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Review

COVID-19. Biology, pathophysiology, and immunology: a pathologist view

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Summary

Even if the SARS-CoV-2 pandemic has been declared over, several risks and clinical problems remain to be faced, including long-COVID sequelae and possible outbreaks of pathogenic variants. Intense research on COVID-19 has provided in these few years a striking amount of data covering different fields and disciplines, which can help to provide a knowledge shield against new potential infective spreads, and may also potentially be applied to other fields of medicine, including oncology and neurology. Nevertheless, areas of uncertainty still remain regarding the pathogenic mechanisms that subtend the multifaceted manifestations of the disease. To better clarify the pathogenesis of the disease, a systematic multidisciplinary evaluation of the many mechanisms involved in COVID-19 is mandatory, including clinical, physiological, radiological, immunological and pathological studies. In COVID-19 syndrome the pathological studies have been mainly performed on autopsy cases, and only a few studies are available on biopsies. Nevertheless, these studies have provided relevant information that can substantially contribute to decipher the complex scenario characterizing the different forms of COVID-19 and long-COVID-19. In this review the data provided by pathological investigations are recapitulated and discussed, in the light of different hypothesis and data provided by clinical, physiological and immunological data.

Key words: SARS-CoV-2, COVID-19, long-COVID, post-COVID, pathogenesis, lung biopsy

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COVID-19

Coronavirus disease 2019 (COVID-19) is characterized by a profound variability in clinical presentation and pathological features with a large majority of patients developing mild symptoms and a minority experiencing an interstitial pneumonia that can rapidly progress to severe life threatening respiratory failure requiring mechanical ventilation or even extra corporeal membrane oxygenation (ECMO) [1]. It is now widely accepted that SARS-CoV-2 infection can trigger a hyper-inflammatory response in susceptible individuals (also termed “cytokine storm” or cytokine release syndrome) [2], and several hypothetic schemes have been proposed to describe the pathogenic role of different cell types and mechanisms leading to different disease phases and endotypes. The heterogeneity of clinical presentations is likely conditioned by the viral burden, the efficacy of innate and adaptive immune responses, a genetic predisposition, and the occurrence and severity of pre-existing comorbidities (such as older age, obesity, hypertension, diabetes) [3]. The complex interactions of

SARS-CoV-2 with human cells and tissues have been explained at the cellular and molecular levels, revealing how viral ligands (mostly the spike protein) and receptors on different cell types can allow viral entry [4]. Interactions between the pathogen and host defenses are mediated by a variety of viral gene products that interfere with normal development of innate immunity, particularly focusing on the cGAS/Sting pathway [5-8].

The cGAS/Sting pathway and COVID-19

The cGAS-STING pathway is a pattern recognition receptor involved in the detection of DNA in the cell cytosol where it triggers a robust type I interferon response against viral and bacterial infections, as well as self DNA released in damaged and senescent cells [9,10]. Upon DNA binding within the cytoplasm cGAS (Cyclic GMP-AMP synthase) is able to generate the second messenger cyclic cGAMP necessary to activate Sting (*Stimulator of INF Genes*) with eventual transcriptional induction of type I interferons [11]. Paradoxically, the activation of cGAS/Sting is able to effectively block the viral infection, but its activation is the main driver of the cytokine storm in severe disease [12-15]. These findings suggest that the activation of innate immunity may be relevant in viral clearance in healthy people, but is a severe pathogenic driver in predisposed individuals. In line with this hypothesis is the experimental observation that in bats, where the cGAS/Sting pathway is partially defective and IFN production is dampened, SARS-CoV-2 infection is not accompanied by disease manifestation [16]. The impairment of IFN production may represent an early key pathogenic factor in COVID-19 [17-19], and several immune mechanisms and involved cell types have been investigated to clarify the role of this impairment in triggering the cytokine storm [3,20-24]. Among the critical issues is how SARS-CoV-2, a single-strand RNA virus, can induce the activation of the DNA sensor cGAS/Sting [25,26]. A genetic basis has also been recently demonstrated in asymptomatic patients, providing robust early defense against the viral infection [27].

