and Collman, 2022), and their role in cancerogenesis is yet to be investigated. Assuming that they may alter the tumor's response to the therapy, elements of such altered microbiomes should be incorporated into the multicomponent 3D cell culture systems too.

Changes in the BBB and BGB (BBB/BGB dysfunction), including those induced by COVID-19, are critical modulators of the metastasis. There are diverse types of

microfluidic models of BBB (Augustine et al., 2021), used as a platform in oncology research. It has been shown that S protein of SARS-CoV-2 alters barrier function in 3D microfluidic models of the BBB (Buzhdygan et al., 2020). Similar approach will allow us to evaluate the role of the COVID-19 sequelae in metastasis to the brain, or in the anti-cancer drug permeability of the BBB.

Finally, the biomarkers for cancer patients with COVID-19 in anamnesis, in particular predictive biomarkers which help to optimize therapy decisions and choose personalized, tailored therapy approaches, are yet to be found and validated. Using the 3D cell culture models described above might be instrumental for discovery of such biomarkers.

Conclusion

The concept of a bi-directional relationship between COVID-19 and cancer suggests that cancer alters susceptibility of the individual to COVID-19 and *vice versa*. Moreover, molecular and mechanical changes of the tissue and organs, caused by COVID-19, may cause long-lasting alterations in pre-malignant and malignant tissue microenvironment, thus affecting cancer cell's response to the therapy. Thus, creating 3D cell culture models accurately recapitulating molecular changes within the TME which are caused by COVID-19 will lay a foundation for the much needed research of cancer as a COVID-19 sequela, allowing to develop tailored therapy.

References

Ahmad, S., Manzoor, S., Siddiqui, S., Mariappan, N., Zafar, I., Ahmad, A., and Ahmad, A. 2021. Epigenetic underpinnings of inflammation: Connecting the dots between pulmonary diseases, lung cancer and COVID-19. *Seminars in Cancer Biology* 83:384–398. https://doi.org/10.1016/j.semcancer.2021.01.003

Allen, C. N., Santerre, M., Arjona, S. P., Ghaleb, L. J., Herzi, M., Llewellyn, M. D., Shcherbik, N., and Sawaya, B. E. 2022. SARS-CoV-2 Causes Lung Inflammation through Metabolic Reprogramming and RAGE. *Viruses* 14(5):983. https://doi.org/10.3390/v14050983

Amin, B. J. H., Kakamad, F. H., Ahmed, G. S., Ahmed, S. F., Abdulla, B. A., Mikael, T. M., Salih, R. Q., Salh, A. M., and Hussein, D. A. 2022. Post COVID-19 pulmonary fibrosis; a meta-analysis study. *Annals of Medicine and Surgery*:103590. https://doi.org/10.1016/j.amsu.2022.103590

Angioni, R., Bonfanti, M., Caporale, N., Sánchez-Rodríguez, R., Munari, F., Savino, A., Buratto, D., Pagani, I., Bertoldi, N., and Zanon, C. 2022. RAGE engagement by SARS-CoV-2 enables monocyte infection and underlies COVID-19 severity. *bioRxiv.* https://doi.org/10.1101/2022.05.22.492693

Augustine, R., Aqel, A. H., Kalva, S. N., Joshy, K., Nayeem, A., and Hasan, A. 2021. Bioengineered microfluidic blood-brain barrier models in oncology research. *Translational Oncology* 14(7):101087. https://doi.org/10.1016/j.tranon.2021.101087

Balc'h, L., Pinceaux, K., Pronier, C., Seguin, P., Tadié, J.-M., and Reizine, F. 2020. Herpes simplex virus and cytomegalovirus reactivations among severe COVID-19 patients. *Critical Care* 24(1):1–3. https://doi.org/10.1186/s13054-020-03252-3

Bartolomé, A., Liang, J., Wang, P., Ho, D. D., and Pajvani, U. B. 2021. Angiotensin converting enzyme 2 is a novel target of the γ-secretase complex. *Scientific Reports* 11(1):1–8. https://doi.org/10.1038/s41598-021-89379-x

