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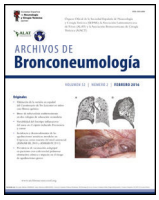

Editorial

Inflammasome and the lung: The link among distress phenotypes☆

Inflamasoma y pulmón: ¿el nexo entre los distintos fenotipos de distrés?

In 1967, Ashbaugh et al.[1] described acute respiratory distress syndrome (ARDS) in a group of severe patients who shared characteristics such as acute hypoxemia, non-cardiogenic pulmonary edema, decreased lung compliance, and need for positive pressure ventilation, but with underlying entities as dissimilar as trauma, pneumonia, or pancreatitis. However, for years efforts have continued to optimize the definition of ARDS, with specific criteria being established in 1992, which were updated in 2012 with the so-called Berlin definition.[2] Although these criteria provide researchers with a framework for including patients in clinical trials and translational studies, they are of little use clinical decision-making. Perhaps their main weakness is that behind a proper operational definition lies a wide spectrum of entities that cannot be evaluated by direct histopathological diagnosis of the lung injury.

Inflammation plays a central role in the pathogenesis of ARDS. The clinical, radiological and gasometric manifestations that make up the syndrome are a consequence of increased vascular and alveolar permeability, inflammatory cell infiltration, and hyaline membrane formation, all abnormalities characteristic of ARDS. Proinflammatory cytokines, such as interleukins (IL) IL-1, IL-6, and IL-17a, are the main mediators that initiate the inflammatory response in the lung, orchestrating the recruitment of macrophages, neutrophils, and chemokines. The synthesis of these cytokines is initiated by the activation of inflammasome, an intracellular multiprotein complex that regulates the maturation and release of inflammatory cytokines of the IL-1 family.

Inflammasomes are an underlying feature of multiple and highly diverse inflammatory diseases, such as autoimmune diseases, arteriosclerosis, and Alzheimer's disease,[3] as well as ARDS. Several inflammasomes have been described. They consist of a protein that acts as a receptor for endogenous and exogenous signals of danger, the effector caspase-1 in its inactive or proenzyme form (procaspase-1) and, in some cases, an adaptor that allows the two to interact.

Of the various known inflammasomes (NLRP1, NLRP3, NLRC4 and AIM2, among others), inflammasome NLRP3 is the best characterized. In baseline situations, the NLRP3 receptor has a self-inhibitory effect, but inflammatory stimuli lead to the oligomerization of NLRP3 and the recruitment of the adaptor and procaspase-1, thus forming the inflammasome. In this complex, caspase-1 acquires its active form, cleaves and then activates the precursors of IL-1 beta and IL-18 cytokines, triggering a type of inflammatory cell death known as pyroptosis. This attracts circulating macrophages and neutrophils to lung injury sites, where they will produce proteases, reactive oxygen species, and cytokines that will amplify the inflammatory response.[4]

Many stimuli are capable of triggering inflammasome activation: viruses, bacteria, fungi, crystals, amyloid and ATP, among others.[4] It is reasonable then to hypothesize that the detection of so many widely diverse stimuli cannot be direct, but that the NLRP3 receptor is instead activated by some host factor that is affected by these agents (potassium efflux, calcium influx, alterations of intracellular levels of chloride, release of mitochondrial DNA or lyosomal cathepsins, for example).[5] Inflammasome NLRP3 activation is involved in the development of ARDS,[6] with higher levels of IL-18 being associated with more severe ARDS and higher mortality of patients in intensive care units[7,8] and in animal models.[7]

Multiple therapeutic strategies aimed at modulating inflammation and avoiding its deleterious effects have historically directed research towards the area of ARDS. For the basic researcher, animal models are a key resource for studying a disease. In ARDS, models such as cecal ligation and puncture, and intratracheal instillation or intraperitoneal injection of LPS[9] are widely used and provide a controlled environment in which to test a hypothesis. However, we often find that therapeutic interventions that seemed promising *in vivo* do not show the same efficacy in clinical trials or do so in a very inconsistent manner, as occurred with salbutamol, keratinocyte growth factor, and statins, for example.[10] These latter strategies, which demonstrated inhibition of inflammasome NLRP3 activation *in vitro* and reduction of inflammation and pulmonary edema *in vivo*,[11] did not show benefits in patients with ARDS in clinical trials.[12] In fact, some patients randomized to receive statins paradoxically had an increase in IL-18 levels which triggered an increase in inflammasome activation.[8]

This brings us back to the issues raised at the beginning of this discussion: the heterogeneity of ARDS patients, the absence of a practical diagnostic "gold standard" for clinical use, and the difficulties of designing experimental models capable of mimicking all aspects of the clinical scenario. In fact, a recent study showed that interobserver concordance for the diagnosis of ARDS using the Berlin criteria is only moderate, due mainly to differences in the interpretation of lung images.[13] Furthermore, the sample collection site (bronchoalveolar lavage *versus* blood) and the methods used to measure biomarkers could also contribute to the variation found in the studies. What about the patients? Returning to heterogeneity,

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this is an issue that applies not only to the types of injury causing the ARDS (direct or indirect), but also to the patients who present different risk factors and comorbidities, generating variations in the pathophysiology of the disease.

So, how feasible would it be to target inflammasome activation as a useful therapeutic intervention in patients with ARDS? Might it be a mistake to try to apply precision medicine to an imprecisely defined entity? As Bertrand Russell once said: "What men really want is not knowledge but certainty." We must rise to the challenge of sweeping aside the false certainties offered by the current definition of ARDS and take on the task of elucidating the inflammatory profiles that will allow the creation of new specific diagnostic and therapeutic strategies.

Conflict of interests

The authors state that they have no conflict of interests.

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