

Review Article

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Sars-Cov-2 Persistent Infection May Evolve into Malignancy, Possibly Curbed by Vaccination: A Hypothesis

Daniel Benharroch* and Karen Nalbandyan

Department of Pathology, Soroka University Medical Center, and Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel

ABSTRACT

The three coronavirus variant infections which evolve onto severe respiratory conditions, have occasionally been associated with persistence. The viral RNA might be solely affected, or else, new symptoms might represent the only disease manifestations, often systemic and neurological. At times, it may associate with variable immunity. A persistent COVID-19 may initiate a “long COVID” episode. It has been hypothesized that, pending an expanded follow-up, the persistence of the SARS-CoV-2 might advance into a cancer: *TMPRSS2* gene might develop into prostate cancer, while ground glass lung opacities might lead to lung cancer. In contrast, vaccines may impede the development of a malignancy. Among these, the BCG vaccine predominates, together with the MMR vaccine; mumps and measles being possibly responsible for tumor handicap. It is too early to discern a similar role for COVID-19 with anti-SARS-CoV-2 vaccines, as they may relate to cancer.

*Corresponding author

Daniel Benharroch, Department of Pathology, Soroka University Medical Center, and Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel. E-mail: danielbenharroch1@gmail.com

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Introduction

SARS-CoV-2 is an RNA virus. Initial reports raised suspicion of its genome integration into the human DNA however, further investigations, including DNA sequencing, do not sustain this thesis [1,2]. Human oncogenic RNA viruses include human T-cell lymphotropic virus – 1 (HTLV-1) and hepatitis C virus (HCV). While the former belongs to the retrovirus family applying its oncogenic effect via the viral genetic material integration into the host DNA, the tumor transformation, induced by the later, presents with both direct and indirect mechanisms. The indirect mechanism, predominant with HCV, is caused through inflammation and oxidative stress. The direct mechanism, less significant, embraces the inhibition of tumor suppressors like *p53*, *p21*, *Rb*, *ATM*, by viral proteins [3].

An interaction of the SARS-CoV-2 S2 subunit with *p53* and *BRCA* tumor suppressor genes has been demonstrated by bioinformatic analysis. These genes are often mutated in malignancy. In addition, the *TMPRSS2* gene function proved critical for the virus entry into the host cell, as a tumor suppressor gene has perhaps been highlighted. Evidence has been presented in favor, but to some extent also, in contradiction with a role for SARS-CoV-2 in cancer initiation [4-6].

Relentless coronavirus infection has been described with SARS-CoV, MERS-CoV, as well as with SARS-CoV-2. Clinically, some of these conditions may present with recurrent RNA positivity, following recovery from COVID -19. Otherwise, the extended

viral RNA may be underlined by new symptoms, mostly of a multisystemic neurological character. A further picture may disclose an unremitting cellular immunity to the virus, highlighted by variable expression of CD4+ and CD8+ cells. The increased persistence of the SARS-CoV-2 in the tissue sections seems more prevalent in lower socioeconomic populations [7-10]. In some reports, the viral constancy has been displayed in stool examination. The viral perseverance has often taken the form of a long COVID case, bearing a pejorative import [11,12].

A Link of COVID-19 with Cancer

The *TMPRSS2* gene with its serine protease, activating SARS-CoV and SARS-CoV-2, is thought to play a role in the prostatic carcinogenesis. The SARS-CoV-2-S glycoprotein is split by *TMPRSS2*, thus activating the virus and the pathogenicity of the host factors. The gene activation represents a major means of cell entry and for viral pathogenesis. Independently, this gene is considered of crucial importance in prostate cancer development and progression. The fusion of *TMPRSS2* with *ERG*, a member of the E-twenty-six family members, have a major role in differentiation, cell proliferation, apoptosis, and inflammation [13, 14].

The SARS-CoV-2, by inducing ground glass lung opacities, in COVID-19 patients, may initiate an immunopathogenesis, not unlike that of other oncogenic viruses, pending an appropriate time lapse, necessary for the malignant transformation. A striking effect of SARS-CoV-2 is felt in the immune system, associated with proinflammatory cytokines. A secondary pulmonary fibrosis develops. COVID-19 survivors are at a high risk of evolving into lung cancer. Two types of ground glass opacities (GGO) are

described. One, the pure GGO nodules, do not contain a solid component. The second is a mixed type. The GGO behavior is not uniform. The advent of lung cancer in GGO patients might reach 83%, mainly in the solid GGO type. It is of note, in this context, that cytokine storms contribute a meaningful effect in both COVID-19 and in the malignant evolution [15,16].

A Role for Vaccination

While expecting the completion of the novel RNA anti-SARS-CoV-2 vaccines, the WHO and similar Alpha medical institutions, have attempted to rely on older vaccines. Most notable among the latter, are the bacillus Calmette and Guerin (BCG), administered successfully, locally to some 130 million infants, world-wide, against tuberculosis, as well as for some cases of leprosy [17,18]. This vaccine is also effective for non-specific respiratory diseases and in reducing the impact of malaria. Moreover, the BCG imparts enhanced innate immunity against viruses. Thus, while waiting for the anti-SARS-CoV-2 vaccine to be finalized, it had been suggested that the BCG could protect against COVID-19. This vaccine is still used successfully in third world countries, notably in Africa, in which the modern vaccines are not fully available yet. Concerning the efficacy of the BCG for COVID-19, countries with <70% coverage of BCG, were found to exhibit 6.5 COVID-19 per 10,000 inhabitants, in contrast with the countries showing no BCG coverage at all. However, these figures are not valid for the Middle East, nor for North-Africa. In addition to its efficacy against bacterial and viral infections, the vaccine contributes a degree of protection onto several cancers, possibly thanks to extended cellular immunity. The malignant tumors in question, include melanoma and bladder cancer [19,18].

Further vaccines – MMR and COVID-19

The MMR vaccination was found to be negatively associated with the severity of the COVID-19 symptoms. Mumps titers, associated with the MMR vaccine are inversely related with the COVID-19 symptoms. In some countries, the COVID-19 mortality is much lower than in others. Some individuals will not become positive, despite prolonged exposure with severe disease. Toddlers are mostly free from serious symptoms. About half of the population tested positive show no symptoms. Hence a thesis is suggested, pointing at the MMR vaccine, as accounting for the variance in the relation between COVID-19 and severe symptoms. Moreover, a possible prior immunity to the coronaviruses has been displayed, by exhibiting titers to spike protein, despite lack of exposure to SARS-CoV-2 [20,21].

A prior MMR vaccination may restrain the severity of the pandemic symptoms, but the mechanism thereof has not been clarified. A cross-immunity might be associated with a particular MMR component, which displays some similarity with the SARS-CoV-2.

Conclusions

The coronaviruses have been shown to persist occasionally. An attempt at defining several of the consequences thereof is presented. In turn, the viral RNA, new symptoms, or a cellular immune variation may predominate. Clinically, a long COVID has been mentioned. As with some other viruses, perseverance might favor the evolution into cancer (see lung and prostate malignant tumors). During the time latency, a further factor comes into effect. Vaccines, like the BCG and the MMR, may obstruct cancer development. It is probably too early to evaluate both the relevance of SARS in the malignant rise, as well as a role for the various vaccines thereof, for its impediment.

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