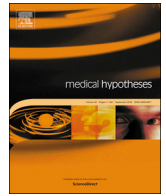




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# A putative role for the tobacco mosaic virus in smokers' resistance to COVID-19

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## ABSTRACT

Reports from various countries suggest that tobacco smoking might protect from SARS-CoV-2 infection, since the prevalence of smoking in COVID-19 hospitalized patients is lower than in the respective general population. Apart from nicotine or other chemicals contained in tobacco smoke, we propose that a single-stranded RNA virus that infects tobacco leaves, tobacco mosaic virus (TMV), might be implicated in this effect. TMV, though non-pathogenic, is found in smokers' airways, and stimulates adaptive and innate immunity, with release of specific antibodies and interferons. The latter may have preventive and/or therapeutic effects against COVID-19.

If confirmed by epidemiological and interventional studies, this might lead to the use of TMV as an immunological adjuvant against SARS-CoV-2 infection and COVID-19 disease.

## Introduction

COVID-19, a new severe acute respiratory syndrome (SARS) emerging in late 2019, and due to a new coronavirus (SARS-CoV-2), has caused a global pandemic, which so far counts more than 13 million cases and more than 570,000 deaths worldwide (European Centre for Disease Prevention and Control, <https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases>, last visit July 14th, 2020).

Though it is intuitively tempting, on the basis of physiopathological common knowledge, to predict a greater risk of contracting the SARS-CoV-2 infection in tobacco smokers, an analysis of studies from various countries shows that hospitalized COVID-19 patients have a lower, and apparently inversely proportional, rate of current tobacco smoking, in comparison with the respective general population, although once the disease has developed *meta*-analyses suggest that smoking is associated with a worse prognosis [1].

Hence, it has been suggested that tobacco smoking might confer some protection against the SARS-CoV-2 infection, at least in its initial phases.

The search for a cause of this puzzling finding started from nicotine, the most important pharmacological agent in tobacco smoke, a psychotropic, addictive alkaloid with an anti-inflammatory activity and an influence on the biosynthesis of angiotensin conversion enzyme 2 (ACE2), the receptor for SARS-CoV-2 cell adhesion [2]. So far, though, no data are available on the effects of pure nicotine on COVID-19.

## Hypothesis

Here we suggest that the resistance of tobacco smokers to the SARS-CoV-2 infection might be immunologically mediated by the chronic exposure to a common tobacco-dwelling virus, the tobacco mosaic virus (TMV).

TMV is a single-stranded, positive-sense RNA virus that infects several plants of the family of Solanaceae, including the tobacco plant, and was the first virus to be discovered, towards the end of the 19th century [3].

Though TMV is known to be not pathogenic to humans, it has been found in sputum [4] and saliva specimens from cigarette smokers, as well as in cigarettes, in the form of viable virions, while being absent in non-smokers [5].

In vitro experiments on human epithelial carcinoma HeLa cells show that after TMV transfection some viral proteins are found in the endoplasmic reticulum, and cleared by autophagy, a defense reaction which activates Toll-Like receptor 7 and initiates innate antiviral responses [6].

In-vivo experiments show that anti-TMV antibodies are produced both by mice after intratracheal inoculation [7] and by humans after exposure to tobacco products [8].

Exogenous RNA, including single-stranded RNA from non-replicating viral particles, has been shown to induce the production of interferons [9]. Accordingly, the oral administration of TMV was found to stimulate the release of endogenous interferon in Rhesus monkeys,

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mice and humans, and to exert a marked protective effect in mice against various experimental viral infections [10].

It is conceivable, then, that the oral use of cigarettes, cigars and other derivatives of tobacco leaves, continuously challenges the airways with an inflow of TMV virions, which may colonize the area without replicating and without inducing an overt disorder. The presence of TMV virions and related RNA, though, may cause a protracted immune alert, inducing the production of interferons and maybe other cytokines, which will be already present when the exposition to SARS-CoV-2 takes place.

Current knowledge about COVID-19 innate immune sensing indicates that the early and properly localized presence of interferon type I can effectively limit coronavirus infections, and initial evidences show that SARS-CoV-2 is sensitive to interferon type I and type III pretreatment *in vitro*; the timing of interferon secretion, though, is critical, because it appears to be protective if early, while on the other hand aggravates the disease if dysregulated, lacking in the early phase and contributing to a cytokines storm later [11]. Incidentally, this behavior reminds the proposed effects of tobacco smoking, protective against initial SARS-CoV-2 infection and deleterious in the florid phase of the COVID-19 disease. Accordingly, it has been suggested that endogenous or medicinal interferons in the initial phase of the SARS-CoV-2 infection may have a therapeutic role in preventing or treating COVID-19 [12], and some clinical trials are under way, with interesting results [13].

Taken together, all these elements suggest that the oral use of tobacco, continuously exposing to non-pathogenic but immunogenic TMV particles, and chronically stimulating a natural antiviral response, may induce a state of resistance to the initial SARS-CoV-2 infection. This in turn could be a plausible explanation for the putative protective effect of tobacco smoking observed so far.

## Discussion

### *Our hypothesis could be tested in various ways*

Similarly to the studies on the putative protective effect of smoking, as a first step it could be possible to assess the prevalence of TMV in airways and related immune parameters in COVID-19 patients vs. the general population, and the findings could be used to infer the effects of TMV on the probability to get infected. This could be completed by searching for a correlation, in selected territories, between the reduction of the rate of smokers among hospitalized COVID-19 patients, and the average content of TMV in the most used cigarettes and tobacco derivatives; theoretically, a higher presence of TMV in tobacco products should determine a larger protective effect in smokers against the SARS-CoV-2 infection.

At a greater level of complexity it could be possible to prospectively follow a cohort of TMV-positive individuals in comparison with a comparable TMV-negative cohort, surveying the incidence of SARS-CoV-2 infection and the development of the COVID-19 disease.

As a third step, it could be possible to investigate the effects of an interventional TMV exposition on SARS-CoV-2 infection and development of COVID-19 in appropriate animal or human experimental models. TMV has been administered to humans without overt signs of

toxicity or disease [10] and like other plant viruses is deemed harmless for mammals, and fit to be used as an immunopotentiating agent [14].

This could lead to the use of TMV virions or TMV-rich plant materials as a cheap, promptly available immune adjuvant to reduce the burden of disease due to SARS-CoV-2 and COVID-19.

Conflict of interest statement Acireale, July 14th, 2020 We hereby declare that there exist no financial or personal relationship with other people or organisations that could inappropriately influence this work. No funding was needed. No sponsor were involved.

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## 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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