The search of factors involved in predisposition to severe disease has produced a striking amount of information, and several lines of evidence have been provided regarding the critical role of conditions and comorbidities in increasing the risk of severe complication (old age and age related diseases, diabetes, neurodegenerative disorders, obesity, hypertension, etc.) [28]. In these conditions a chronic low-grade systemic inflammation (inflammaging) related to progressive dysregulation of cGas/Sting axis is often present [29-33].

Human endogenous retroviruses and COVID-19

It has been widely demonstrated that in severe and critical patients a highly impaired (IFN) type I response occurs, characterized by no IFN-β and low IFN-α production and activity [34]. In a proportion of cases the deficiency can be ascribed to genetic inborn errors in genes that regulate interferon production [35-38]. Another possible cause of innate immune deficiency in COVID-19 is the presence of anti-interferon auto-antibodies [39-41]. Interestingly, these auto-antibodies are found in severe COVID-19 patients together with human endogenous retroviruses (HERV-W-env) auto-antibodies [42]. Endogenous retroviruses (HERVs) are ancient integrations of exogenous viruses into the germ cells of mammalian ancestors (between 100 and 40 million years ago), and they now occupy approximately 8% of the human genome [43,44]. HERV genes are defective and are not able to produce infectious viral particles, but some HERV can produce retroviral transcripts and proteins, which are pathologically related to various diverse conditions including autoimmune, infectious, neurological and oncologic diseases and also represent promising therapeutic targets [45-51]. Abnormal levels of HERV transcripts have been demonstrated in COVID-19 and post-COVID-19, and a direct correlation has been demonstrated between the severity of COVID-19 and HERV expression [52-55]. A complex modulation of HERVs characterizes different COVID-19 endotypes as revealed by high-throughput analysis of HERV loci expression and this diversity may have an impact on the immune-pathogenesis and clinical manifestations and outcome of the disease [56]. In particular, the *in vitro* exposure to SARS-CoV-2 is able to activate the expression of the HERV-W pro-inflammatory envelope protein (ENV) in peripheral blood mononuclear cells [57,58]. When abnormally expressed, HERV transcripts can profoundly alter the innate immunity [59], and their “awakening” is considered a key factor in triggering the cGAS/Sting and other pro-inflammatory pathways with eventual development of cytokine storm and severe disease evolution in predisposed individuals [59]. HERV-mediated cGAS/Sting triggering of innate inflammation in nervous tissues is a major pathogenic mechanism in neurological and psychiatric diseases and may be also involved in the neurological complications observed in COVID-19 and long-COVID-19 [49, 60-62]. Most HERVs are epigenetically silenced, a process ensuring genomic stability that is progressively reduced in aging and toxic or infection-related stress, all conditions representing also risk factors for severe COVID-19 disease [63-65]. Retroviral-like particles are abnormally induced in se-

nescent cells and their repression may alleviate tissue degeneration and organismal aging thus representing a potential therapeutic target [66].

The contribute of Pathology

From the beginning of the pandemic a large number of post-mortem studies have been performed worldwide, providing relevant information regarding the organ damages occurring in severe cases [67-69]. The most frequent pathological pattern observed in autoptic lung is "diffuse alveolar damage" (DAD), with hyaline membranes, alveolar fibrinous edema and type-II alveolar-epithelial cell (AECII) hyperplasia. In many studies the occurrence of thrombotic events was reported, varying from small capillary clots to thrombosis in the larger vessels [70-72]. Nevertheless, these post-mortem studies did not explain the clinical heterogeneity of COVID-19, as revealed by immunological, radiological, and clinical studies, accounting for the evidence of different disease phenotypes [73,74]. A possible explanation of this heterogeneity has been provided by studies of lung biopsies of patients with early/mild COVID-19 pneumonia as defined by typical lung opacities at CT scan, variable degree of hypoxemia but with no needs of intubation and mechanical ventilation [75,76]. In this series a common and peculiar pattern of lung modifications was observed, characterized by acute lung injury but without the typical features of the DAD pattern. Hyaline membranes were in fact absent and interstitial fibrosis was either focal or absent. Alveolar epithelial type II cells (*AECII)* hyperplasia was heterogeneous and characterized by an unusual "patchy" distribution, with AECII clusters ranging from isolated small aggregates to wide proliferation of micronodular and/or pseudo-papillary sprouts, interposed to normally looking type-I pneumocytes. An unexpected finding was the occurrence of a diffuse enlargement of pulmonary interstitial blood vessels (both capillaries and venules). At immunohistochemical analysis abnormal phenotypes were demonstrated in both the epithelial (AECII) and vascular components, with robust expression of molecules involved in the STAT3 pathway (pSTAT3, IL-6). An interesting finding was the strong and diffuse expression of molecules related to innate-immune activation (PDL1 and Ido1) in interstitial blood vessels [75,76].