Basu, A., Pamreddy, A., Singh, P., and Sharma, K. 2022. An adverse outcomes approach to study the effects of SARS-CoV-2 in 3D organoid models. *Journal of Molecular Biology* 434(3):167213. https://doi.org/10.1016/j.jmb.2021.167213

Bornstein, S. R., Cozma, D., Kamel, M., Hamad, M., Mohammad, M. G., Khan, N. A., Saber, M. M., Semreen, M. H., and Steenblock, C. 2022. Long-COVID, metabolic and endocrine disease. *Hormone and Metabolic Research* 54(08):562–566. https://doi.org/10.1055/a-1878-9307

Bowe, B., Xie, Y., and Al-Aly, Z. 2022. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. *Nature Medicine* 28(11):2398–2405. https://doi.org/10.1038/s41591-022-02051-3

Breisnes, H., Leeming, D., Fazleen, A., and Sand, J. 2022. COVID-19 Effects on lung extracellular matrix remodeling, wound healing, and neutrophil activity: a proof-of-concept biomarker study; A3165–A3165 in: *B57. CUTTING EDGE COVID RESEARCH*: American Thoracic Society.

Burgstaller, G., Oehrle, B., Gerckens, M., White, E. S., Schiller, H. B., and Eickelberg, O. 2017. The instructive extracellular matrix of the lung: basic composition and alterations in chronic lung disease. *European Respiratory Journal* 50(1):1601805. https://doi.org/10.1183/13993003.01805-2016

Buzhdygan, T. P., DeOre, B. J., Baldwin-Leclair, A., Bullock, T. A., McGary, H. M., Khan, J. A., Razmpour, R., Hale, J. F., Galie, P. A., and Potula, R. 2020. The SARS-CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic in-vitro models of the human blood–brain barrier. *Neurobiology of Disease* 146:105131. https://doi.org/10.1016/j.nbd.2020.105131

Charvet, B., Brunel, J., Pierquin, J., Iampietro, M., Decimo, D., Queruel, N., Lucas, A., del Mar Encabo-Berzosa, M., Arenaz, I., and Marmolejo, T. P. 2022. SARS-CoV-2 induces human endogenous retrovirus type W envelope protein expression in blood lymphocytes and in tissues of COVID-19 patients. *medRxiv.* https://doi.org/10.1101/2022.01.18.21266111

Chen, A., Zhao, W., Sun, G., Ma, Z., Peng, L., Shi, Z., Li, X., and Yan, J. 2022. Comprehensive oncogenic features of coronavirus receptors in glioblastoma multiforme. *Frontiers in Immunology* 13:840785. https://doi.org/10.3389/fimmu.2022.840785

Chen, J., Dai, L., Barrett, L., James, J., Plaisance-Bonstaff, K., Post, S. R., and Qin, Z. 2021. SARS-CoV-2 proteins and anti-COVID-19 drugs induce lytic reactivation of an oncogenic virus. *Communications Biology* 4(1):1–6. https://doi.org/10.1038/s42003-021-02220-z

Chen, Q., Langenbach, S., Li, M., Xia, Y. C., Gao, X., Gartner, M. J., Pharo, E. A., Williams, S. M., Todd, S., and Clarke, N. 2022. ACE2 expression in organotypic human airway epithelial cultures and airway biopsies. *Frontiers in Pharmacology* 13:813087. https://doi.org/10.3389/fphar.2022.813087

Cheon, I., Li, C., Son, Y., Goplen, N., Wu, Y., Cassmann, T., Wang, Z., Wei, X., Tang, J., and Li, Y. 2021. Immune signatures underlying post-acute COVID-19 lung sequelae. *Science Immunology* 6(65):eabk1741. https://doi.org/10.1126/sciimmunol.abk1741

