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Mini Review Article

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Role of Immunometabolism and Mitochondrial Health in Inflammaging and Fight against Viral Diseases

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The immune system provides defense against pathogens and functions to maintain tissue homeostasis for the life of the organism. These diverse functions of immunity are bio energetically expensive, requiring precise control of cellular metabolic pathways.

Activation of immune cells by environmental signals results in dramatic reprogramming of their cellular metabolism. The major goal of this metabolic rewiring is to provide the immune cell with sufficient energy (ATP) and metabolic intermediates to perform its effector functions in host defense and tissue homeostasis. In most instances, activated immune cells achieve this goal by simultaneously engaging in *cataplerosis and *anaplerosis.

Augmentation of certain metabolic programs might be clinically useful in dampening pathogenic autoimmunity or chronic inflammation in a diverse group of metabolic and degenerative diseases.

The transitions of immune cells from quiescence to activation and back to memory formation (at least for the adaptive immune cells) are highly dependent on and regulated by nutrients, metabolic intermediates, and the canonical regulators of cellular metabolism.

Infection with Coronavirus2 displays increasing fatality with age and underlying co-morbidity, in particular, with markers of the metabolic syndrome and diabetes, which seems to be associated with a "cytokine storm" and an altered immune response. This suggests that a key contributory factor could be immunosenescence that is both age-related and lifestyle-induced. As the immune system it is heavily reliant on mitochondrial function, then maintaining a healthy mitochondrial system may play a key role in resisting the virus. Furthermore, as viruses in general, and quite possibly this new virus, have also evolved to modulate immunometabolism and thus mitochondrial function to ensure their replication, this could further stress cellular bioenergetics. Unlike most sedentary modern humans, one of the natural hosts for the virus, the bat, has to "exercise" regularly to find food, which continually provides a powerful adaptive stimulus to maintain functional muscle and mitochondria. In effect the bat is exposed to regular hormetic stimuli, which could provide clues on how to resist this virus. Mitochondrial health, induced by a healthy lifestyle, could be a key factor in resisting the virus, and for those people who are perhaps not in optimal health, treatments that could support mitochondrial function might be pivotal to their long-term recovery.

The risk of severe morbidity associated with infection by Coronavirus2 rises with age and underlying co-morbidities, which indicate that up to 1.7 billion people, or 22% of the global population, could be at severe risk; the increased risk seems to be largely associated with an imbalanced and/or an excessive inflammatory response. One suggestion is that the severity could be related to a failure of inflammation resolution, leading to pulmonary hyper-inflammation and "cytokine storms". With increasing age there is often an exaggerated innate immune response to respiratory infections and rising inflammatory tone.

Overall, it seems that susceptibility to the virus is related to an age-related loss of adaptive immunity combined with an increased innate immune response. This "inflammaging" seems to be associated with T-cell immunosenescence and thymic atrophy; critically, exercise seems to be protective. The protective effect of exercise is informative, as the pathological severity of Coronavirus2 infection seems to be associated with many obesity-related co-morbidities, such as diabetes, in contrast, physical fitness is emerging as a preventative strategy against the virus.

This suggests that as well as age, lifestyle could be important in determining susceptibility to the virus. A modern sedentary lifestyle has effectively removed exogenous hormetic stimuli, such as physical activity, which is leading to an accelerated ageing phenotype. In short, a modern lifestyle could be accelerating the process of "inflammaging": obesity is associated with a pro-inflammatory state, increased inflammatory macrophages and altered T-cell homeostasis.

In contrast, exercise is largely anti-inflammatory, which is thought to explain its many benefits. A key player in this adaptation is the mitochondrion, as mitochondrial stress enhances mitochondrial function not only in muscle, but in multiple other organs with myokines playing a key role. For example irisin, which protects mitochondria, can protect against ischaemia/reperfusion (IR) injury in the lung. Irisin has also been found to favourably alter genes in adipocytes that are affected by the Coronavirus2 and to modulate macrophage reactive oxygen species (ROS), displaying anti-oxidant and anti-inflammatory properties. Critically, exercise can enhance mitochondrial function and capacity in peripheral blood mononuclear cells (PBMCs).

