Mécanismes pathogènes dans le COVID Long

Hypothèses immunitaires et virologiques

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Différentes cinétiques de la réponse immune antivirale dans l’infection par le SARS-CoV-2

**Cas idéal d’une infection contrôlée**

**Infection SARS2 modérée**

**Infection SARS2 sévère**

*Contrôle viral efficace*

*Rétard de la réponse innée*

*Rétard et faible intensité de la réponse T*

Adapté de: A. Sette and S. Crotty, Cell 184:861, 2021
Rydzynski / Crotty, Cell 183:996, 2020
Swadling / Maini, medRxiv 2021.06.26.21259239
Différentes cinétiques de la réponse immune antivirale dans l’infection par le SARS-CoV-2

Cas idéal d’une infection contrôlée

Infection SARS2 modérée

Infection SARS2 sévère

Contrôle viral efficace

Retard de la réponse innée

Retard et faible intensité de la réponse T
RÉPPLICATION VIRALE PERSISTANTE
Réponse innée persistante -> inflammation

Adapté de: A. Sette and S. Crotty, Cell 184:861, 2021
Réponses immunes exacerbées dans le COVID Long ?

- Inflammation persistante?
- Autoimmunité?
n=121 patients (n=48 no PASC; n=73 PASC)
- Documented SARS-CoV-2 infection
- PASC: at least 1 symptom at >90 days
- 78% not hospitalized
- History of autoimmune disease:
  - No PASC: 2%
  - PASC: 11% (P=0.08)

Persistent immune activation may be associated with Long COVID
Persistent Symptoms and Association With Inflammatory Cytokine Signatures in Recovered Coronavirus Disease 2019 Patients

Sean Wei Xiang Ong,1,2,3* Siew-Wei Fong,1,4 Barnaby Edward Young,1,5 Yi-Hao Chan,4,5 Bernett Lee,6 Siti Naziah Amran,1,6 Rhonda Sia-Ling Chee,1,4 Nicholas Kim-Walk Yeo,1,4 Paul Tanthyah,1,4 Surinder Pada,5 Seow Yen Tan,5 Ying Diang,1,5 Laurent Renia,5,3 Yee-Siai Lee,5,3,7 Lisa F. P. Ng,3,7,8 and David Chew Lye,1,3,5

1 National Centre for Infectious Diseases, Singapore

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n = 183)</th>
<th>No Persistent Symptoms (n = 161)</th>
<th>Persistent Symptoms at Day 90 or 180 (n = 22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>45 (24.6)</td>
<td>38 (23.6)</td>
<td>7 (31.8)</td>
<td>.43</td>
</tr>
<tr>
<td>Age, years</td>
<td>44 (33–58)</td>
<td>43 (31–58)</td>
<td>50.5 (39–68)</td>
<td>.042</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
<td>.040</td>
</tr>
<tr>
<td>Mild</td>
<td>81 (44.3)</td>
<td>75 (46.6)</td>
<td>6 (27.3)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>47 (25.7)</td>
<td>43 (26.7)</td>
<td>4 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>55 (30.1)</td>
<td>43 (26.7)</td>
<td>12 (54.6)</td>
<td></td>
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</tbody>
</table>

Patients with persistent symptoms: 7% at day 90, 11% at day 180 (lower than in European and American cohorts)

Stronger inflammation during acute infection in patients who develop persistent symptoms
Persistent Symptoms and Association With Inflammatory Cytokine Signatures in Recovered Coronavirus Disease 2019 Patients

Angiogenesis / endothelial inflammation during the late recovery phase?
Syndrome d’Activation des Mastocytes (SAMA) dans le COVID Long ?

MCAS: inappropriate activation of mastocytes
- Release of granule content, including histamine, heparin, proteases (such as tryptase), ...
- De novo synthesis of arachidonic metabolites (prostaglandin D2, leukotriene E4, ...) 
- Chemokine and cytokine secretion (TNF-α, ...)

MCAS associated symptoms:
- Tachycardia, hypotension, syncope
- Pruritus, urticaria, angioedema
- Wheezing, shortness of breath
- Gastrointestinal symptoms

POTS?
Long COVID following mild SARS-CoV-2 infection: characteristic T cell alterations and response to antihistamines

Paul Glynne,1 Natasha Tahmasebi,2 Vanya Gant,3 Rajeev Gupta4,5

Table 1  Clinical features of study participants

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Long COVID (symptomatic, n=49)</th>
<th>Post-COVID controls (asymptomatic, n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range (median)</td>
<td>25–65 (43)</td>
<td>25–72 (34.5)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>30 (61.2%)</td>
<td>8 (50%)</td>
</tr>
<tr>
<td>Allergy or atopy</td>
<td>16 (32.7%)</td>
<td>1 (5.8%)</td>
</tr>
<tr>
<td>Mean days from acute COVID to study testing</td>
<td>271.8 days</td>
<td>321.6 days</td>
</tr>
<tr>
<td>Vaccination history at time of recruitment (at least one dose)</td>
<td>1/49 (2.0%)</td>
<td>14 (87.5%)</td>
</tr>
<tr>
<td>SARS-CoV-2 antibodies detected</td>
<td>20/49 (40.8%)</td>
<td>13/16 (81.3%)</td>
</tr>
</tbody>
</table>