Costa, B. A., da Luz, K. V., Campos, S. E. V., Lopes, G. S., Leitão, J. P. V., and Duarte, F. B. 2022. Can SARS-CoV-2 induce hematologic malignancies in predisposed indi-

viduals? A case series and review of the literature. *Hematology, Transfusion and Cell Therapy* 44:26–31. https://doi.org/10.1016/j.htct.2021.11.015

Coussens, L. M. and Werb, Z. 2002. Inflammation and cancer. *Nature* 420(6917):860–867. https://doi.org/10.1038/nature01322

Däster, S., Amatruda, N., Calabrese, D., Ivanek, R., Turrini, E., Droeser, R. A., Zajac, P., Fimognari, C., Spagnoli, G. C., and Iezzi, G. 2017. Induction of hypoxia and necrosis in multicellular tumor spheroids is associated with resistance to chemotherapy treatment. *Oncotarget* 8(1):1725. https://doi.org/10.18632/oncotarget.13857

de Melo, B. A., Benincasa, J. C., Cruz, E. M., Maricato, J. T., and Porcionatto, M. A. 2021. 3D culture models to study SARS-CoV-2 infectivity and antiviral candidates: From spheroids to bioprinting. *Biomedical Journal* 44(1):31–42. https://doi.org/10.1016/j.bj.2020.11.009

Dinnon III, K. H., Leist, S. R., Okuda, K., Dang, H., Fritch, E. J., Gully, K. L., De la Cruz, G., Evangelista, M. D., Asakura, T., and Gilmore, R. C. 2022. A model of persistent post SARS-CoV-2 induced lung disease for target identification and testing of therapeutic strategies. *bioRxiv.* https://doi.org/10.1101/2022.02.15.480515

Di Paolo, N. C. 2014. Recognition of human oncogenic viruses by host pattern-recognition receptors. *Frontiers in Immunology* 5:353. https://doi.org/10.3389/fimmu.2014.00353

Frank, M. G., Nguyen, K. H., Ball, J. B., Hopkins, S., Kelley, T., Baratta, M. V., Fleshner, M., and Maier, S. F. 2022. SARS-CoV-2 spike S1 subunit induces neuroinflammatory, microglial and behavioral sickness responses: Evidence of PAMP-like properties. *Brain, Behavior, and Immunity* 100:267–277. https://doi.org/10.1016/j.bbi.2021.12.007

Gaglia, M. M. and Munger, K. 2018. More than just oncogenes: mechanisms of tumorigenesis by human viruses. *Current Opinion in Virology* 32:48–59. https://doi.org/10.1016/j.coviro.2018.09.003

George, P. M., Wells, A. U., and Jenkins, R. G. 2020. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *The Lancet Respiratory Medicine* 8(8):807–815. https://doi.org/10.1016/S2213-2600(20)30225-3

Gottschalk, G., Knox, K., and Roy, A. 2021. ACE2: At the crossroad of COVID-19 and lung cancer. *Gene Reports* 23:101077. https://doi.org/10.1016/j.genrep.2021.101077

Goubran, H., Stakiw, J., Seghatchian, J., Ragab, G., and Burnouf, T. 2022. SARS-CoV-2 and cancer: the intriguing and informative cross-talk. *Transfusion and Apheresis Science* 61(4):103488. https://doi.org/10.1016/j.transci.2022.103488

Graeber, M. B., Scheithauer, B. W., and Kreutzberg, G. W. 2002. Microglia in brain tumors. *Glia* 40(2):252–259. https://doi.org/10.1002/glia.10147

Guizani, I., Fourti, N., Zidi, W., Feki, M., and Allal-Elasmi, M. 2021. SARS-CoV-2 and pathological matrix remodeling mediators. *Inflammation Research* 70(8):847–858. https://doi.org/10.1007/s00011-021-01487-6

