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1. PROGRESIÓN DE LA EPOC

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Nuestro conocimiento actual sobre la evolución de la enfermedad pulmonar obstructiva crónica (EPOC) sigue mostrando importantes limitaciones. Esto es la consecuencia de: 1) La EPOC es una enfermedad compleja con etiopatogenia multifactorial y heterogeneidad fenotípica clínica; 2) Aunque en los últimos años, algunos estudios observacionales y, el seguimiento de grandes cohortes poblacionales, han aportado nuevos datos, todavía tenemos carencias significativas que requieren ser abordadas.

Desde finales de los años setenta y hasta hace una década, teníamos una visión general bastante sesgada sobre la evolución de esta enfermedad, posiblemente, condicionada por una interpretación parcialmente errada del estudio clásico de Fletcher y Peto sobre la historia natural de la EPOC. En los últimos años, las nuevas aportaciones científicas, han supuesto cambios conceptuales en la progresión de la EPOC que podrían resumirse en los siguientes mensajes: a) Existe una marcada heterogeneidad individual en el declinar del FEV1; b) La mayor parte de los pacientes con EPOC no tienen un declinar anual excesivo del FEV1 y, cuando este ocurre, es más prevalente en los pacientes con fenotipo enfisema; c) Aunque el tabaco es el factor etiopatogénico fundamental, en un porcentaje importante de pacientes con EPOC (sobre todo en la EPOC diagnosticada en el adulto joven) coexisten alteraciones en el desarrollo pulmonar (fundamentalmente, asociada al diagnóstico de asma en la infancia); d) Algunos pacientes que no alcanzan el desarrollo pulmonar normal, pueden llegar a tener una EPOC sin una caída acelerada del FEV1; e) La EPOC en pacientes sin enfisema es, generalmente, no progresiva: f) La progresión de la afectación pulmonar muestra una débil correlación entre la afectación de la vía aérea y a nivel alveolar; g) La progresión de la afectación pulmonar y extrapulmonar puede ser discordante; h) El declinar del FEV1 en los pacientes con EPOC por biomasa (humo de leña) es de menor cuantía y menos heterogenea que la que ocasionada por el tabaco; i) Ningún fármaco ha demostrado modificar de forma clínicamente significativa el declinar del FEV1; j) Hasta el momento el efecto de los biomarcadores en la progresión del enfisema y/o declinar del FEV1 es marginal.

Para mejorar nuestro conocimiento sobre la progresión de esta enfermedad, necesitamos más datos, sobre tramos de la vida poco analizados y, poder definir con más precisión sus posibles trayectorias: “La EPOC temprana (the early COPD)”, sobre todos los periodos de adolescencia-adulto joven (final del desarrollo pulmonar) y entre 35–50 años (periodo donde podemos comenzar a ver el impacto del tabaco); Estudios “a largo plazo” en la EPOC adulta (en la mayoría son de corto-medio plazo de seguimiento). Además, es necesaria información más allá del FEV1 (capacidad de difusión de monóxido de carbono-DLco, enfisema, comorbilidades, etc.) para conseguir una mejor fenotipización de nuestros pacientes y conseguir llegar a la enfermedad en una fase más precoz.

La posibilidad de que encontremos biomarcadores capaces de predecir la evolución de la EPOC, probablemente vaya en paralelo, con el hecho, de que consigamos una adecuada fenotipización de los pacientes. Los avances tecnológicos están facilitando la accesibilidad en algunas pruebas como la DLco y, sobre todo, a la tomografía computarizada. Esta última herramienta es la que parece ofrecer mejores perspectivas para el futuro. Su menor emisión de radiación y el desarrollo de los software están favoreciendo su mayor aplicabilidad en la práctica clínica y en la investigación. Su desarrollo y continuos avances, previsiblemente, nos permitirán entender mejor los cambios estructurales que ocurren en la EPOC, a nivel del parénquima pulmonar y en la afectación extrapulmonar.

Conflicto de interés

Ciro Casanova ha recibido honorarios como conferenciante o consultor de AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Novartis y becas de investigación de GlaxoSmithKline, Menarini y AstraZeneca.