**Treatment with Histamine Receptor Antagonists (HRA)**
Combination of H1 (loratadine) and H2 (famotidine or nizatidine)
HRA for > 4 weeks

Possible beneficial effects of HRA in Long COVID
Duration of post-COVID-19 symptoms are associated with sustained SARS-CoV-2 specific immune responses

Jacob K. Files, …, Paul A. Goepfert, Nathan Erdmann


Persistence of a high frequency of spike-specific CD4+ T cells in Long COVID patients
(Duration of post-COVID-19 symptoms are associated with sustained SARS-CoV-2 specific immune responses)

Jacob K. Files, …, Paul A. Goepfert, Nathan Erdmann

Possible confounder: difference in severity of the original SARS-CoV-2 infection between groups

Persistence of a high frequency of spike-specific CD4+ T cells in Long COVID patients
CORONAVIRUS

Immune signatures underlying post-acute COVID-19 lung sequelae

Cheon IS1,2,*, Li C1,2,*, Son YM1,2,*, Goplen NP1,2, Wu Y1,3, Cassmann T1,2, Wang Z1,2, Wei X1,4, Tang J1,2, Li Y1, Marlow H1, Hughes S1, Hammel L1, Cox TM1, Goddery E1, Ayasoufi K1, Weiskopf D1, Boonyaratanaokornkit J1, Dong H1, Li H1, Chakraborty R2, Johnson AJ1, Edel E1, Taylor JJ1, Kaplan MH1, Sette A1,2, Bartholmai BJ1,2, Kern R1, Vassallo R1,3, and Sun J1,2,3,4,5

COVID patients
➢ > 60 years old
➢ had severe pneumonia
➢ Experience persistent respiratory dysfunction

Controls
n=5
n=10

<table>
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<th>CON (4M/1F)</th>
<th>CVD (7M/3F)</th>
</tr>
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<tbody>
<tr>
<td>Age (Avg)</td>
<td>69.6 ± 6.18</td>
<td>68.4 ± 6.62</td>
</tr>
<tr>
<td>TLC (%)</td>
<td>100.5 ± 11.5</td>
<td>90.4 ± 11.4</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>85.6 ± 17.9</td>
<td>85.9 ± 17.9</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>84 ± 17.0</td>
<td>88.5 ± 16.8</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>110.8 ± 13.8</td>
<td>87.3 ± 22.6</td>
</tr>
<tr>
<td>Cough (%)</td>
<td>2.1 ± 1.14</td>
<td>3.0 ± 1.14</td>
</tr>
<tr>
<td>Fatigue (%)</td>
<td></td>
<td>5.0 ± 1.14</td>
</tr>
<tr>
<td>Inability to return to work (%)</td>
<td>30</td>
<td></td>
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</table>

DLCO: diffusion capacity for carbon monoxide
FEV1: forced expiratory volume in 1 s

Inverse association between the presence of activated Tissue Resident Memory CD8+ T cells and pulmonary function
CORONAVIRUS

Immune signatures underlying post-acute COVID-19 lung sequelae

Cheon IS\textsuperscript{1,2,3}, Li C\textsuperscript{1,2,3}, Son YM\textsuperscript{1,2,3}, Goplen NP\textsuperscript{1,2,3}, Wu Y\textsuperscript{1,3}, Cassmann T\textsuperscript{1,2,3}, Wang Z\textsuperscript{1,2,3}, Wei X\textsuperscript{1,2,3}, Tang J\textsuperscript{1,2,3}, Li Y\textsuperscript{1,2,3}, Marlow H\textsuperscript{4}, Hughes S\textsuperscript{4}, Hammel L\textsuperscript{4}, Cox TM\textsuperscript{4,5}, Goddery E\textsuperscript{4}, Ayasoufi K\textsuperscript{4}, Weiskopf D\textsuperscript{4}, Boonyaratankornkit J\textsuperscript{5}, Dong H\textsuperscript{5}, Li H\textsuperscript{5}, Chakraborty R\textsuperscript{5,7}, Johnson AJ\textsuperscript{6}, Edell E\textsuperscript{6}, Taylor JJ\textsuperscript{6}, Kaplan MH\textsuperscript{6}, Sette A\textsuperscript{8,9}, Bartholmai BJ\textsuperscript{10}, Kern R\textsuperscript{3}, Vassallo R\textsuperscript{3,11} and Sun J\textsuperscript{1,2,3,11,14,17}