Gutman, H., Aftalion, M., Melamed, S., Politi, B., Nevo, R., Havusha-Laufer, S., Achdout, H., Gur, D., Israely, T., and Dachir, S. 2022. Matrix metalloproteinases expression is associated with SARS-CoV-2-induced lung pathology and extracellular-matrix remodeling in K18-hACE2 mice. *Viruses* 14(8):1627. https://doi.org/10.3390/v14081627

Gómez-Carballa, A., Martinón-Torres, F., and Salas, A. 2022. Is SARS-CoV-2 an oncogenic virus? *Journal of Infection* 85(5):573–607. https://doi.org/10.1016/j.jinf.2022.08.005

Hemminki, K., Li, X., Försti, A., Sundquist, J., and Sundquist, K. 2014. Cancer risk in amyloidosis patients in Sweden with novel findings on non-Hodgkin lymphoma and skin cancer. *Annals of Oncology* 25(2):511–518. https://doi.org/10.1093/annonc/mdt544

Hikmet, F., Méar, L., Edvinsson, Å., Micke, P., Uhlén, M., and Lindskog, C. 2020. The protein expression profile of ACE2 in human tissues. Molecular Systems Biology 16(7):e9610. https://doi.org/10.15252/msb.20209610

Hohmann, U., Walsleben, C., Ghadban, C., Kirchhoff, F., Dehghani, F., and Hohmann, T. 2022. Interaction of glia cells with glioblastoma and melanoma cells under the influence of phytocannabinoids. *Cells* 11(1):147. https://doi.org/10.3390/cells11010147

Iourov, I. Y. and Vorsanova, S. G. 2022. COVID-19 and aging-related genome (Chromosome) instability in the brain: another possible time-bomb of SARS-CoV-2 infection. *Frontiers in Aging Neuroscience* 14. https://doi.org/10.3389/fnagi.2022.786264

Jacobs, J. J. 2021. Persistent SARS-2 infections contribute to long COVID-19. *Medical Hypotheses* 149:110538. https://doi.org/10.1016/j.mehy.2021.110538

Johnson, S. D., De Costa, A.-M. A., and Young, M. R. I. 2014. Effect of the premalignant and tumor microenvironment on immune cell cytokine production in head and neck cancer. *Cancers* 6(2):756–770. https://doi.org/10.3390/cancers6020756

Kapałczyńska, M., Kolenda, T., Przybyła, W., Zajączkowska, M., Teresiak, A., Filas, V., Ibbs, M., Bliźniak, R., Łuczewski, Ł., and Lamperska, K. 2018. 2D and 3D cell cultures — a comparison of different types of cancer cell cultures. *Archives of Medical Science* 14(4):910–919. https://doi.org/10.5114/aoms.2016.63743

Khiali, S., Rezagholizadeh, A., and Entezari-Maleki, T. 2022. SARS-CoV-2 and probable lung cancer risk. *BioImpacts: BI* 12(3):291. https://doi.org/10.34172/bi.2022.23266

Kiener, M., Roldan, N., Machahua, C., Sengupta, A., Geiser, T., Guenat, O. T., Funke-Chambour, M., Hobi, N., and Kruithof-de Julio, M. 2021. Human-based advanced in vitro approaches to investigate lung fibrosis and pulmonary effects of COVID-19. *Frontiers in Medicine* 8:644678. https://doi.org/10.3389/fmed.2021.644678

Law, A. M., de la Fuente, L. R., Grundy, T. J., Fang, G., Valdes-Mora, F., and Gallego-Ortega, D. 2021. Advancements in 3D cell culture systems for personalizing anti-cancer therapies. *Frontiers in Oncology* 11. https://doi.org/10.3389/fonc.2021.782766

Lehner, G. F., Klein, S. J., Zoller, H., Peer, A., Bellmann, R., and Joannidis, M. 2020. Correlation of interleukin-6 with Epstein–Barr virus levels in COVID-19. *Critical Care* 24(1):1-3. https://doi.org/10.1186/s13054-020-03384-6

