Réplica

Reply

Sr. Editor:

Agradezco el interés despertado por el editorial recientemente publicado en Reumatología Clínica[1]. Paso pues a comentar las interesantes cuestiones versadas en la elegante carta al editor recién llegada[2].

Hace unos meses fui propuesto por los coordinadores de la VIII edición Reumatopics 2019 con objeto de participar en una mesa llamada «Fibromialgia a debate». El formato era el clásico: un ponente a favor y otro en contra. Se me propuso ir en contra de la fibromialgia. Lo consulté con varios colegas: unos me decían que aceptase; otros que no me «metiese en ese jardín». Acepté y la mesa redonda fue un éxito; puede usted comprobar la ponencia en: portaldelsocio.ser.es/reumatopics19. Posteriormente recibí la valoración de los asistentes de la mesa: fue muy bien valorada y lo que es más importante: tendió vínculos entre los partidarios y los contrarios de la fibromialgia. Vínculos de los que carece su carta.

Suelo siempre escribir mis ponencias. Así fue como se lo propuse al Comité Editorial de Reumatología Clínica. Yo mismo escogí el formato de editorial; cabe recordar que un editorial es un artículo breve que expresa una opinión o se interpretan los hechos de otros. El editorial debe ser brillante, claro, argumentado, imperativo o conciliador. Estimula a los lectores emotivamente e intelectualmente; puede ser el origen de sustanciosas reacciones de controversia y debate. El editorial expresa una opinión personal sobre el tema. Es más, entrevé posiciones ideológicas que trascienden la mera argumentación crítica[3]. En mi humilde opinión el editorial hecho, cumple con las expectativas y satisfecho estoy en haber despertado controversia. Exima de responsabilidad al Comité Editorial de Reumatología Clínica.

Comenta usted la palabra «rescate». Yo no pretendo rescatar nada en mi editorial. Insisto, es una opinión personal, es un relato de la historia de la fibromialgia, tal como lo he vivido yo y probablemente muchos reumatólogos de mi generación. Puede que el concepto de reumatismo psicógeno —creado por los pioneros de la reumatología— fuese equívoco, pero no le quepa la menor duda que sin el concepto de reumatismo psicógeno no existiría a día de hoy la fibromialgia. En la historia de la medicina hay numerosos ejemplos.

Lamento que perciba el escaso conocimiento del escribidor, acerca de la terminología usada. No pretendo que la fibromialgia sea una de mis áreas específicas. Acepto sus comentarios acerca de la nomenclatura, no así en la desautorización que me parece un término inapropiado.

Finalmente me alegra mucho que estemos de acuerdo en el coste económico de la fibromialgia. Son datos que no ofrecen dudas. Las políticas sanitarias llevadas a cabo no han tenido éxito. Por último y no menos importante es un deber de los especialistas dedicados a la fibromialgia y de las sociedades científicas reclutar reumatólogos jóvenes, en otras palabras: hacerla atractiva científicamente. Hecho plasmado en el editorial y que confirma usted con su docta opinión.

Finalizo: «*Toda sabiduría, no es nueva sabiduría*»[4].

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Alejandro Olive Marqués

Servicio de Reumatología, Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona, España

Correo electrónico: aolive.germanstrias@gencat.cat

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Why choose cyclosporin A as first-line therapy in COVID-19 pneumonia☆

¿Por qué elegir ciclosporina A como primera línea terapéutica para la neumonía causada por COVID-19?

Dear Editor:

The use of immunosuppressive therapies in COVID-19 infection is a recently raised topic which comes to fill an unmet need in the management of the patients.[1] Intriguingly, not only COVID-19 but also SARS and MERS CoVs – all members of the Betacoronavirus genus – associate to an increased risk of respiratory distress syndrome. Already in patients with SARS-CoV, the development of respiratory failure was thought to be the consequence of a vigorous innate immune response, while effectiveness of tocilizumab in COVID-19 infected patients also supports the participation of a cytokine storm in severe phenotypes.[1,2] A factor underlying this explosive response could be the capacity of betacoronaviruses to invade immune-competent cells, particularly macrophages, thereby hijacking the major drivers of innate immune responses. Nonetheless, targeting pro-inflammatory cytokines is neither the sole nor the first-line immunomodulatory approach in combating the infection. As represented in the figure, complex virus-host cell interactions providing opportunities for therapeutics should be regarded (Fig. 1).