In contrast to previous reports studies have shown an inverse association between the presence of activated Tissue Resident Memory (CD8+ T cells) and pulmonary function. Further immunophenotypic analysis revealed a downregulation of cluster of differentiation 8 (CD8) positive T cells in the lung tissue compared to peripheral blood. Additionally, a high percentage of CD8+ T cells also expressed intracellular granzyme B, which are important cytotoxic markers. It is hypothesized that the presence of CD8+ TRM cells which are involved in protection, can also contribute to tissue sequelae of COVID-19 infection. Further studies are needed to fully understand the role of CD8+ TRM cells in the persistence of pulmonary lesions.
Detectable autoantibodies against multiple GPCRs in Long COVID patients

Contribution to dysautonomia and cardiovascular symptoms?
Réponses immunes antivirales inefficaces dans le COVID Long?

- Persistance virale?
- Lésions tissulaires induites par le virus?
- Longitudinal study of PCR+ patients with no or mild symptoms during acute SARS-CoV-2 infection

- 353 patients completed the 3 visits:
  - 123 with persistent symptoms
  - 230 without symptoms

Low SARS-Cov-2-specific IgG at the first visit is associated with persistent symptoms at the third visit (month 7)
A compromised specific humoral immune response against the SARS-CoV-2 receptor-binding domain is related to viral persistence and periodic shedding in the gastrointestinal tract

More frequent detection of SARS-CoV-2 viral RNA in anal samples of patients who retest PCR+ after the acute stage

Lower RBD-specific IgG in patients with viral rebound

Lack of a robust antibody response may be associated with viral persistence

Example of viral rebound
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COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters


Post-COVID-19, Case #10 with persistent signs

Persistence of viral antigen (NP+) in the olfactory epithelium

Inflammation: presence of Iba1+ MF/microglia in the epithelium

Link with anosmia?

Detection of SARS-CoV-2 RNA in the olfactory mucosa of Long COVID patients
Refining “Long-COVID” by a Prospective Multimodal Evaluation of Patients with Long-Term Symptoms Attributed to SARS-CoV-2 Infection


- Two groups of Long COVID patients: with or without detectable adaptive responses
- No significant differences in symptoms except for higher thoracic oppression in the « non-immunized » group
Antibody responses in Long COVID patients

S-flow assay

IgG: % Spike+ cells bound

IgG: MFI of Spike+ cells

HD healthy donor
AC acute infection
CO convalescent
LC Long COVID

S-flow assay by I. Staropoli in O. Schwartz Unit

Antibody measurements distinguish two groups of Long COVID patients
CD4+ T cell responses in Long COVID patients

Examples of primary CD4+ T cell line responses to a SARS-CoV-2 M peptide

- strong response to M141 in one seropositive Long Covid patient
- weaker but detectable response in one seronegative Long Covid patient

Suggests previous infection in the seronegative patient

J Kervevan, D. Salmon-Ceron
Anti-spike antibody response to natural SARS-CoV-2 infection in the general population

- 7,256 UK COVID-19 Infection Survey participants who were PCR+
- 24% were seronegative
  - Older
  - Lower initial viral load
  - Fewer symptoms

Persistently low or absent antibodies in a significant fraction of the SARS-CoV-2 infected population
Evaluer l’effet de la vaccination dans le COVID Long

Réponses immunes adaptatives

- Persistance virale ?

SARS-CoV-2

- Clairance virale ?
- Inflammation controlée ?
An immunological component to Long COVID that may be amenable to intervention

Vaccination doubled the rate of Long COVID patients in complete remission at 120 days
Conclusions :

Possibles mécanismes pathogènes du COVID Long (1)

Effets délétères d’une inflammation précoce :
- Micro-caillots dans les capillaires ?
- Dommage neuronal ou vasculaire ?
- Autre ?
Possibles mécanismes pathogènes du COVID Long (2)

- Traitement anti-inflammatoire ?
- Traitement anti-histaminique ?
- Inflammation chronique ?
- Activation des mastocytes ?
- Risque accru d’autoimmunité ?
Possibles mécanismes pathogènes du COVID Long (3)

- Vaccination ?
- Traitement antiviral ?

- Faibles réponses des cellules T et B
- Persistance virale dans sites sanctuaires?
- Dommage tissulaire localisé ?
Possibles mécanismes pathogènes du COVID Long (4)

- Différents types de COVID Long ?
- Besoin d’analyser la qualité des réponses immunes antivirales

- Réponses adaptatives de forte intensité mais de faible qualité
- Persistance virale dans sites sanctuaires ?
- Inflammation persistante
Remerciements

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