Li, C., Wang, R., Wu, A., Yuan, T., Song, K., Bai, Y., and Liu, X. 2022. SARS-COV-2 as potential microRNA sponge in COVID-19 patients. *BMC Medical Genomics* 15(2):1–10. https://doi.org/10.1186/s12920-022-01243-7

Li, J., Yang, M., Li, P., Su, Z., Gao, P., and Zhang, J. 2014. Idiopathic pulmonary fibrosis will increase the risk of lung cancer. *Chinese Medical Journal* 127(17):3142–3149. https://doi.org/10.3760/cma.j.issn.0366-6999.20141346

Li, Y.-S., Ren, H.-C., and Cao, J.-H. 2022. Correlation of SARS-CoV-2 to cancer: Carcinogenic or anticancer? *International Journal of Oncology* 60(4):1–17. https://doi.org/10.3892/ijo.2022.5332

Lin, S.-L., Chang, D. C., Chang-Lin, S., Lin, C.-H., Wu, D. T., Chen, D. T., and Ying, S.-Y. 2008. Mir-302 reprograms human skin cancer cells into a pluripotent ES-cell-like state. *RNA* 14(10):2115–2124. https://doi.org/10.1261/rna.1162708

Loretelli, C., Abdelsalam, A., D'Addio, F., Nasr, M. B., Assi, E., Usuelli, V., Maestroni, A., Seelam, A. J., Ippolito, E.,

and Di Maggio, S. 2021. PD-1 blockade counteracts post–COVID-19 immune abnormalities and stimulates the anti–SARS-CoV-2 immune response. *JCI Insight* 6(24). https://doi.org/10.1172/jci.insight.146701

Ma, M.-J., Qiu, S.-F., Cui, X.-M., Ni, M., Liu, H.-J., Ye, R.-Z., Yao, L., Liu, H.-B., Cao, W.-C., and Song, H.-B. 2022. Persistent SARS-CoV-2 infection in asymptomatic young adults. *Signal Transduction and Targeted Therapy* 7(1):1–4. https://doi.org/10.1038/s41392-022-00931-1

Malkani, N. and Rashid, M. U. 2021. SARS-COV-2 infection and lung tumor microenvironment. *Molecular Biology Reports* 48(2):1925–1934. https://doi.org/10.1007/s11033-021-06149-8

Mao, K., Tan, Q., Ma, Y., Wang, S., Zhong, H., Liao, Y., Huang, Q., Xiao, W., Xia, H., and Tan, X. 2021. Proteomics of extracellular vesicles in plasma reveals the characteristics and residual traces of COVID-19 patients without underlying diseases after 3 months of recovery. *Cell Death & Disease* 12(6):1–18. https://doi.org/10.1038/s41419-021-03816-3

McIlvanna, E., Linden, G. J., Craig, S. G., Lundy, F. T., and James, J. A. 2021. Fusobacterium nucleatum and oral cancer: a critical review. *BMC Cancer* 21(1):1–11. https://doi.org/10.1186/s12885-021-08903-4

Merenstein, C., Bushman, F. D., and Collman, R. G. 2022. Alterations in the respiratory tract microbiome in COVID-19: current observations and potential significance. *Microbiome* 10(1):1–14. https://doi.org/10.1186/s40168-022-01342-8

Mojic, M., Takeda, K., and Hayakawa, Y. 2017. The dark side of IFN-γ: its role in promoting cancer immunoevasion. *International Journal of Molecular Sciences* 19(1):89. https://doi.org/10.3390/ijms19010089

Morales-Sánchez, A. and Fuentes-Panana, E. 2014. Human viruses and cancer. *Viruses* 6:4047–4079. https://doi.org/10.3390/v6104047

Mozaffari, S. A., Salehi, A., Mousavi, E., Zaman, B. A., Nassaj, A. E., Ebrahimzadeh, F., Nasiri, H., Valedkarimi, Z., Adili, A., and Asemani, G. 2022. SARS-CoV-2-associated gut microbiome alteration; a new contributor to colorectal cancer pathogenesis. *Pathology-Research and Practice* 239:154131. https://doi.org/10.1016/j.prp.2022.154131