As mitochondria are pivotal in the immune response and many viruses in turn modulate mitochondria, it is possible that altered mitochondrial function may explain at least some of the variance in responses to Coronavirus2. As most cells in the body contain mitochondria, including immune cells, this would be expected and is now embraced by the concept of "immunometabolism". This is perhaps most clearly seen in the clinical phenotype of subjects with inherited mitochondrial defects who often display immunodeficiency and a much higher rate of infections – highlighting the reliance of the immune system on mitochondria.

It therefore seems that maintaining "mitochondrial health" is vital, which probably correlates with an effective mitochondrial reserve induced by factors like physical activity, such that when the system is "stressed" (e.g., by a virus), it can cope. Although the virus may only infect certain cells, the immune response is global and dependent on mitochondrial function in multiple tissues and organs. What is clear is that severity is associated with the hyperinflammation syndrome and involves dysregulation of many different cell types. This is to be expected, as throughout evolution, viruses have evolved to manipulate the immune system to hide from it, and can invoke immunosuppression, which in itself can become pathological, for instance, by modulating T-cells.

It now seems that the spike protein of Coronavirus2 can bind to T-cell receptors (TCRs), acting as a super-antigen and causing excessive activation of the adaptive immune system – potentially resulting in the hyperinflammatory syndrome. This is perhaps relevant as persistent antigenic stimulation can lead to T-cell exhaustion, which is associated with decreased oxidative phosphorylation and loss of mitochondrial function despite enhanced glycolysis – but can be reversed using anti-oxidants.

Data is now showing that COVID-19 patients do have populations of T-cells displaying mitochondrial dysfunction, as well as altered mitochondrial markers in monocytes – hinting that immune-metabolic phenotyping could be used to understand disease pathogenesis and possible treatments; this could include targeting mitochondria. In short, the immune system itself could well be a target for this virus. Apart from the virus targeting the TCR as a super antigen, there is evidence that other than it binding to the angiotensin converting enzyme (ACE) as its main receptor, it may also bind receptors on immune cells, such as CD147 and CD26, or neuropilin-1 (Nrp-1).

A poor lifestyle accelerates "inflammaging" which is associated with mitochondrial ill-health, and in some populations this predisposes them to a worse outcome. The implication of this idea in relation to current and suggested drug-based treatments and vaccine efficacy, the "long-COVID" syndrome, as well as how environmental factors may make some people more vulnerable. Understanding these concepts may help inform clinical strategy.

Mitochondrial Function in Inflammaging and Immunosenescence

Circulating extracellular vehicles (EVs) derived from immune cells seem to have emerged as a means of studying immunosenescence. In particular, they show an age-related decline in mitochondrial function – which could be related to dysfunctional mitophagy. In fact, mice engineered to have dysfunctional T- cell mitochondria display accelerated senescence and "inflammaging", highlighting the point that T-cells can determine organismal fitness and lifespan. This data indicates the importance of a healthy T-cell response in defending against the virus.

The underlying aetiology for "inflammaging" has long thought to be associated with mitochondrial dysfunction as suggested by Nick Lane in 2003. Decreasing mitochondrial function can reduce T-cell function and enhance immune senescence, as mitochondria are pivotal in metabolic reprogramming towards the Warburg effect. Indeed, as mitochondrial dysfunction can lead to "inflammaging", the observed increase in older people of mitokines could be an attempt by the system to restore homeostasis as many are anti-inflammatory. Unfortunately, for many, this response doesn't fully compensate. This is why "exogenous" factors, such as physical activity or calorie restriction seem to be required to optimise function; these were normal factors during evolution, but are not in our modern sedentary and obesogenic environment.
One aspect of ageing is a failure to remove damaged components, for instance, dysfunctional mitochondria via mitophagy, which could lead to immune dysfunction. It has been suggested that imbalances in mitochondrial mass could be responsible for ageing-related T-cell subset dysfunction, which would suggest a failure of mitophagy. Indeed, activation of mitophagy/autophagy is thought to be a pivotal mechanism in slowing ageing and inhibiting inflammation during calorie restriction (CR): CR/intermittent fasting has been suggested as a defence against the Coronavirus2 as it is anti-inflammatory.

