Editorial

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COVID-19 Physiopathology

Fisiopatología del COVID-19

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In any clinical situtation physiopathology is of paramount importance in critical care. The disease caused by the new virus SARS-CoV-2, imposes important challenges and requires an understanding of the pathophysiological mechanisms involved in it as a means to design better management and life support protocols. This process is currently under construction, but progress has been made, which is summarized below.

The final path of severe COVID-19 pneumonia is like that of many other serious medical conditions: ARDS, whose classical pathophysiological hallmarks are neutrophil-mediated inflammation, excessive transmigration and activation of leukocytes and platelets, incresed activation of coagulation pathways and enhanced permeability through the thin alveolar-capillary membrane, with three different overlaping stages, one exudative, defined by diffuse alveolar damage with a severe inflammation process, cell death, loss of surfactant, alveolar edema, decreased pulmonary compliance and gas exchange impairment. Some time later the proliferative phase is added with the resolution of the pulmonary edema and regeneration of damaged tissue by proliferation and phenotypic changes in type II alveolar cells, myofibroblasts and fibroblasts, and new matrix deposition. In the absence of recovery, this may progress to a fibrotic stage, characterized by diffuse fibrosis and irreversible change of lung architecture.

The linking of final microbial products and/or cell injury-associated endogenous molecules (danger-associated molecular patterns or DAMPS) to certain recognition receptors (Toll-like receptors or TLR) on lung epithelial cells and alveolar macrophages, as well as neutrophil extracelular traps (NETs) formed by releasing DNA dying neutrophils, the highly cytotoxic extracellular histones and granular proteins (myeloperoxidase and neutrophil elastase) through the amplification of pulmonary and systemic inflammation have been identified in this complex lung immune response.

There are five different known stages in the new coronavirus life cycle in the human lower respiratory tract: attachment, penetration, biosynthesis, maturation and release. Once viruses bind to host human angiotensin converting enzyme 2 functional receptors (hACE2), (attachment), they enter host cells through endocytosis or membrane fusion mechanisms (penetration). Once viral contents are released inside the host cells, viral RNA material enters the nucleus for replication. Viral mRNA is used to make viral proteins (biosynthesis). Then, new viral particles are made (maturation) and released. Coronaviruses consist of four structural proteins: Spike (S), membrane (M), envelop (E) and nucleocapsid (N). At the same time spike is composed of a transmembrane trimetric glycoprotein protruding from the viral surface, which determines the characteristic diversity of coronaviruses and host tropism. Meanwhile spike comprises two functional subunits: S1 subunit is responsible for binding to the host cell receptor and S2 subunit specialized in the fusion of the viral and cellular membranes.

It is known that hACE2 expression is specialy high at the lung level (particularly at the apical side of its epithelial cells in the alveolar wall, as -well as at the vascular endotelial cells (EC) and innate lymphoid cells (ILC2 and ILC3), heart, ileum, kidney and bladder.

Following the binding process, the spike protein undergoes a protease cleavage that activates it for membrane fusion via irreversible, conformational changes. A unique characteristic to SARS-CoV-2 among the rest of coronaviruses is the existence of a furin cleavage site («RPPA» sequence) at the S1/S2 site, making this virus very pathogenic because the ubiquitous expression of furin. In this way the alveolar epithelial cells are easily destroyed in spite of airway innate immunity response mediated by the alveolar macrophages (AM), the epithelial cells themselves and the dendritic cells (DCs) arranged in a sandwich fashion from the alveolar space to the basal membrane.

After antigen presentation via DCs and AM, the T cell responses are initiated; virus-infected apoptotic epithelial cells can be phagocytized by DCs and AM, which leads to antigen presentation to T cells. In the other hand, other target for SARS-CoV-2, as specific intercellular adhesion molecule-3-grabbing nonintegrin, can help the virus to directly infect DCs and AM.

These antigen presenting cells get their way to the draining lymph nodes to present viral antigens to the T cells. Certain cells as CD4+ and CD8+ T play a critical role. CD4+ T cells activate B cells to promote the production of virus-specific antibodies, while CD8+ T cells

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can definitely kill viral infected cells but also contribute to lung injury.

The more severe cases have increased plasma concentrations of proinflammatory cytokines, including interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP)1α, tumor necrosis factor (TNF)-α and an activation and eventual exhaustion of CD4+ and CD8+ T cells, probably related with clinical disease pregression. Virus infected lung epithelial cells produce IL-8 (in addition to IL-6), a well-known chemoattractant for neutrophils and T cells. Infiltration of a large number of inflammatory cells has been observed in the lungs from severe COVID-19 patients.

The granulocyte-macrophage colony-stimulating factor (GM-CSF) production by T cells in response to viral infection helps to differentiate innate immune cells and augment T cell function, but in other hand it can initiate a huge tissue damage. Circulating monocytes respond to GM-CSF released by these pathological T cells: the CD14+CD16+ inflammatory monocyte subsets, with a high expression of IL-6, which accelerate the progression of systemic inflammatory response.

From the vascular side, we find the endothelium whose complex function besides maintaining vascular integrity includes between others promotion of vasodilation, fibrinolysis, and anti-aggregation and that presents different EC phenotypes. Because endothelium plays a significant role in thrombotic regulation, hypercoagulable profiles seen in severe diseases likely indicate significant active SARS-CoV-2 endothelial injury. As said, the abundant EC also express hACE2. Increased microvascular permeability as a result of the endothelial injury can facilitate pulmonary intersticial and systemic viral invasion. It has been suggested a role for an EC subtype as a antigen-presenting cell and a putative function in immune surveillance against respiratory pathogens.

