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Persistent SARS-CoV-2 infection and the risk for cancer

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ABSTRACT

The current SARS-CoV-2 has put significant strain on healthcare services worldwide due to acute COVID-19. However, the potential long-term effects of this infection haven't been extensively discussed.

We hypothesize that SARS-CoV-2 may be able to cause persistent infection in some individuals, and should this be the case, that in a few years we may see a rise in cancer incidence due to carcinogenic effects of this coronavirus.

Non-retroviral RNA viruses such as Coronaviridae have been shown to cause persistent infection in hosts. Empirical evidence of viral genomic material shedding weeks after apparent clinical and laboratorial resolution of COVID-19 may be an indirect proof for persistent viral infection. Furthermore, tropism towards certain immune-privileged territories may facilitate immune evasion by this virus.

Structural homology with SARS-CoV-1 indicates that SARS-CoV-2 may be able to directly impair pRb and p53, which are key gatekeepers with tumor suppressor functions. Additionally, COVID-19 features preeminent inflammatory response with marked oxidative stress, which acts as both as initiator and promotor of carcinogenesis.

Should there be a carcinogenic risk associated with SARS-CoV-2, the implications for public health are plenty, as infected patients should be closely watched during long periods of follow-up.

Additional investigation to establish or exclude the possibility for persistent infection is paramount to identify and prevent possible complications in the future.

Introduction

The current SARS-CoV-2 pandemic has put significant stress on healthcare services worldwide. While the spotlights are on the acute complications of COVID-19, discussion on the possible long-term complications of this infection is necessary.

SARS-CoV-2 belongs to the Coronaviridae family of non-retroviral RNA viruses, which feature a positive-sense single-stranded RNA genome. This large family of viruses show significant interspecies genetic and clinical diversity. Indeed, many Coronaviridae present as mild coryza, while others, such as SARS-CoV-1 and SARS-CoV-2 may present as life-threatening pneumonitis.

Non-retroviral RNA viruses usually present as an acute infection, characterized by rapid viral replication and shedding, followed by a recovery phase where the individual clears the virus and develops immunity against re-infection for variable periods of time. In order to be maintained in a population, most such RNA viruses have developed strategies to prevent eradication: i) infection through mucosal membranes, where lasting immunity is harder to obtain; ii) high mutation rates that lead to antigenic variability, thus allowing some viral particles to evade acquired immunity; iii) capability to infect multiple species, thus allowing the existence of reservoirs from which infection can be perpetuated; iv) development of specific mechanisms that allow for persistent infection in some individuals (eg. Hepatitis C or Borna disease) [1].

While persistent viral infection has significant impacts on the epidemiology of an infectious disease, allowing for transmission of the virus from a single individual over extended periods of time, one has also to consider the effects of such persistence on the host. One of the most significant long-term consequences may be the risk of carcinogenesis, as is the case of chronic hepatitis C.

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Hypothesis

We hypothesize that SARS-CoV-2 may be able to maintain persistent infection inside the host and that in a few years' time we may observe a surge in neoplasms due to this virus. For this to be presumed, two main assumptions must be verified, simultaneously: there should be evidence for persistent SARS-CoV-2 infection; and there should be evidence for carcinogenic mechanisms due to this infection.

Some Coronaviridae have been shown to feature persistent infection of the host [2]. While such capability for SARS-CoV-2 is yet to be proven, one must consider the shedding of viral genetic material that persists long after resolution of the acute disease (and negative RT-PCR) as evidence for either re-infection or reactivation of latent infection [3]. SARS-CoV-2 appears to have tropism towards endothelium [4] which may facilitate persistence in tissues not primarily featured in the typical symptomatology of COVID-19. We should also note that cases of central nervous system involvement with positive RT-PCR in cerebrospinal fluid have been described [5], raising the possibility of persistent infection in immune-privileged territories where immune evasion is easier.

Regarding the possible oncogenic mechanisms of SARS-CoV-2, little is known. A primary mechanism may relate to quantitative and qualitative disruption of tumor suppressor proteins such as pRb. It was shown that SARS-CoV-1 Endoribonuclease Nsp15 both downregulates and impairs pRb function, and promotes its degradation through ubiquitin-proteasome pathway [6]. The same authors have demonstrated these changes favor cellular proliferation due to loss of cell-cell contact inhibition. While these data are yet to be replicated for SARS-CoV-2, the structure of NSP15 endonuclease is highly conserved as it shares 88% homology and identical quaternary structure to that of SARS-CoV-1 [7]. Thus, similar effects of SARS-CoV-2 NSP15 endonuclease on pRb are expected. Concomitantly, destruction of p53 tumor suppressor protein seems to be promoted by SARS-CoV-1 [8]. While this has yet to be shown in SARS-CoV-2, it could prove to be an additional contribution towards carcinogenic risk.

Another mechanism that may lead to carcinogenesis is oxidative stress. One of the hallmarks of SARS-CoV-2 infection seems to be viral internalization through binding to angiotensin-converting enzyme 2 (ACE2). This carboxypeptidase is a key regulator of the renin-angiotensin-aldosterone pathway, promoting conversion of angiotensin II into angiotensin-1,7. This offers ACE2 an anti-hypertensive, anti-inflammatory, anti-fibrotic and anti-oxidative role. When bound to SARS-CoV-2 spike protein, ACE2 is internalized but not activated. Thus, SARS-CoV-2 binding may deplete ACE2 on cellular surface, contributing towards an imbalance that favors the pro-inflammatory and oxidative action of angiotensin II [9]. It is also believed that the macrophage might be an important player in acute COVID-19 [10], through significant cytokines and reactive oxygen species (ROS) production. Indeed, inflammatory response, cytokine storm and oxidative stress may be the cause of Acute Respiratory Distress Syndrome, rather than direct viral cytopathic damage. A third source of ROS may come from treatment, as high tidal volumes and FiO_2 during mechanical ventilation are associated with increased oxidative damage in lung tissue [11].

Oxidative stress is recognized as both an initiator and promotor of carcinogenesis, through direct mutagenic action of ROS, promotion of DNA single and double strand breaks, DNA cross-linking, and inhibition of DNA mismatch repair mechanisms. Furthermore, through interactions with intracellular signaling pathways, ROS can promote proliferation, tissue invasion, angiogenesis, cancer cell survival and even chemoresistance [12].

Consequences and discussion

The long-term effects of global pandemics on morbidity and mortality cannot be overlooked [13]. While much is still unknown regarding SARS-CoV-2 infection, empirical indication for reinfection/reactivations and evidence for persistent infection due to closely related viruses raise the hypothesis of possible long-term consequences of SARS-CoV-2 infection. One of the most relevant, based on pathophysiological knowledge, is the risk for malignant neoplasms that may become a public health concern in the coming decades. Further investigation is needed to clarify this risk. It will also be important to monitor "cured" patients for possible viral reactivation. Serial RT-PCR could be offered to a cohort of patients over time to clearly determine if persistent SARS-CoV-2 is indeed possible and the frequency of this phenomenon. Additionally, *in vitro* and animal studies for direct mutagenic potential of SARS-CoV-2 should be carried, but interpretation must be cautious, as much of DNA damage comes from sustained immune response. Looking into the natural hosts of closely related zoonotic Coronaviridae may also shed some light into this matter. While definite answers are not available, patients affected by COVID-19 should maintain long-term follow-up as the possibility for late complications cannot be yet excluded.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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