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2. SENESCENCE AND SENOLYTICS: NEW THERAPEUTIC OPTIONS IN RESPIRATORY DISEASES

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Senescent cells have experienced unrepairable damage or stress, but have not activated a cell elimination program.[1,2] During aging, senescent cells accumulate diffusely (up to 5–10% of all cells) throughout tissues.[3] Interestingly and of relevance here, senescent cells accumulate massively in lung fibrotic diseases (up to 30–50% of all cells).[1,2] In this regard, lung fibrosis can be considered a process of accelerated aging selectively affecting the lung. Senescent cells present many changes in their biology, including their inability to proliferate and an abundant secretome, known as Senescence-Associated Secretory Phenotype (SASP).[4] The SASP is considered the most harmful component of senescence because it contains pro-inflammatory and pro-fibrotic factors. Exogenous toxic agents, infectious agents, genetic defects, and loss of telomeres are considered important primary triggers of senescence in alveolar epithelial cells (known as primary senescence). In turn, the SASP of the primary senescent cells is also able to trigger paracrine senescence in the neighbor cells, most notably the interstitial fibroblasts, a process known as secondary senescence. In this manner, cellular senescence is a non-proliferative state but it is a progressive pathological agent.

We have recently developed a novel mouse model for lung fibrosis that we call, Senescence-Initiated Lung Fibrosis (SILF). In this mouse model, fibrosis is initiated by human lung fibroblasts that are rendered senescent ex vivo. These human senescent fibroblasts are then delivered intra-tracheally into recipient (immunodeficient) mice. Upon engraftment, senescent human fibroblasts, but not their non-senescent counterparts, initiate the process of paracrine senescence involving the host mouse interstitial cells and resulting in progressive lung fibrosis. This new model of mouse lung fibrosis presents an important advantage over the classical model of bleomycin-induced fibrosis. Specifically, SILF responds very well to the approved anti-fibrotics pirfenidone and nintedanib. This is in contrast to the classical bleomycin-induced fibrosis that responds poorly or inconsistently to these drugs.[5,6]

We have also explored the mechanism of action of pirfenidone and nintedanib and we have found that these drugs selectively reduce the secretion of TGFb and PAI1 by senescent cells, without affecting other components of the SASP, such as inflammatory IIL-6 cytokine. This type of activity is known as senomorphic because it modifies the SASP of senescent cells.

The discovery of drugs that preferentially kill senescent cells (senolysis) is attracting high attention because of its remarkable therapeutic activity on mouse models of fibrosis. The BCL2-family inhibitor navitoclax is one of the most potent senolytic drugs.[3] This drug is very effective in reducing bleomycin-induced fibrosis, and we have observed that it is also very effective in reducing senescence-initiated lung fibrosis (SILF).

In summary, we conclude that: (1) cellular senescence is a causal and active component of lung fibrosis; (2) current antifibrotic drugs act on senescent cells with high selectivity reducing their pro-fibrotic secretion, i.e. senomorphic activity; and (3) experimental drugs that kill senescent cells, i.e. senolytic activity, constitute a promising complementary approach to treat lung fibrosis.

Conflict of interest

Manuel Serrano is co-founder of Senolytic Therapeutics, Inc. and RejuverSen, AG.

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3. LUNG CANCER SCREENING

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In 2020, the NELSON trial published as second largest lung cancer screening trial their mortality results.[1] The positive results of both the Dutch-Belgian screening trial (NELSON; $n = 15{,}792$), with relatively low referral rates, and the NLST ($n = 53{,}454$) in the USA[2,3] provides conclusive evidence on efficacy (and possible harms) now.

In the NELSON trial, 13,195 males and 2594 females aged 50–74 at high risk for developing lung cancer were included in the screen (4 CT screens) or control arm (usual care). On average, 9.2% of the screened participants underwent at least one additional CT scan (initially indeterminate). The overall referral rate for suspicious nodules was only 2.1%. At 10 years of follow-up, the incidence of lung cancer was 5.58 cases per 1000 person-years in the screening group and 4.91 cases per 1000 person-years in the control group; lung-cancer mortality was 2.50 deaths per 1000 person-years and 3.30 deaths per 1000 person-years, respectively (male population). The cumulative rate ratio for death from lung cancer at 10 years was 0.76 (95% confidence interval [CI], 0.61 to 0.94; $P = 0.01$) in the male screening group as compared with the control group. Among women, the rate ratio varied from 0.41 to 0.67 in years 7–10. These results confirmed efficacy as previously shown in the NLST, emphasized sex-specific differences in effect, and, despite low referral rates, reported greater effects than the NLST (0.78 in NELSON for "NLST eligibles" versus 0.92 in NLST, both for males in year 8; 0.37 in NELSON versus 0.73 in NLST, both for females in year 8).[1,4] We found no detrimental effects in other causes of deaths,[5] but did not have, by intent, sufficient power for a statistically significant effect on all-cause mortality.[6]