That T-cell mediated immunity may be playing a powerful role in protecting against the virus, as many asymptomatic people, or those who have only had mild symptoms, show low levels of anti-Coronavirus2 antibodies but a strong T-cell mediated response against the virus. In contrast, more severe disease is associated with more rapid seroconversion and the presence of inflammatory markers, such as C-reactive peptide (CRP). In fact, it now appears that the severity of infection positively correlates with a decreased type 1 interferon (IFN1) response, but an exaggerated inflammatory response, characterised by high levels of interleukin 6 (IL-6) and tumour necrosis factor alpha (TNFα) – possibly related to excessive activity of nuclear factor kappa B (NF-κB). This latter finding could be related to an auto-inflammatory loop in the lungs. It does seem that in some people that the transcriptional

response to Coronavirus2 is imbalanced, with a less than optimal interferon-I and -III response, but an exaggerated chemokine one; this may represent an evolved manipulation of the immune system by the virus that worsens the outcomes for older patients with co-morbidities as they cannot clear the virus properly.

Data from autopsies of deceased COVID-19 patients show that tissue inflammation and organ dysfunction do not map to the cellular distribution of the virus, hinting at tissue-specific tolerance. In fact, severe inflammatory changes seem to be largely restricted to the lungs and the reticulo-endothelial system. This suggested that COVID-19 related deaths were due to immune-mediated, rather than pathogen-mediated organ inflammation and injury. It may therefore be relevant that IFN1 can also have some anti-inflammatory actions, modulating for instance, NLRP1/3 inflammasomes and inhibiting interleukin-1 (IL-1) production. Type 1 interferons are key in modulating T-cell responses and resistance to viruses.

The Immunological Profile of COVID-19 Patients

There is consensus that in severe COVID-19 infection, an exacerbated pulmonary and systemic inflammatory response occurs, with increased serum levels of inflammatory markers, such as C-reactive protein (CRP), lactic dehydrogenase (LDH), ferritin, D-dimer, and IL-6, all of which may result in cytokine storm, similarly to SARS and MERS. Table 1: Compares the Blood Immunological Profile of Patients with Moderate and Severe COVID-19.

Table 1: Immunological Findings in Blood of Patients with Moderate or Severe COVID-19.

References	COVID-19 Moderate	COVID-19 Severe
Zohu et al.	No Data	↓ Lymphocyte ↓ CD4
Huang et al.	↑ PMNs ↓ Lymphocyte	↑ IL-2, IL-7, IP10, MP1A, TNF
Wu et al	↑ PMNs, ↓ Lymphocytes, ↓ CD4	↑ IL-6 (at risk of Death)
Qin etal.	No Data	↑ PMNs, ↓ Lymphocytes, ↓ T (Th1 & Treg), B, NK, ↑ T Naïve, ↓ T memory, ↑ IL-2R, IL-6, IL-8, IL-10
Chen et al	↓ Lymphocytes, ↑ IL-2R, IL-6, IL-10, TNF, IL-1B, IL-8	↓ ↓ Lymphocytes, ↓ CD4 & CD8 ↑ ↑ IL-2R, IL-6, IL-10, TNF
Wan et al	↓ CD4, CD8, B, NK, IL-4, IL-10, IL-17, TNF, ↑ IL-6, IFN	↓ ↓ CD4, CD8, B, NK, ↑ ↑ IL-6
Zheng et al	↓ CD8, NK	↓ ↓ CD8, NK
Lei et al	↓ NK, PD-1	
Zhou et al	↓ Lymphocytes, ↓ Monocytes, ↓ CD-4, PMNs, B, NK, ↑ PD-1^{+}, ↑ Monocytes, CD14^{+}, CD16^{+}	↓ ↓ Lymphocytes, ↓ ↓ Monocytes, ↓ CD4, (↑ CD69^{+}, CD38^{+}, CD44^{+}), CD8, ↑ PD-1^{+}, ↓ CD8^{+} IFN-γ^{+}GM-CSF^{+}
Xu et al		↑ ↑ CD4^{+}, HLA-DR^{+}, ↑ ↑ CD8^{+}, CD38^{+}, ↑ ↑ CD4^{+}, CCR6^{+}, Th17
Bordoni et al	↓ Lymphocytes, ↓ CD3, ↑ MDSC, ↑ IL-1b, IL-6, IL-8, TNF	↓ Lymphocyte, ↓ CD-3, ↑ MDSC, ↓ NK, IL-1b, IL-6, IL-8, TNF

Changes in Circulating Cells.

