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A contribution to the hypothesis of nicotinic challenge as therapeutic option for COVID-19 patients

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Abstract

The pandemic caused by SARS-CoV-2 represents an open and unresolved challenge for the global health system. The need to identify drugs that demonstrate efficacy in countering both the mechanisms of interaction of SARS-CoV-2 with host cells and to control the devastating inflammatory phenomena that characterize the late stages of viral infection, requires increasingly urgent answers. The biomedical research approach based on the repurposing of already approved drugs seems to be one of the most viable strategies in this struggle. Through a computational pharmacology approach and on the basis of what has been recently reported on the potential of nicotinic receptors in countering both phases of COVID-19, in this work we propose a hypothesis aimed at widening the spectrum of pharmacological tools currently available to medical doctors. Our proposal specifically concerns the possibility of using tropisetron, a 5-HT3 receptor antagonist at the same time positive allosteric interactor of the nicotinic alpha-7 receptor, in order to inhibit unexplored virus-host interaction and restore the physiological control mechanisms of the excessive inflammation caused by SARS-CoV-2.

In the context of the frantic search for therapeutics useful to tackle the current pandemic of SARS-CoV-2 and to limit the enormous burden on the intensive care units and health systems of the countries involved, relevant emphasis has been put on strategies aimed at repurposing drugs already approved for other conditions. An original and, in our opinion, remarkable contribution has been recently put forward, based on clinical epidemiological analyses [1] and on the current knowledge of neuroimmune modulation of the inflammatory response [2], proposing the use of nicotine to interfere with unexplored virus-host interactions and to face the tremendous impact of the cytokine storm syndrome characterizing the second phase of COVID-19. Here, we would like to extend and integrate such hypothesis and suggest further therapeutic options based on the challenge of alpha-7 nicotinic acetylcholine receptor (α7nAchR, gene name: CHRNA7).

We are currently finalizing an extensive investigation of SARS-CoV-2 host interactome, performed via a network medicine approach [3] based on available virus-host protein-protein interaction (PPI) data, and on integrated computational analyses (including machine learning) aimed to identify a limited host gene set as a possible drug target (the methodological details of such analysis will be illustrated and extensively discussed elsewhere (Tieri P. et al , manuscript in preparation)). In our preliminary computational analysis of the SARS-CoV-2-host interactome we identified genes with high centrality (betweenness centrality rank <50) and a strong connection with some peculiar symptoms of COVID-19 patients, such as anosmia and ageusia (VarElect suite, [4]) (preliminary unpublished data at https://www.iac.cnr.it/~tieri/projects/COVID-19/covid-19.html), that may be potential pharmacological targets for the treatment of COVID-19. Among high scoring genes, our attention was attracted in particular, as neuropharmacologists, by the HTR3A gene, which protein is a direct interactor of FURIN [5], this latter proposed as a critical and specific protease for Sars-CoV-2 S protein cleavage, and subsequently suggested as a potential drug target [6] . HTR3A gene codifies for the A subunit of the serotonin ionotropic 5-HT3 receptor, that is a neurotransmitter receptor belonging to the Cys-loop superfamily of ligand-gated ion channels (LGICs), expressed in the central and peripheral nervous system with relevant pharmacological value in psychiatric and gastrointestinal diseases [7]. Searching for specific correlates of 5-HT3 dysfunction and SARS-CoV-2 infection, we noticed that this serotonin receptor is important, among others, in the signaling between taste buds and gustatory nerves, accounting for a significant proportion of the neural taste response [8]. Thus a possible correlation between 5-HT3 and the taste dysfunction (ageusia/dysgeusia) reported as a peculiar symptom in a great percentage of COVID-19 patients [9], is conceivable.

The hypothesis of a possible complex interplay among viral proteins, Furin and the 5-HT3 receptor, supported by previous [5,10] and our ongoing computational analyses (preliminary unpublished data at https://www.iac.cnr.it/~tieri/projects/COVID-19/covid-19.html) could account for its loss-of-function. It is well established that the receptor-binding domains on the SARS-CoV-2 Spike (S) protein bind with high affinity to human ACE2, an interaction accounting for virus entry in the host cell and for its transmissibility [11]. However, the awareness that additional virus-host interactions, not necessarily related with viral transmission of disease, could determine the insurgence and progression of symptoms is gaining ground. Zhou et al. noted unique features on a separate (N-terminal) domain of the SARS-CoV-2 S proteins that may confer binding to alternative host-cell receptors[12] and it is known that analogous domains on several human CoVs have important auxiliary cell-binding functions [13]. Evidence for alternative interaction of virus Spike protein with receptors other than ACE2 have been also recently suggested by computational analysis [14]. Notably, Changeux and colleagues also based their nicotinic hypothesis on the assumption of possible direct interaction of viral proteins with nAChRs [2].