Naendrup, J.-H., Garcia Borrega, J., Eichenauer, D. A., Shimabukuro-Vornhagen, A., Kochanek, M., and Böll, B. 2022. Reactivation of EBV and CMV in severe COVID-19 — epiphenomena or trigger of hyperinflammation in need of treatment? A large case series of critically ill patients. *Journal of Intensive Care Medicine* 37(9):1152–1158. https://doi.org/10.1177/08850666211053990

Naqvi, A. R., Schwartz, J., Brandini, D. A., Schaller, S., Hussein, H., Valverde, A., Naqvi, R. A., and Shukla, D. 2022. COVID-19 and oral diseases: Assessing manifestations of a new pathogen in oral infections. *International Reviews of Immunology* 41(4):423–437. https://doi.org/10.1080/08830185.2021.1967949

Nguyen, H.-N. T., Kawahara, M., Vuong, C.-K., Fukushige, M., Yamashita, T., and Ohneda, O. 2022. SARS-CoV-2 M protein facilitates malignant transformation of breast cancer cells. *Frontiers in Oncology* 12:923467. https://doi.org/10.3389/fonc.2022.923467

Nystrom, S. and Hammarstrom, P. 2022. Amyloidogenesis of SARS-CoV-2 spike protein. *Journal of the American Chemical Society* 144(20):8945–8950. https://doi.org/10.1021/jacs.2c03925

Odun-Ayo, F. and Reddy, L. 2022. Gastrointestinal microbiota dysbiosis associated with SARS-CoV-2 infection in colorectal cancer: the implication of probiotics. *Gastroenterology Insights* 13(1):35–59. https://doi.org/10.3390/gastroent13010006

Onabajo, O. O., Stanifer, M., Banday, A. R., Vargas, J., Yan, W., Obajemu, A., Ring, T., Kee, C., Doldan, P., and Boulant, S. 2021. An interferon-stimulated transcriptionally independent isoform of ACE2 inhibits SARS-CoV-2 infection. *The Journal of Immunology* 206:20.28. https://doi.org/10.4049/jimmunol.206.Supp.20.28

Pavlacky, J. and Polak, J. 2020. Technical feasibility and physiological relevance of hypoxic cell culture models. *Frontiers in Endocrinology* 11:57. https://doi.org/10.3389/fendo.2020.00057

Perera, M. R., Greenwood, E. J., Crozier, T. W., Elder, E. G., Schmitt, J., Crump, C. M., Lehner, P. J., Wills, M. R., and Sinclair, J. H. 2022. Human cytomegalovirus infection of epithelial cells increases SARS-CoV-2 superinfection by upregulating the ACE2 receptor. *The Journal of Infectious Diseases* 227(4):543–553. https://doi.org/10.1093/infdis/jiac452

Pánico, P., Ostrosky-Wegman, P., and Salazar, A. M. 2022. The potential role of COVID-19 in the induction of DNA damage. *Mutation Research / Reviews in Mutation Research* 789:108411. https://doi.org/10.1016/j.mrrev.2022.108411

Ramírez-Martínez, G., Jiménez-Álvarez, L. A., Cruz-Lagunas, A., Ignacio-Cortés, S., Gómez-García, I. A., Rodríguez-Reyna, T. S., Choreño-Parra, J. A., and Zúñiga, J. 2022. Possible role of matrix metalloproteinases and TGF-β in COVID-19 severity and sequelae. *Journal of Interferon & Cytokine Research* 42(8):352–368. https://doi.org/10.1089/jir.2021.0222

Rosa, R. B., Dantas, W. M., do Nascimento, J. C., da Silva, M. V., de Oliveira, R. N., and Pena, L. J. 2021. In vitro and in vivo models for studying SARS-CoV-2, the etiological agent responsible for COVID-19 pandemic. *Viruses* 13(3):379. https://doi.org/10.3390/v13030379