However, despite these positive results of two large-scale RCTs, implementation is likely to be limited, slow and of variable quality throughout Europe, and current guidelines could easily require up to 25 million CT screens annually. The most optimal strategy in risk-based lung-thoracic screening therefore seems still uncertain regarding the optimal and most cost-effective (e.g., targeted) strategy 1) to recruit, 2) to integrate smoking cessation and co-morbidity-reducing services, and 3) to determine the (risk-based) screening interval. Personalized regimens based on the baseline CT result (e.g., if negative) can potentially retain 85% of the mortality reduction achievable through screening at 45% less screens, thus potentially saving much unnecessary harm associated with screening, and 0.5–1 billion Euros per year.

The heart of 4-IN-THE-LUNG-RUN is a randomized controlled trial amongst 24,000 individuals evaluating whether it is safe (in terms of limited stage distribution differences) to have risk-based less intensive screening intervals after a negative baseline CT.[7] Various methods to improve participation of hard-to-reach individuals will be assessed in five different European healthcare settings. Innovative co-morbidity reducing strategies will be tested including other markers on CT imaging, as Calcium Score.[8] Cost impact and cost-effectiveness analyses using a natural history model will likely steer implementation throughout Europe. The experienced consortium will strongly interact with key stakeholders and discuss interim results with key other international initiatives on CT screening, biomarkers, and smoking cessation practices. This implementation will form the evidence base for risk-based lung cancer screening with huge benefits for the EU, on health outcomes, cost savings, and innovation in the long run.

Conflict of interest

No conflicts of interest.

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4. MITOCHONDRIAL DYSFUNCTION AT THE CROSSROAD OF AGING AND LUNG FIBROSIS

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Aging is a natural and inevitable process that represents a progressive loss of physiological integrity, leading to impaired function and lower adaptive capacity to environmental stress. Aging is associated with increased susceptibility to a variety of chronic conditions[1,2] and lung pathologies are no exception. The prevalence of lung diseases, such as idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and acute lung injury (ALI), increases considerably with age. However, the molecular mechanisms connecting the aging process with these age-related pathologies have not been completely elucidated.[3–5]

Only limited knowledge is available for the cellular and molecular processes that define healthy aging. Our studies have found that a decline in mitochondrial quality and activity is associated with lung aging and correlates with the development of IPF, an age-related disease.[6–8] Mitochondrial dysfunction contributes to the pathogenesis of several age-related diseases. Age has been associated with decreased bioenergetic capacity, related to an increased number of mutations in mtDNA, decreased mitochondrial biogenesis and increased levels of mitochondrial ROS, a physiological signaling molecule that at high levels can be detrimental.[9] Additionally, mitochondrial dysfunction may contribute to DNA damage, senescence, SASP, telomere attrition, stem cell exhaustion, inflammation and other key age-related cell processes.[10,11] Signaling pathways regulating autophagy of mitochondria (mitophagy) seem to be critical to attenuate mitochondrial impairment, and mitigate deleterious consequences of mitochondrial dysfunction. Markers of reduced mitophagy and accumulation of damaged mitochondria are common findings in aging cells. Our studies have shown evidence that the mitochondrial kinase PINK1, which is a positive regulator of mitophagy, is expressed at low levels in alveolar type II lung epithelial cells of aging and IPF lung patients, leading to the accumulation of damage mitochondria, and release of mtDAMPS.[6,7,12] Furthermore, we have shown that deficient mitophagy accelerates senescence,[13] another hallmark of aging characterized by irreversible cell-cycle arrest, resistance to apoptosis and secretion of biologically active factors that contribute the development of fibrosis in the lung after injury.

In summary, mitochondrial dysfunction in lung cells can drive cells to senescence and increase the susceptibility to disrepair and fibrosis in the lung. Thus, therapies that target mitochondria could be beneficial for treating many age-related impaired cellular functions.

Conflict of interest

No conflicts of interest.