Regarding cellular changes, most studies show that lymphopenia, although present in moderate infections, is more pronounced in severe COVID-19 and affects mainly T cells, including CD4 Th1 and Tregs, but particularly CD8. Also, in severe COVID-19 the number of circulating naive T cells increases and the number of memory T cells decreases. Circulating CD8 in patients with severe COVID 19 exhibited phenotypes associated with abnormal functionality (CD8+IFN-γ+GM-CSF+) and exhaustion (Tim3+Pd-1+) or (NKG2+CD107a+IFN-γ+grzB+). The latter phenotype is also found in NK cells. Interestingly, a negative correlation has been reported between serum levels of IL-6 and IL-8 and the perforin content of NK and CD8+ cells, which also negatively correlate with the increased number of circulating myeloid-derived suppressor cells (MDSC). Although the number of CD4 cells decreased, they expressed activation markers such as CD69, CD38, CD44, and HLA-DR, including Th17 CD4+CCR6+ cells. NK cells also decreased in both moderate and severe cases of the disease. Monocytopenia is also found in COVID-19 patients, particularly in severe cases, but the circulating monocytes belong mainly to the CD14+CD16+ inflammatory monocyte subset.

Changes in Cytokine/Chemokine Plasma Levels

Plasma levels of cytokines and chemokines are also increased in COVID-19, but are higher in severe infections, and includes IL-2, IL-2R, IL-6, IL-7, IL-8 IL-10, IP10, MIP1A, and TNF-α. High levels of plasmatic IL-6 have been consistently reported in COVID-19 and even appear to be associated with poor prognosis and risk of death. Thus, its measurement has been proposed as a good biomarker to monitor these patients. Liu et al. studied sixty COVID-19 patients, half of whom had a severe case of the disease and high IL-6 levels. Baseline IL-6 was higher in more severe cases and correlated with bilateral interstitial lung involvement and high body temperature, as well as with other serum markers for acute inflammation. Of the 30 patients with severe disease, 25 improved clinically and showed a significant decrease in IL-6 levels, while these levels increased in three patients with disease progression. Coomes et al. performed a meta-analysis of 16 papers that included 10,798 Chinese patients, in order to test the evidence that IL-6 levels correlate with COVID-19 severity, and the effectiveness of treatment with Tocilizumab, a humanized monoclonal antibody against IL-6 receptor. All COVID-19 patients had increased levels of serum IL-6, but it was 2.9-fold higher in patients with severe COVID-19. Twenty-one patients treated with tocilizumab improved clinically with no adverse effects or deaths. Also, Xu et al. reported very promising results using Tocilizumab treatment in 20 patients with severe COVID-19; all patients improved remarkably within a few days and all were discharged from the ICU within an average of 15 days.