Indoleamine 2,3-dioxygenase (Ido1 and Ido2) in COVID-19

Indoleamine 2,3-dioxygenase enzyme activity is the rate-limiting step of the aminoacid tryptophan (Trp) degradation in extra-hepatic sites. IDO1 expression in normal tissues is negligible, but inflammatory stimuli can trigger its expression, mainly mediated by IFN-gamma [77-79]. Ido1 has a relevant role in immune regulation suppressing effector T cell functions and favoring the development of regulatory T cells by Trp depletion at the local site of inflammation and the production of immunosuppressive Trp metabolites (kynurenine, kynurenic acid, xanthurenic acid). The only tissue where Ido1 is constitutively expressed and functional is the human placenta, where the enzyme is able to maintain feto-maternal immune-tolerance and antimicrobial functions. Ido1 is constitutively expressed in chorionic vascular endothelium, with highest levels in the microvasculature, where it regulates vascular tone and placental perfusion, thus providing a regular blood flux to the growing fetus [80-82]. Accordingly, Ido1 deficiency is related to pregnancy disorders such in intrauterine growth restriction (IUGR) and pre-eclampsia [82-86]. Critical levels of endothelial and/or perivascular concentrations of vasoactive Trp metabolites may be necessary for effective control of the vascular tone [87]. Interestingly, the activity of endothelial Ido1/kynurenine axis on vascular tone is likely more effective in organs characterized by peculiar circulatory systems such as the placenta and lung, both characterized by reduced blood pressure and both constitutively expressing Ido1 [88, 89]. Accordingly, Ido1 protects against development of pulmonary hypertension [90]. An endothelial protective role of Ido1 has been also demonstrated in experimental ischemia-reperfusion, atherosclerosis and acute lung allograft injury, thus suggesting a role for the TKP activation in contrasting vascular dysfunction [91-95]. Vascular dysfunction (vascular inflammation, disruption of the endothelial homeostasis, edema, and life-threatening coagulation abnormalities) is a distinct feature of severe COVID-19 and is common in conditions predisposing to severe COVID-19 (diabetes, obesity, older age, etc.) [96-99].

Two Ido paralogs exist (Ido1 and Ido2) characterized by distinct expression patterns and roles in immune and vascular tone regulation [100-102]. Ido2 is prevalently expressed in severe COVID-19 pneumonia [103], and a pathogenic mechanism based on Ido1/ Ido2 imbalance has been hypothesized in COVID-19, switching from protective vasodilatation to vascular dysfunction and hypertansion [104]. The concurrent immunosuppressive and vasodilator activity of Ido1 in COVID-19 early/mild pneumonia may have a negative role in inducing vasoplegia, ventilation/perfusion mismatch (accounting for the hypoxia occurring in COVID-19) and lymphocyte depletion, but might help in contrasting the life threat-

ening consequences of hypertension and vascular dysplasia as observed in severe COVID-19 pneumonia. It is worthwile to note that the concurrent promotion of pulmonary hypertension can be exerted in COVID-19 by up-regulation of HERV-K [105].

Vascular dilatation is also evident at CT scan in early/mild COVID-19 pneumonia (described as "vascular enlargement pattern") [106-108], and this pattern is likely responsible of the peculiar pulmonary hemodynamic profile, perfusion abnormalities, and hypoxia ("happy hypoxia") characterizing mild COVID-19 pneumonia [109-111].