Some patients develop an inadequate and extremely severe inflammatory response to SARS-CoV-2 with progressive diffuse lung damage, resulting from an increased pulmonary vascular permeability, leading to intersticial edema, and eventually endotheliitis, activation of coagulation pathways with potential development of disseminated intravascular coagulation (DIC) and deregulated and overwhelming inflammatory cell infiltration. Parallel to the key role of ECs in ARDS associated to different etiologies, ECs play a central role in the pathogenesis of ARDS and multiorgan failure in patients affected by the new virus.

Microvascular leakage and pulmonary edema in patients in severe pneumonic forms of COVID-19 are a multidimensional problema; in first place, the SARS-CoV-2 can directly infect ECs, producing a type of endothelitis with cell dysfunction, lysis and death. Second, to enter cells, SARS-CoV-2 binds to the hACE2 receptor, which impairs the activity of ACE2 indirectly activating the kallikrein-bradykinin pathway, and increasing microvascular permeability. Third, recruited activated neutrophils, produce diverse histotoxic mediators as reactive oxygen species (ROS). Fourth, immune cells, inflammatory cytokines and vasoactive molecules lead to a direct enhanced EC contractility with the loosening of inter-endothelial junctions, pulling ECs apart and forming some inter-endothelial gaps. Fifth, the cytokines IL-1β and TNF activate glucuronidases that degrade the glycocalyx but also upregulate hyaluronic acid synthase 2, leading to increased deposition of hyaluronic acid in the extracellular matrix and promoting with this fluid retention. Together, these mechanisms lead to increased vascular permeability, vascular leakage and intersticial edema.

Severe COVID-19 pneumonia abnormaly activates coagulation pathways with coagulations problems and the potential development of DIC. This is also related to EC activation and dysfunction because the disruption of vascular integrity and EC death leads to exposure of the highly thrombogenic basement membrane, resulting in the pathological activation of the clotting cascade. Additionally, IL-1β and TNF activated ECs initiate coagulation by expressing P-selectin, von Willebrand factor and fibrinogen, to which platelets bind. In turn, ECs release trophic cytokines that further increase platelet production. Platelets also release Vascular Endothelial Cell Growth Factor (VEGF), which triggers ECs to upregulate the expression of tissue factor, the leading activator of the coagulation system. The body reaction are aimed at dissolving the fibrin-rich blood clots, explaining the D-dimers elevation and poor outcome of this patients. As a result of the DIC and clogging/congestion of the small capillaries by inflammatory cells, as well as possible thrombosis in larger vessels, futher lung tissue ischaemia and dysfunction occurs.

An exuberant inflammatory response named as cytokine storm as been described in COVID-19 with high levels of cytokines that amplify the destructive process by leading to further EC dysfunction, DIC, inflammation and vasodilation of the pulmonary capillary bed. This results in ARDS and ultimately multiorgan failure and death. EC dysfunction and activation likely co-determine this uncontrolled immune response. This is because ECs promote inflammation by expressing leukocyte adhesion molecules, thereby facilitating the accumulation and extravasation of leukocytes, including neutrophils, which enhance tissue damage and recruiting lymphocytes away from the blood with a secondary lymphopenia.

Possibly the denudation of the pulmonary vasculature could lead to activation of the complement system,

promoting the accumulation of neutrophils and pro-inflammatory monocytes that enhance the cytokine storm. At this point, the damaged pulmonary vascular endothelium no longer offers a natural barrier against viral spread from the primary infection site.

We know various common mediators of pulmonary vasoconstriction in different forms of pulmonary hypertension including oxidative stress, increased PASMC (pulmonary arterial smooth muscle cells) Ca^{2+} sensitivity, elevated Ca^{2+}, PKCB-induced mitoROS (protein kinase C beta type induced mitocondrial reactive oxygen species) generation and simply hipoxemia, probably associated with a desregulated signaling the drive for hypoxemic vasoconstriction seldom get lost in these patients who show abnormal pulmonary vascular dilation and increased perfusion surrounding areas of CT lung opacity leading to V/Q mismatch and hipoxemia not responding to PEEP.

If all theses findings translate in a common ARDS or not is yet under discussion; but if so, it constitutes a kind of dual simultaneous intrapulmonary (direct) ARDS, with an initial insult to the alveolar epithelium, with ground glass and consolidation of lung tissue as normally occurs in viral pneumonia, followed shortly after by another severe one to the vast pulmonary vascular endothelium, as typically we thought it occurs in extrapulmonary (indirect) ARDS, say for sepsis, with interstitial edema and alveolar collapse, which is probably in line with the different functional phenotypes recently described as H and L (1 and 2) and with the ARDS hyperinflamatory subphenotype described by Calfee et al some years ago, and characterized by high plasmatic inflammatory biomarkers, higher vasopressors needs, lower HCO_3 concentrations (hypoperfusion), more frequent sepsis, higher mortality and less ventilator and multiple organ failure (MOF) free days.

Great emphasis is being placed around the world on better understanding the pathophysiology of COVID-19 and to the extent that this could be successful, regardless of the advancement of science, we will surely be able to have better targeted therapies while pursuing the race for the development of a future vaccine.

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