Dynamics of the Immune and Inflammatory Responses

During the course of COVID-19 infection, viral replication, immune response, and inflammatory reaction are dynamic events that can change rapidly, resulting in different outcomes; several reports have addressed these changes. Thevarajan et al. reported the case of a patient with mild to moderate infection that was clinically, virologically, and immunologically followed over the course of the disease, including her recovery 13 days after the initiation of symptoms, and through to Day 20 at which point she had recovered. The virus was detected on Days 4 and 5 via nasopharyngeal swabs but was undetectable thereafter. IgM and IgG antibodies progressively increase from Day 7 through to Day 20. Circulating antibody-secreting B cells, CD3−CD19+CD27hiCD38hi, appeared in the blood at the time of viral clearance (Day 7), peaked on Day 8, and remained high through to Day 20. Follicular helper T cells (TFH), CD4+CXCR5+ICOS+PD-1+, were also detected on Day 7 and continued increasing through to Day 20. Activated cytotoxic CD8 T cells, CD8+CD38+HLA-DR+, were also present on Day 7, increased through to Day 9, and then decreased through to Day 20, although with values higher than in healthy controls. There was no increase in inflammatory CD14+CD16+ monocytes, nor in activated NK CD3−CD56+HLA-DR+ cells. Regarding serum cytokines, of the 17 pro-inflammatory cytokines studied, only low levels of MCP1/CCL2 were found on Days 7–9. This case is interesting since there are very few studies on patients with mild infections and because IgM and IgG antibodies, antibody secreting B cells, CD4 TFH cells, and activated cytotoxic CD8 cells were shown to be circulating before resolution of the symptoms.

Ong et al. compared the blood transcriptional profile of three patients in early phases of Infection -one of whom evolved to a severe disease- with 10 healthy volunteers. The main findings in the patient who progressed to severe disease was that only IL-1A and IL-1B preceded the nadir of the respiratory function, and that the expression of most inflammatory genes, particularly IL-6, IL-2, TNF-α, and IFNA1/13, peaked thereafter. Also, in this patient, transcripts associated with HLA, CD4, and CD8 T cell activation were diminished, while in the other two patients, who did not progress to severe disease, the transcription profile was comparable to that of healthy controls. The authors suggest that in the first case the decreased T cell activation may have helped the inflammatory response by the IL-1 pathway, while in the other two cases the low inflammatory response allowed a moderate T cell response.

Effect of Age

One of the risk factors most strongly associated with severe COVID-19 and death is advanced age. Immunosenescence present in the elderly affects innate immunity, but mainly T cell-dependent adaptive responses. In addition, experimental evidence suggests that elderly mice have increased levels of proinflammatory cytokines and that their alveolar macrophages are refractory to activation by IFN-γ. This finding is relevant since the protective response that eliminates the virus depends on cytotoxic CD8 cells and Th1 responses, with IFN-γ playing an important role in both responses, as demonstrated in SARS and MERS.

Increased susceptibility in the elderly to present with severe COVID-19 forms contrasts with the lower frequency of these forms in children and young adults. Ludvigsson reviewed 45

publications on COVID-19 and found that 1–5% of the patients are children who, although they present with fever and respiratory symptoms, experience milder symptoms and among whom death was extremely rare. The increase in inflammatory markers and lymphocytopenia were also less common in children. Brodin postulated the following three explanations for the milder COVID-19 presentation in children:

1. The immune response is qualitatively different in children and adults, something that has been extensively studied;
2. The simultaneous presence of other viruses in the mucosa of the respiratory tract, common in children, could limit the growth of Coronavirus2 by direct virus-to-virus competition;
3. The treatment with ACE2 inhibitors and angiotensin receptors blockers, a common procedure in hypertensive adults, up-regulates ACE2 expression, increasing susceptibility to Coronavirus2 infection. These theoretical possibilities require clinical and experimental validation.

Studies in Bronchoalveolar Lavage Fluid (BALF)

Findings in blood do not necessarily explain the events occurring in tissues directly affected by the infection, thus studies in bronchoalveolar lavage fluids (BALF) are very relevant (Table 2). Xiong et al. used RNA-seq to study BALFs and peripheral blood mononuclear cells (PBMC) transcriptome from three COVID-19 patients and from three healthy subjects. The BALF cells in these patients expressed 9,609 genes, 679 of which were up-regulated and 325 down-regulated, as opposed to controls. In PBMC, 15,726 genes were expressed, with 707 up-regulated and 316 down-regulated. BALF cells from patients showed a differential expression of genes related to viral invasion and replication (viral RNA was detected in BALFs of all three patients) such as membrane-associated proteins, endoplasmic reticulum, and viral transcription. In contrast, PBMCs showed increased expression of genes related to complement activation, immunoglobulins, and B cell-mediated responses, while some genes corresponded to the acute inflammatory response. The down-regulated genes in patients' BALF were mostly related to activation of the immune response. Comparison of the cytokine genes showed that in BALFs the genes for IL-10, CCL2/MCP-1 (together with its CCR2 receptor), CXCL10/IP-10, CCL3/MIP-1A (together with its CCR5 receptor), and CCL4/MIP1B were differentially up-regulated. Another relevant finding was that in PBMC, genes related to autophagy, apotopsis, and p53 pathways were up-regulated, a finding that could be related to the lymphopenia detected in the three patients. Interestingly, IL-6 transcripts were not increased in PBMCs, although the patients had high plasma levels of such cytokine, suggesting that circulating IL-6 could have been produced in the lungs, either by alveolar epithelial cells or by recruited inflammatory cells.