Ryan, F. J., Hope, C. M., Masavuli, M. G., Lynn, M. A., Mekonnen, Z. A., Yeow, A. E. L., Garcia-Valtanen, P., Al-Delfi, Z., Gummow, J., and Ferguson, C. 2022. Long-term perturbation of the peripheral immune system months after SARS-CoV-2 infection. *BMC Medicine* 20(1):1–23. https://doi.org/10.1186/s12916-021-02228-6

Sahu, S., Singh, B., and Rai, A. K. 2022. Human endogenous retrovirus regulates the initiation and progression of cancers. *Molecular and Clinical Oncology* 17(4):1–11. https://doi.org/10.3892/mco.2022.2576

Sant, S., Wang, D., Agarwal, R., Dillender, S., and Ferrell, N. 2020. Glycation alters the mechanical behavior of kidney extracellular matrix. *Matrix Biology Plus* 8:100035. https://doi.org/10.1016/j.mbplus.2020.100035

Scagnolari, C., Bitossi, C., Viscido, A., Frasca, F., Oliveto, G., Scordio, M., Petrarca, L., Mancino, E., Nenna, R., and Riva, E. 2021. ACE2 expression is related to the interferon response in airway epithelial cells but is that functional for SARS-CoV-2 entry? *Cytokine* 140:155430. https://doi.org/10.1016/j.cyto.2021.155430

Shen, X.-R., Geng, R., Li, Q., Chen, Y., Li, S.-F., Wang, Q., Min, J., Yang, Y., Li, B., and Jiang, R.-D. 2022. ACE2-independent infection of T lymphocytes by SARS-CoV-2. *Signal Transduction and Targeted Therapy* 7(1):1–11. https://doi.org/10.1038/s41392-022-00919-x

Shirvaliloo, M. 2021. The blood-gas barrier in COVID-19: An overview of the effects of SARS-CoV-2 infection on the alveolar epithelial and endothelial cells of the lung. *Tissue Barriers* 9(4):1937013. https://doi.org/10.1080/21688370.2021.1937013

Simula, E. R., Manca, M. A., Noli, M., Jasemi, S., Ruberto, S., Uzzau, S., Rubino, S., Manca, P., and Sechi, L. A. 2022. Increased presence of antibodies against type I interferons and human endogenous retrovirus W in intensive care unit

COVID-19 patients. *Microbiology Spectrum* 10(4):e01280–01222. https://doi.org/10.1128/spectrum.01280-22

Spirina, L. V., Masunova, N. V., Masunov, V. N., Makova, V. V., Dagbaeva, Y. S., and Kovaleva, I. V. 2022. SARS-CoV2 infection and comorbidities, role in oncogenesis. *Asian Pacific Journal of Cancer Prevention* 23(7):2191–2197. https://doi.org/10.31557/APJCP. 2022.23.7.2191

Sun, K., Chen, J., and Viboud, C. 2020. Early epidemiological analysis of the coronavirus disease 2019 outbreak based on crowdsourced data: a population-level observational study. *The Lancet Digital Health* 2(4):e201–e208. https://doi.org/10.1016/S2589-7500(20)30026-1

Umesh, A., Pranay, K., Pandey, R. C., and Gupta, M. K. 2022. Evidence mapping and review of long-COVID and its underlying pathophysiological mechanism. *Infection* 50:1053–1066. https://doi.org/10.1007/s15010-022-01835-6

Victor, J., Deutsch, J., Whitaker, A., Lamkin, E. N., March, A., Zhou, P., Botten, J. W., and Chatterjee, N. 2021. SARS-CoV-2 triggers DNA damage response in Vero E6 cells. *Biochemical and Biophysical Research Communications* 579:141–145. https://doi.org/10.1016/j.bbrc.2021.09.024

Victor, J., Jordan, T., Lamkin, E., Ikeh, K., March, A., Frere, J., Crompton, A., Allen, L., Fanning, J., and Lim, W. Y. 2022. SARS-CoV-2 hijacks host cell genome instability pathways. *Research Square* https://doi.org/10.21203/rs.3.rs-1556634/v1