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5. PATHOPHYSIOLOGY OF EXERTIONAL DYSPNOEA IN MILD COPD

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Patients with mild COPD (by GOLD stage 1 criteria) can experience significant dyspnoea during physical exertion, contributing to reduced habitual physical activity, poor quality of life, and increased morbidity and mortality.[1–5] In such individuals, heterogeneous pathophysiological abnormalities can manifest during exercise and point to derangements of dynamic respiratory mechanics and pulmonary gas exchange.[6–9] These, in turn, require compensatory responses by the respiratory controller (increased inspiratory neural drive, IND) to maintain alveolar ventilation in pace with increasing metabolic demands.[10,11] While such physiologic adaptations are usually successful in maintaining arterial blood gas and acid–base homeostasis during exercise, the cost is often increased perceived exertional dyspnoea and reduced exercise tolerance.

Small airway loss and dysfunction are the hallmark of mild COPD and can lead to variable expiratory flow limitation, dynamic lung hyperinflation and prematurely reduced inspiratory reserve volume at relatively low ventilation ($\dot{V}E$) during exercise.[1,7,12,13] Thus, increased resistive and elastic loading of the inspiratory muscles have been shown to lead to compensatory increases in IND and associated perceived increased respiratory effort or discomfort.[10,11]

Seminal studies by the Barcelona Group have shown the presence of significant ventilation-perfusion abnormalities at rest in mild to moderate COPD.[14–18] Importantly, Barberà and colleagues showed intimal thickening and luminal narrowing of pulmonary arteries in lung resection specimens in individuals with mild to moderate COPD; this, in turn, leading to high physiological dead space and a skewed ventilation dispersion.[15,17] Recent studies have consistently shown that ventilatory inefficiency during exercise, measured as increase in the ventilatory equivalent for carbon dioxide ($\dot{V}E$-/$\dot{V}CO2$), is higher in mild COPD than in healthy controls.[1,6–8,11] High $\dot{V}E$¬/$\dot{V}CO2$ reflects high physiological dead space (i.e., regional pulmonary blood perfusion is diminished relative to alveolar ventilation) rather than increased central chemosensitivity.[7,19] In addition to high exercise $\dot{V}E$¬/$\dot{V}CO2$, reduced resting diffusing capacity for carbon monoxide (DLCO) is an indirect marker of microvascular dysfunction.[20,21] Both these related measurements are influenced by reduced pulmonary capillary hypo-perfusion which imaging studies have confirmed even

in non-emphysematous regions of the lung in mild COPD.[22–24] These related physiological markers have been closely linked to higher dyspnoea ratings and reduced exercise capacity in this population.[20,21]

This consistent association between high ventilatory inefficiency/demand and exertional dyspnoea, has been corroborated by the recent study of Philips and colleagues who showed that in mild COPD, selective vasodilation by inhaled Nitric Oxide (compared with placebo) was associated with decreased V̇E/V̇CO2 and corresponding dyspnoea intensity.[25] Importantly, this symptom benefit was evident in the absence of any change of dynamic lung mechanics and O_2 sat during treatment. This adds to the evidence that reduced ventilatory efficiency of CO_2 clearance (and increased central chemo-stimulation) contribute to dyspnoea during exercise in patients with mild airway obstruction.

Summarizing, recent physiological studies have consistently shown that IND during exercise is relatively high in smokers with mild airway obstruction, particularly in those with lower DLCO. Ultimately, the low DLCO and increased ventilatory inefficiency reflect abnormalities of pulmonary blood perfusion and higher ventilatory demand, which in the presence of dynamic mechanical constraints, conflate to increase IND and dyspnoea during physical activity. It follows that measurement of DLCO and exercise V̇E/V̇CO2 (when available) should be considered as part of a comprehensive physiological and clinically useful evaluation of symptomatic smokers with ostensibly mild airway obstruction.

Conflict of interest

The author declares no conflicts of interest.

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6. DANCING WITH THE MUSIC OF LIFE

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In this lecture I introduce a new way of thinking about living organisms, in which genes are the puppets of the organism, not their controller.

It is now 20 years since the first human genome sequence was announced in 2001.

The expectation was that by now we would have cures for cancer and for most of the diseases of the organs and systems.

We have made incremental progress, but nothing like the step change that was predicted. Why is that the case?