Betacoronaviruses replicate and carry out transcriptional activities at the cell cytosol, where the viral genome is detected by RIG-1 like receptor (RLR) helicases. Upon binding of vRNA, RLR activate mitochondrial antiviral proteins (MAVS). These in turn trigger phosphorylation of transcription factors and gene expression of interferons and cytokines, which are pivotal for an effective antiviral response.[3] Mitochondrial function is thus essential for the antiviral defense, while these organelles also need to provide for the increased energetic needs of infected cells. This fact points to mitochondrial failure as the mechanism unchaining severe forms of COVID-19 infection.[4] In brief, infected cells

☆ All authors have contributed to the conception of the manuscript, have revised it critically, have approved the final version and agree to be accountable for all aspects of the work.

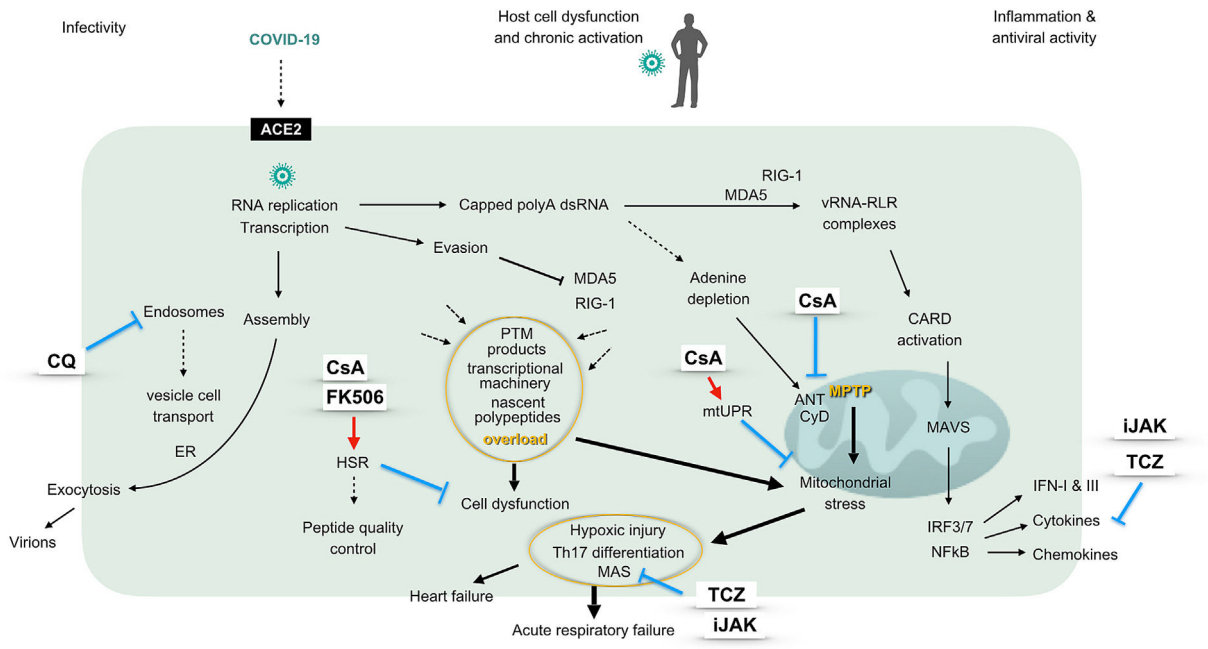

Fig. 1. The graphic represents a pathogenic model of 2019-nCoV considering different virus-host cell interactions. The virus entry, replication, assembly and shedding indicating infectivity are shown at the left, while the right side displays the innate antiviral response characterized by an interferon signature. The center of the figure represents intracellular events unchained by the presence of the virus, driving cell and mitochondrial stress and eventually ending in hypoxic damage. The sites of action of different immunomodulatory drugs are marked. ACE2: angiotensin converting enzyme 2, ANT: adenine nucleotide translocation, CARD: caspase activation and recruitment domains, CQ: chloroquine, CyD: cyclophilin D, ER: endoplasmic reticulum, FK506: tacrolimus, HSR: heat shock response (also unfolded-protein response of the cytosol), IFN: interferon, IRF: interferon regulatory factor, iJAK: inhibitor of Janus kinases, MAS: macrophage activation syndrome, MAVS: mitochondrial antiviral proteins, MDA5: melanoma differentiation-activated protein 5, mtUPR: mitochondrial unfolded-protein response, NFκB: transcriptional activator kappa B, polyA: polyadenylated, PTM: postranslational modifications, RIG-1: retinoic acid inducible gene 1, RLR: RIG-1-like receptors, Th: T helper lymphocytes, TCZ: tocilizumab, vRNA: viral RNA.