We thus searched for other 5-HT3 structurally-related proteins, possibly correlating with one or more COVID-related symptoms and disease manifestations, in particular the uncontrolled and sustained inflammatory response, obviously mediated by over-activity of pro-inflammatory cytokines, as IL-1beta, TNF-alpha or IL-6. This search attracted our attention to another neurotransmitter receptor, belonging to the LGICs superfamily, with great structural and pharmacological similarities to the 5-HT3 receptor, namely the α7nAchR, [15]. Thus we may hypothesize that the SARS-CoV-2 virus interacts with and affects the function of LGICs, and that such interactions could account for the development of peculiar COVID-19 clinical manifestations.

As put forward by Changeux and colleagues [2], α7nAchR presents some peculiar characteristics that make it a strong candidate as a therapeutic target in the COVID-19 pandemic. Besides its distribution and role in the central and peripheral nervous system, this receptor plays a crucial role in the homeostatic regulation of inflammatory processes. According to the inflammatory reflex theory [16–18], the α7nAchR is at the interface between the immune and nervous systems, expressed on cytokine-producing monocytes and its activation by acetylcholine (ACh) dampens the inflammatory process by downregulating pro-inflammatory cytokines production. It is worth noting that the blockade of α7nAchR functions by viral interactors may selectively worsen the SARS-CoV-mediated uncontrolled inflammation in the lungs [19].

Thus, we hypothesize that both 5-HT3 and α7nAchR, due to their structural similarities [15], may represents possible alternative targets for virus-host interaction, with possible de-sensitization or de-activation of both receptors and the consequent development of at least lung inflammation and ageusia. Our working hypothesis, actually based on the preliminary bioinformatics analyses and pharmacological speculations, is thus to recover the conceivable α7nAchR loss-of-function by a pharmacological approach based on its shared structural/pharmacological features with the 5-HT3 receptor [15]. The use of a positive allosteric modulator of α7nAchR, such as the 5-HT3 antagonist tropisetron, yet used for gastro-enteric symptoms, is, in our opinion, a valuable choice, in order to firstly maintain a proper safety profile in patients yet challenged by a potentially lethal condition [20]. A similar approach has been proposed, suggesting the positive allosteric α7nAchR modulator ivermectin [2], which has been already reported as a possible inhibitor of

SARS-CoV-2 replication [21]. In our opinion, the possibility to target two possible virus-interacting host proteins by a single drug may represent a significant advantage. Indeed, tropisetron is both a selective serotonin receptor antagonist, which competitively blocks the action of serotonin at 5HT3 receptors [22] and a positive allosteric modulator of the α7nAchR [23]. Furthermore, the α7nAchR-based anti-inflammatory action of the drug has already been demonstrated in preclinical studies [20,24]. It is thus conceivable that, by physical interacting with both receptors, tropisetron may positively interfere with some of the mechanisms of virus entry into host's cells, at the same time triggering the activation of physiological mechanisms controlling and damping excessive inflammation. In conclusion, based on the cholinergic anti-inflammatory pathway as a potential target for drug repurposing in the fight against SARS-CoV-2 pandemics, we strongly support the hypothesis of nicotinic challenge as a proper pharmacological strategy to prevent or dampen over-inflammation characterizing the second phase of viral infection. We propose a therapeutic strategy aimed at potentiating the activity of α7nAchR and at interfering with possible LGICs-viral direct interactions, based on the use of the anti-emetic drug tropisetron. Such drug may probably be combined with nicotine, in a supportive interaction. The evidence that an approach based on the pharmacological enhancement of the endogenous ACh content by means of anti-cholinesterase, proposed for an ongoing patient-recruiting trial in Mexico [25] strengthens such working hypothesis. Indeed, it suggests the possibility for a combination therapy based on Tropisetron and/or nicotine and/or Pyridostigmine, aimed at restoring the cholinergic anti-inflammatory pathway by increasing both the availability of the ligand (ACh or nicotine) and the responsivity of its specific α7nAch receptor.

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