Cross-talk of Idos and HERVs in COVID-19

Several links exist between HERV-mediated mechanisms and the Ido1/Trp/Kyn pathway. HERVs can act as proximal regulatory elements in promoting interferon responses and the expression of Ido enzymes strictly depends on IFNs [79,112]. Both Ido1 and HERVs are physiologically expressed in the placenta and exert important concurrent roles in mammalian placental development and functions [113]. Ido1 enzyme activity is in fact necessary to provide sufficient vascular perfusion and to avoid immune rejection of the fetus. HERVs are also necessary for placental morphology and trophoblast invasiveness, inducing syncytialization through the synthesis of syncitins, highly fusogenic env-like glycoproteins expressed at high levels in human placenta [47,114]. Syncitins help maintain trophoblast stem cell proliferation, placental angiogenesis and contribute to maternal immune system suppression and tolerance toward the fetus [115-118]. In addition, syncytins have a role in amino acid transport and allow protection against viral infection [119]. In line with this evidence, a decrease in syncytin levels has been demonstrated in fetal growth restriction and pre-eclampsia [120-124]. It is possible to speculate that in COVID-19 an abnormal fusogenic activity of syncitins may be related to the observed formation of AECII clusters in mild pneumonia [75], and epithelial multinucleated syncitia in severe pneumonia [125]. When abnormally activated in infected lungs these molecular mechanisms likely determine perturbations of immune responses and vascular tone control with eventual triggering of autoinflammatory responses and vascular dysplasia in aging and susceptible individuals.

Long-COVID-19 (PACS)

A proportion of patients may suffer from post-acute sequelae experiencing complications affecting different organs (a condition defined as "long COVID-19", or "post-acute COVID syndrome" (PACS) [126-133]. Most common symptoms in PACS include systemic manifestations (fatigue, asthenia, poor concentration, wandering fever), pulmonary functional impairment (dyspnea, cough, reduced DLCO), neuropsychiatric manifestations (sleep disturbances, cognitive dysfunction, depression, mood changes, anxiety, headache, taste, and/or smell loss), and cardiac manifestations (chest pain, palpitations, tachycardia, dysrhytmias), as well as a variety of muscle-skeletal, renal, dermatological, and gastrointestinal manifestations [131]. In a series of lung biopsies the most frequent findings were similar to those observed in acute early/mild COVID-19 pneumonias (vascular enlargement and abnormal endothelial expression of Ido1, PD-L1 and STAT3) [75,134]. The persistence of Ido1 activity in pulmonary vessels may be involved in vasoplagia and hypoxia. In both COVID-19 and PACS, dysregulation of the Tryptophan/Kynurenine pathway is likely to be involved in the development of neurological complications by decreasing the availability of Trp (necessary for conversion to 5-HT and melatonin, and by altering the physiological proportions of neurotoxic (quinolinic acid, 3-hydroxykynurenine) versus neuroprotective (kynurenic acid, picolinic acid, and the essential cofactor NAD+) Trp metabolites [135-138]. Persistence of HERV transcription products may be involved in PACS inducing long-lasting symptoms of chronic inflammation in different organs [49,54,139].

Conclusions

In conclusion, a pathogenic scenario can be hypothesized where a cascade of events follow SARS-CoV-2 infection of ACEII expressing epithelial cells. Central in this scheme is the production of a variety of HERV products that can interfere with the functions of non-infected cell types (monocytes, myeloid-derived suppressor cells, dendritic cells, lymphocytes, endothelial cells, etc.) in different tissue compartments. The clinical development and severity of the disease (asymptomatic, mild, severe) is likely determined by genetic background and physiopathogical status (age, comorbidities) interfering with the many biological mechanisms and pathways regulating immunity and cardio-vascular and pulmonary systems. A rational catalog of chronology and relevance of these mechanisms is needed to obtain a meaningful comprehension of COVID-19 pathogenesis.

Conflicts of interest

The authors report no competing interests.

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Authors' contributions

MC, CD and VP contributed to the design of the work; MC, CD, VP, LS and CR have drafted the work; MC, CD, CR, SP, AD, LS and VP have revised the manuscript. All authors have read and agreed to the published version of the manuscript

Ethical consideration

Not applicable.

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