Wang, G., Xiong, Z., Yang, F., Zheng, X., Zong, W., Li, R., and Bao, Y. 2022. Identification of COVID-19-associated DNA methylation variations by integrating methylation array and scRNA-Seq data at cell-type resolution. *Genes* 13(7):1109. https://doi.org/10.3390/genes13071109

Wolff, L., Martiny, D., Deyi, V. Y. M., Maillart, E., Clevenbergh, P., and Dauby, N. 2021. COVID-19-associated Fusobacterium nucleatum Bacteremia, Belgium. *Emerging Infectious Diseases* 27(3):975. https://doi.org/10.3201/eid2703.202284

Wu, Q., Zhou, L., Sun, X., Yan, Z., Hu, C., Wu, J., Xu, L., Li, X., Liu, H., and Yin, P. 2017. Altered lipid metabolism in recovered SARS patients twelve years after infection. *Scientific Reports* 7(1):1–12. https://doi.org/10.1038/s41598-017-09536-z

Xiao, X., Shan, H., Niu, Y., Wang, P., Li, D., Zhang, Y., Wang, J., Wu, Y., and Jiang, H. 2022. TMPRSS2 serves as a prognostic biomarker and correlated with immune infiltrates in breast invasive cancer and lung adenocarcinoma. *Frontiers in Molecular Biosciences* 9:647826. https://doi.org/10.3389/fmolb.2022.647826

Yang, L., Yang, S., Ren, C., Liu, S., Zhang, X. and Sui, A. 2022. Deciphering the roles of miR-16-5p in Malignant Solid Tumorsmalignant solid tumors. *Biomedicine & Pharmacotherapy* 148:112703. https://doi.org/10.1016/j.biopha.2022.112703

Yao, Y., Subedi, K., Liu, T., Khalasawi, N., Pretto-Kernahan, C. D., Wotring, J. W., Wang, J., Yin, C., Jiang, A., and Fu, C. 2022. Surface translocation of ACE2 and TMPRSS2 upon TLR4/7/8 activation is required for SARS-CoV-2 infection in circulating monocytes. *Cell Discovery* 8(1):1–17. https://doi.org/10.1038/s41421-022-00453-8

Zalpoor, H., Akbari, A., Nayerain Jazi, N., Liaghat, M., and Bakhtiyari, M. 2022. Possible role of autophagy induced by COVID-19 in cancer progression, chemo-resistance, and tumor recurrence. *Infectious Agents and Cancer* 17(1):1–4. https://doi.org/10.1186/s13027-022-00450-2

Zhang, C.-Y., Liu, S., and Yang, M. 2022. Crosstalk between gut microbiota and COVID-19 impacts pancreatic cancer progression. *World Journal of Gastrointestinal Oncology* 14(8):1456. https://doi.org/10.4251/wjgo.v14.i8.1456

Zhang, M., Wang, P., Luo, R., Wang, Y., Li, Z., Guo, Y., Yao, Y., Li, M., Tao, T., and Chen, W. 2021. Biomimetic human disease model of SARS-CoV-2-induced lung injury and immune responses on organ chip system. *Advanced Science* 8(3):2002928. https://doi.org/10.1101/2020.07.20.211789

Zhang, S., Wang, J., Wang, L., Aliyari, S., and Cheng, G. 2022. SARS-CoV-2 virus NSP14 Impairs NRF2/HMOX1 activation by targeting Sirtuin 1. *Cellular & Molecular Immunology* 19(8):872–882. https://doi.org/10.1038/s41423-022-00887-w

Østergaard, L. 2021. SARS CoV-2 related microvascular damage and symptoms during and after COVID-19: Consequences of capillary transit-time changes, tissue hypoxia and inflammation. *Physiological Reports* 9(3):e14726. https://doi.org/10.14814/phy2.14726