SARS-CoV2 infection: ‘A silent threat for smokers/vapers’

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Coronavirus Disease-2019

Globally, as of 10:26am CEST, 4 August 2020, there have been 18,100,204 confirmed cases of COVID-19, including 690,257 deaths, reported to WHO.

SARS-CoV2: not an unknown virus!

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Influenza</th>
<th>SARS</th>
<th>MERS</th>
<th>Covid-19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causative Agent</strong></td>
<td>Influenza A &amp; B</td>
<td>SARS-CoV</td>
<td>MERS-CoV</td>
<td>SARS-CoV2</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Fever, chills, runny nose, soar throat, head and body aches with fatigue.</td>
<td>Fever, headache, dry cough, shortness of breath without upper respiratory tract symptoms.</td>
<td>Fever, cough, shortness of breath.</td>
<td>Fever or chills, cough, shortness of breath, muscle or body ache, loss of sense of smell and taste, sore throat and congestion.</td>
</tr>
<tr>
<td><strong>Reproduction number</strong></td>
<td>1.3</td>
<td>3</td>
<td>0.3-0.8</td>
<td>2.2-2.7 *</td>
</tr>
<tr>
<td><strong>Case Fatality Rate</strong></td>
<td>0.05-0.1%</td>
<td>9.6-11%</td>
<td>34.4%</td>
<td>~3.4% -6.4%*</td>
</tr>
<tr>
<td><strong>Incubation Period</strong></td>
<td>1-4 days</td>
<td>2-10 days</td>
<td>6-14 days</td>
<td>2-14 days*</td>
</tr>
</tbody>
</table>

* Covid-19 data as of July 2020.

Table adapted from Epidemiological Comparison of Respiratory Viral Infections (Akiko Iwasaki / Yale University / BioRender) and updated data from CDC.
Crown-like appearance attributed to glycosylated cell surface spike (S) protein with two functional domains-S1 and S2.

Has polybasic cleavage site, that can be processed by furin-like proteases, is reason of pathogenicity.

Interacts with hACE2 via S protein C-Terminal Domain
Entry into the cell and potential targets

Entry into the cell and potential targets

SARS-CoV2

Structural Targets
(E protein, Mpro3CLpro, Furin-like cleavage site)

ACE2
ACE inhibitors

TMPRSS2
TMPRSS2 inhibitor (camostat mesylate)

Membrane fusion & endocytosis

Early Endosome

Virions

Viral Replication

Viral Packaging

Viral Release

Virions

Immune Cells

Cytokine

Immune-modulation (Tocilizumab and Sarilumab)

Antivirals (Remdesivir, Ripavirin, Favipiravir)

Furin Inhibitor

Source: Adapted from Kaur et al (2020), J Inflamm
**Immune responses:** Normal and Diseased

Source: BD Biosciences; COVID19: Snapshot of Immune Response
Host-immune responses against SARS-CoV-2 infection?

Key Highlights:

- SARS-CoV-2 infection induces **low IFN-I and -III levels** with a moderate ISG response.
- **Strong chemokine expression** is consistent across in vitro, ex vivo, and in vivo models.
- **Low innate antiviral defenses** and **high pro-inflammatory cues** contribute to COVID-19.

T-cell mediated Adaptive Immunity?

**Key Findings:**

- CD4+ and CD8+ T cells detected in the epitope pools of 100% and 70% of convalescent COVID patients.

- T cell responses were focused not only on spike but also on M, N, and other ORFs.

- T cell reactivity to SARS-CoV-2 epitopes was also detected in non-exposed individuals.

Source: Grifoni et al. (2020), Cell.
Susceptibility amongst Smokers

Increased expression of ACE2 in the lungs of Cigarette smoke (CS) exposed p16-3MR mice.

Result from three independent experiment. Data is shown as a mean ± SEM (n=4-5/group/experiment). SE: * p<0.05 vs Air as determined using unpaired t-test.

Source: Kaur (unpublished)
Sub-chronic e-cig exposure differentially affects the protein abundance of ACE2 in mouse lungs

Key Findings:

**Gender-based variation** in ACE2 expression on exposure to nicotine containing e-cig aerosol.

Lowering of the nicotine-induced ACE2 abundance on nAChRα7 knockdown.

Possible link between nicotine-induced ACE2 expression and nAChRα7 abundance.

ACE2, Furin and TMPRSS2 are increased in patients with COPD.

**Key Findings:**

Lung homogenates of smokers and COPD patients revealed increased protein abundance of important proteases and spike proteins like **TMPRSS2 and furin** in association with a slight increase in SARS-CoV-2 receptor **ACE2** levels.

ACE2 Activity in Serum samples from Covid19 Positive and Recovered patients

Unpublished data by our group:

ACE2 activity was significantly lowered in Covid-19 positive patients with a smoking history compared to patients who never smoked.

\[
\text{Viral Invasion} = \text{ACE2 Activity}
\]
Furin Activity in Serum samples from Covid19 Positive and Recovered patients

Unpublished data by our group:

• Furin activity is relatively higher amongst Covid19 positive and recovered patients as compared to Covid19 negative samples.

• The Furin activity amongst Covid19 positive patients with a smoking history was subtly higher than patients who never smoked.

Adapted from: Marcus Hoffman (https://www.eurekalert.org/multimedia/pub/230843.php)
Questions to be addressed in Future

- **Link between air pollution and COVID-19 susceptibility** (Wu et al, 2020).

- **Effect of pre-existing pulmonary conditions on COVID-19 severity?**

- **Gender-based variations in disease severity and why?**

- **Effect of infection on pre-natal care?**

- **Phenotypic switching of macrophages** amongst Covid19 positive patients?

- **Contribution of NETs in alveolar inflammation** in SARS-Cov2 epithelial entry?

- **Health implications of recovered population?**

- **Role of genetic and epigenetic factors** in governing the disease?
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