Table 2: Differentially expressed genes (DEGs) up-regulated in bronchoalveolar lavage fluid (BALF) of patients with moderate or severe COVID-19.

References	Upregulated Genes
Xiong et al	IL-10, CCL2/MCP-1, CCR2, CXCL10/IP-10, CCL3/MIP-1A, CCR5, CCL4/MIP-1B
Liao et al	FCN1-SPP1 inflammatory Monocytes/Macrophages in severe disease, CD8 activation and effector molecules and higher CD8 TCR Repertoire in moderate ilnesse
Zhou et al	CXCL17, CXCL8, and CXCL2, CXCR2, CCL2, CCL7, IL-1β, ISGs, IL-17, TNF, and NF-KB signaling Pathways.

In another study, Liao et al. used scRNA-seq and scTCR-seq to determine BALF cells' transcriptional signature in three patients with severe and another three with moderate COVID-19, and compared them with eight healthy subjects, previously studied. Their main findings were related to macrophages and CD8 cells. Macrophages were predominant in BALFs from patients with severe infection, with a minor proportion of T and NK cells, as compared with patients with moderate disease. Macrophages were classified in 22 clusters, according to their expression of FCN1 (monocyte-derived), SPP1 (pro-fibrotic), and FABP4 (alveolar macrophages). These genes were differentially expressed both among the two groups of patients and the healthy controls. FABP4 was preferentially expressed in healthy controls and in patients with moderate COVID-19, while FCN1 and SPP1 were expressed in patients with severe COVID-19. Further macrophages classification resulted in four groups: Group 1, FCN1hi only; Group 2, FCN1loSPP1+; Group 3, FCN1−SPP1+; and Group 4, FABP4+. Group 1 macrophages expressed genes associated with inflammatory monocytes; Group 2 expressed chemokines and interferon stimulated genes (ISG); Group 3, genes related with immune regulation and profibrotic events; and Group 4 were alveolar macrophage typical genes. According to the investigators, these results suggest that during Coronavirus2 infection, inflammatory monocytes (FCN1+) are recruited from the circulation into the lungs, where they differentiate into SPP1+ macrophages, constituents of the severe inflammatory reaction. Analysis of the BALF transcriptome showed that T and NK cells are increased in COVID-19 patients, compared to healthy controls, which according to their gene expression can be classified in NK, CD8, CD4, Tregs, and proliferating cells. An important finding was that genes related to activating molecules, migration, calcium signaling, and effector molecules were highly expressed by CD8 cells in patients with moderate infection, compared with patients with severe COVID-19; this further supports the role of CD8 cells in the elimination of the virus and their subsequent, protective immunity. In contrast, patients with severe disease had a higher expression of genes related to proliferation, energy generation, and initiation of translation. These results suggest that in patients with moderate infection CD8 cells are more differentiated and efficient, while in severe Infection T cells are in a proliferative stage. Additionally, the finding that the TCR repertoire is higher in CD8 than in CD4 cells, suggests a larger clonal expansion of the CD8 cells taking part in the resolution of the infection.