The answer is that we got genetic causation the wrong way round. The organism activates, controls, and modifies its genome, not the other way round. What is the evidence and what are the implications for studies of lung pathology?

All genes contribute to many or even all functions. Many genes show very low association data. Linear addition of such data is invalid. Gene-centric views of development and evolution therefore need revising.

That is the topic of my recent books, The Music of Life and Dance to the Tune of Life. I document the evidence for reversing our ideas on genetic causation.

Why is it important to reverse our ideas of genetic causation? The simple answer is that the gene-centric view has led us to an impasse. We have more data on genome sequences than ever before. But what we have found does not support genetic determination. On the contrary, most of the association scores between genes and phenotypes show very low levels.

Lung cancer is a good example of the problem. The 1- and 5-year survival figures for all patients with later forms of the disease have changed little over the last 30 years. My explanations follow the following summary:

- Tissue stochasticity exists and is extensive.
- Stochasticity is harnessed and is directional.
- Controlled by regulatory networks.
- Cells under stress will hypermutate
- Hypermutation could be very rapid.
- This would explain ineffectiveness of treatment of late stage cancers.
- Severe treatment may even be provoking cells to hypermutate.

Conflict of interest

No conflicts of interest.

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7. ENDOTIPOS Y RESPUESTA AL TRATAMIENTO EN BRONQUIECTASIAS

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Las bronquiectasias son una enfermedad pulmonar inflamatoria crónica que se define por una dilatación irreversible de la luz bronquial que comporta un cuadro clínico caracterizado por tos, expectoración e infecciones respiratorias recurrentes. Actualmente, se consideran la tercera enfermedad inflamatoria de la vía aérea, después del asma y de la EPOC. Su diagnóstico va en aumento debido al incremento de la esperanza de vida y al uso generalizado de la tomografía computarizada de alta resolución (TCAR).[1,2]

Su etiopatogenia es, a día de hoy, desconocida. Una de las hipótesis más establecidas es la del círculo vicioso, dónde se plantea que la alteración del aclaramiento mucociliar conlleva a un aumento en las secreciones bronquiales, lo cual a su vez disminuye su capacidad de barrera inmunológica, facilitando así el desarrollo de una infección crónica. Esta imposibilidad para eliminar microorganismos patógenos produce una respuesta inflamatoria sostenida que resulta en lesión del epitelio bronquial e induce una remodelación patológica, perpetuando el ciclo. No obstante, se ha observado que tratar de romper este círculo vicioso en un único punto no evita eficazmente su perpetuidad y los distintos ensayos clínicos con esa finalidad con terapias antibióticas, antiinflamatorias o mucolíticas han obtenido resultados controvertidos.[3]

Durante los últimos años, distintos trabajos han diferenciado los pacientes con bronquiectasias en distintos fenotipos clínicos, principalmente caracterizados por la frecuencia de agudizaciones y la presencia de infección bronquial crónica. De todos ellos, el fenotipo con agudizaciones frecuentes (más de 2 al año) e infección bronquial crónica por Pseudomonas aeruginosa es quien ha demostrado peor pronóstico, al asociar deterioro de la función pulmonar, mala calidad de vida, riesgo aumentado de hospitalización e incremento de mortalidad.[4] Sin embargo, al realizarse ensayos clínicos aleatorizados con antibióticos inhalados que incluyan sólo a esta población, los resultados obtenidos también han sido muy heterogéneos, sin observarse claras diferencias a favor de los tratamientos.[5,6] Para evitarlo, se cree fundamental realizar un enfoque personalizado para el manejo de cada paciente, siendo la identificación de biomarcadores y endotipos de la enfermedad de una importancia crucial.

Distintos biomarcadores han sido estudiados recientemente en pacientes con bronquiectasias. Hasta la fecha, se han estudiado tanto a nivel local (pulmonar) como sistémico (suero), siendo los hallazgos mucho más contundentes a nivel pulmonar, sobre todo en aquellos que se han determinado en esputo. Entre ellos, la Elastasa de Neutrófilo es uno de los marcadores con mayor potencial para predecir la gravedad, frecuencia de exacerbaciones y colonización bronquial por P. aeruginosa.[7] Otros trabajos han demostrado que proteínas de defensa de la vía aérea como las mucinas y los péptidos antimicrobianos, las metaloproteinasas de la matriz o la proteína de la zona de embarazo en esputo pueden ser biomarcadores útiles que se relacionan con la gravedad de la enfermedad.[8–10] A nivel sistémico, los estudios son menos concluyentes, y algunos trabajos han relacionado los niveles de TNF-alfa y proteína C reactiva con presencia de infección bronquial y riesgo de agudizaciones.[11]