are exposed to an overload of nascent polypeptides, transcriptional machinery and by-products of helicases activation, altogether jeopardizing maintenance of protein folding and triggering cell and mitochondrial stress.[5,6] In addition, COVID-19 genome polyadelnylation at the cytosol could waste adenine deposits and challenge mitochondrial permeability transition pore (MPTP). Ultimately, mitochondrial proteostasis collapse would drive caspases activation and irreversible cell damage. According to available literature, calcineurin inhibitors could confer protection from these pathogenic processes. Briefly, these compounds help restore the unfolded-protein response (UPR) at the cytosol, and may in this way rescue cells from necrosis.[7] In addition, upon targeting cyclophilin D, cyclosporin A inhibits MPTP opening, activates mitochondrial UPR (mtUPR) and prevents mitochondrial failure.[8,9] Moreover, through this mechanism, cyclosporin A has shown cardioprotective effects in patients with myocardial infarction.[10]

Of interest, there is a subtype of clinically amyopathic dermatomyositis (CADM) identified by the presence of antibodies against melanoma differentiation activated protein 5 (MDA5), which is an RLR helicase and also the putative cytoplasmic receptor for COVID-19. Patients with MDA5 syndrome are prone to the development of rapidly progressive interstitial pneumonia and refractory respiratory failure. Even though MDA5 syndrome is a rare condition, its resemblance with the clinical features of CoV infections cannot go unnoticed. Notably, critically ill MDA5+ CADM patients can be rescued when a calcineurin inhibitor is administered early in the course of respiratory failure.[11]

Finally, it should be emphasized that cyclosporin A has shown remarkable antiviral activities in a variety of RNA viruses, including the family of betacoronavirus, which employ cyclophilins as chaperones and nuclear factor of activated T cells (NFAT) as a major signaling pathway.[12,13]

On the whole, we suggest that COVID-19 deadly action on host cells including pneumocytes and T lymphocytes, results from their failure to adapt to cell and mitochondrial stress, while dysfunctional macrophages remain as virus reservoir at the target tissue. According to this model, cyclosporin A could confer protection upstream of the cytokine storm in COVID-19 infected patients, a hypothesis which it is planned to be tested in a randomized clinical trial in the coming weeks.

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Olga Sanchez-Pernaute [a,*], Fredeswinda I. Romero-Bueno [a], Albert Selva-O'Callaghan [b]

[a] *Rheumatology Division, Jiménez Díaz Foundation University Hospital and Health Research Institute, Universidad Autónoma de Madrid, Madrid, Spain*
[b] *Department of Internal Medicine, Hospital Universitari Val d'Hebron, Universitat Autonoma de Barcelona, Barcelona, Spain*

* Corresponding author.
E-mail address: osanchez@fjd.es (O. Sanchez-Pernaute).

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