Zhou et al. used metatranscriptomic sequencing to profile immune signatures in the BALF of eight COVID-19 patients, compared to 146 community-acquired pneumonia patients and 20 healthy controls. Their results show that in BALF from COVID-19, the differentially expressed genes (DEGs) included up-regulated proinflammatory chemokines genes, such as CXCL17, CXCL8, and CXCL2, as well as the CXCR2 receptor, critical to neutrophil recruitment, and CCL2 and CCL7, needed for monocyte recruitment. These authors also found that COVID-19 patients up-regulated IL-1β, antiviral Interferon stimulated genes (ISGs), and genes related to the IL-17, TNF, and NF-κB signaling pathways. In addition, the cellular analysis showed an increased neutrophil to lymphocyte ratio (NLR) in patients with COVID-19 compared to patients with other pneumonias.

Taken together, findings in BALF demonstrate both a highly dysregulated innate and adaptive immune response in the affected lungs of patients with COVID-19.

Conclusions

After the initiation of the COVID-19 pandemic in China, which extended quickly worldwide to greatly impact public health and economies, the amount of information gathered on all aspects of the infection and the celerity with which the international scientific community has shared such information is truly amazing. A note of caution is therefore in order, if such information is to be used in defining new diagnostic, therapeutic, or prophylactic protocols. It is also important to consider the brief amount of time elapsed since the beginning of the pandemic, during which time it has not been possible to gather sufficient results from in vitro and experimental animal models to ensure further understanding of COVID-19's biology.

Although studies of asymptomatic infected individuals are lacking, the immunological profiles of patients with moderate infections indicate a protective T cell-dependent response, in contrast to patients with severe disease who exhibit an exacerbated systemic inflammation, with signs of T cells exhaustion [1-15].

The following fundamental aspects need to be defined through close collaboration between clinicians and basic researchers, with strong support from the public and private financial agencies:

1. The alterations of the immune regulation that allow the disease to advance from an asymptomatic or mild infection to a severe disease with poor prognosis. Translational immunological research focusing on the cellular and molecular aspects of the virus-host interaction, using sophisticated bioinformatics and system biology tools, must be pursued. This includes experimental animal models required for a deep understanding of COVID-19's immunopathogenesis. Besides patients with moderate and severe COVID-19, studies in humans must include seropositive asymptomatic individuals and patients with virologically confirmed mild infections. These subjects should be studied in long-term follow-up cohorts.
2. The genetics of resistance/susceptibility at the various stages of the infection and the disease. Topics like the resistance per se in exposed non-infected individuals, and the genetic risk factors for the progression from asymptomatic to moderate and severe disease must be prioritized. Initiatives like "COVID Human Genetic Effort" (www.covidhge.com) are working in that direction.
3. Based on the previous points it is necessary to find correlates of protective immunity and prognostic biomarkers to guide personalized management of infected individuals in order to prevent their progression to severe forms of the disease.
4. New pharmacological and immune-based treatments must be developed simultaneously with rigorous evaluation of treatments already available. The analysis of the currently available pharmacological treatments, or those under development, is beyond the scope of this review. Possible immunotherapies may include: convalescent plasma, already assayed in a small number of patients; monoclonal antibodies against the IL-6 receptor and interferon β; and Leronlimab CCR5 blocking antibody, among others. Fortunately, a good number of controlled clinical assays have been initiated under strict supervision from regulatory agencies (https://clinicaltrials.gov/ct2/results?cond=covid&term=&cntry=&state=&city=&dist=) which will hopefully provide, within a prudential time, therapeutic agents for the efficient treatment of COVID-19 patients.
5. Development of vaccines to prevent, and hopefully eliminate, Coronavirus2 and other coronavirus2 infections. As expected, many investigators and biotechnology companies are dedicating all their efforts and resources to obtaining an effective vaccine in the shortest time possible. It is important to note that development of an efficient vaccine requires a deep understanding not only of the viral antigens and epitopes, but also of the immunological events leading up to the epitope presentation and recognition resulting in the establishment of a protective immune memory, the effector mechanisms in response to the antigens, and the adjuvants present in the proposed vaccine, one that would have minimal side effects.

Finally, it is important to remember what many investigators of SARS and MERS have written in their publications, long before the emergency of COVID-19 pandemics: what will be learned from this pandemic must be used to prevent future coronavirus2 epidemics.

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