Todos estos biomarcadores pueden facilitar el reconocimiento de endotipos moleculares que ayuden a predecir la respuesta al tratamiento. En esta dirección, se ha demostrado que los pacientes con

carga bacteriana elevada en la vía aérea tienen mayor inflamación de la vía aérea, y que una carga elevada (mayor de 107 unidades formadoras de colonia/mililitro) puede ser un potencial marcador de respuesta al tratamiento antibiótico inhalado.[12] En la misma dirección, la presencia de un elevado número de eosinófilos en sangre periférica ha demostrado ser un buen marcador para la respuesta a los corticosteroides inhalados.[13] Finalmente, un reciente trabajo ha demostrado que la administración de brensocatib, un inhibidor de la dipeptil peptidasa-1 (DPP-1), disminuye la presencia de neutrofilo elastasa en la vía aérea y tiene un importante impacto clínico al disminuir el número de agudizaciones.[14]

En resumen, las bronquiectasias son una enfermedad muy heterogenea, dónde la caracterización de los fenotipos clínicos no permite predecir una correcta respuesta a los tratamientos administrados. El estudio de biomarcadores, sobre todo a nivel pulmonar, y de los endotipos moleculares asociados ha permitido avanzar en la identificación de los pacientes que pueden recibir una terapia dirigida. Futuros estudios son necesarios para mejorar el conocimiento de los endotipos de una enfermedad tan compleja, que permitan entender su heterogenicidad y dirigir futuras indicaciones terapéuticas.

Conflicto de interés

Oriol Sibila ha recibido honorarios como conferenciante o consultor de Grifols, Bayer y Zambon y becas de investigación de Zambon y Menarini.

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8. THE TWO SIDES OF THE SAME COIN OF THE IMMUNE RESPONSE TO SARS-COV2: HYPERINFLAMMATION AND IMMUNE PROTECTION

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In the present pandemic, it is well established that asymptomatic or mild patients are the main number of people infected by SARS-CoV-2. And except for those with letal infection, the presence of the virus is finally cleared by the immune system (IS). Immune response is in the basis of the evolution of SARS-CoV-2 infection but also a major component for the severe development of disease, and specially those who die after a systemic hyperinflammatory process, often called cytokine storm. Therefore, IS is “the friend but also the foe” of this pandemic, their response can cure or kill us (“a coin” with two opposite sides). The innate immune response is the initial component of protection (being type I interferons, the paradigmatic elements of these protective function) and its key role has been demonstrated when near 15% of the severe patients can be explained by disorders in these interferons.[1,2] But when the production of cytokines (specially IL-6 or IL-1) becomes out of control, the hyperinflammatory systemic state in form of cytokine storm can compromise the patient’s life. In fact this compromise

arrive when the second component of IS, adaptive immune response, tries to eliminate the infected cells by introducing specificity of antibodies and T-cells, but increases the hyperinflammation producing the release of huge quantity of cytokines that reinforce innate response and other systemic disorders. To control this hyperinflammation (Corticosteroids, kinase inhibitors or biologics anti-IL6 or anti-IL-1) is the best tool (when not the only one) to treat patients in severe state.[3,4] But for the final control of the pandemic, by now the only tool that we have available is to immunize the population. The protection by the adaptive immune response against SARS-CoV-2 is clearly possible (as the extremely low number of cases of reinfection is showing and as the initial global data about vaccination corroborates). Although antibodies play a role in this protection (and their detection in the sera of convalescent or vaccinated people is the easy way to visualize this immunization), T-cell response is the main component to verify this protection. In fact, there are few individuals who are not able to develop detectable antibodies and determining T-cell specificity is the way to visualize their protection against the virus.[5] Despite some unexpected but possible immune-scape for virus variants, natural immunization or vaccination are the unique way to finish this pandemic, allowing us a protection that now it is clear that is for at least 8 months[6]/1.2 years, but it is predictable (by available information from similar virus) that it can be useful enough for several years.

Conflict of interest

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