

Open Access New Avenues for Antiinflammatory Signaling of Nur77 in Acute Lung Injury

Acute respiratory distress syndrome (ARDS) in humans can be caused by systemic or local pulmonary infection and is characterized by damage of the endothelial–epithelial barrier, which leads to protein-rich edema with subsequent detrimental effects on pulmonary gas exchange. Recently, ARDS has gained sad fame due to the current coronavirus disease 2019 (COVID-19) pandemic. Thus, studies that elucidate the underlying pathogenic mechanisms of acute lung injury (ALI) in ARDS and that discover novel treatment targets are urgently needed. An aberrant immune response of the host leading to hyperinflammation has long been regarded as a major contributor to ARDS and ALI. Inflammasome activation in both the lung parenchyma and resident immune cells can trigger deleterious effects on the pulmonary endothelium that lead to the increase in endothelial permeability (1). Caspase-1 is a crucial component of inflammasome signaling and triggers the release of proinflammatory IL-1 β and IL-18. Caspase-1 expression can be regulated by IFN regulatory factor-1 (IRF-1) (2). Along this line, previous studies have shown that inhibition of inflammasome signaling attenuated the development of ALI (1). However, the mechanisms that trigger inflammasome activation in ARDS and lead to endothelial dysfunction are incompletely understood.

Against this background, in this issue of the *Journal*, Ding and colleagues (pp. 288–299) focus on Nur77, a transcription factor belonging to the nuclear receptor 4A (NR4A) family of nuclear hormone receptors (3). Different stimuli, including inflammatory signals, quickly induce Nur77 expression and stimulate its transcriptional activity. Transcription of target genes, in turn, attenuates the immune response, primarily by suppressing NF- κ B signaling (4). Most importantly, the authors of the current study have shown previously that expression of Nur77 was increased in lungs of LPS-treated mice and that Nur77 deficiency promoted lung vascular leakage in ALI, suggesting a beneficial effect of Nur77 antiinflammatory signaling in ALI (5).

Extending their previous work, the group here investigated the underlying mechanism of Nur77-mediated inhibition of inflammation using *in vitro* endothelial cell models and an *in vivo* Nur77 knockout (Nur77^{-/-}) mouse model with LPS-induced ALI (3). They show that Nur77 inhibited inflammasome activation (determined by release of IL-1 β), at least in part by inhibition of IRF-1-dependent promoter activation of caspase-1 (Figure 1). Accordingly, Nur77^{-/-} mice exhibited exacerbation of IL-1 β release and endothelial barrier dysfunction after exposure to LPS. Thus, the current study identifies a novel mechanism of protective antiinflammatory signaling of Nur77 in ALI. Furthermore, it demonstrates the relevance of the Nur77^{-/-}-induced increase in caspase-1 expression by showing that caspase-1 inhibition could reverse the exacerbation of ALI in Nur77^{-/-} mice.

Although the beneficial effects of caspase-1 inhibition may not come as a surprise because previous studies have shown the protective effects of inflammasome inhibition in ALI (1, 6), the current study connects Nur77 with the regulation of IRF-1–caspase-1 signaling, thus opening up a new approach to more specific therapeutic targeting of ALI.

In the future, alternative mechanisms of Nur77 that confer its antiinflammatory potential and inhibitory effects on caspase-1 expression/activation in ALI may be identified. One candidate may be Toll-like receptor 4 (TLR4), because Nur77^{-/-} macrophages exhibited increased TLR4 expression, which is an important activator of the inflammasome (7) and is necessary for the activation of IRF-1 (6). Moreover, the *in vivo* relevance of Nur77 in endothelial cells should be further explored using cell type-specific knockout models. Although the protective effects of Nur77 were largely attributed to its antiinflammatory effects in endothelial cells (5, 8), other cell types—in particular immune cells—may contribute to the beneficial effects of Nur77. In this regard, Nur77 was shown to restrict T-cell activation and autoimmunity (9), as well as the macrophage inflammatory response through metabolic reprogramming of these cells (10). In favor of the hypothesis that inflammasome activation, specifically in endothelial cells, governs endothelial damage in ALI, endothelial inflammasome activation was shown to be the major contributor to increased pulmonary vascular permeability using bone marrow transfer in the model of intestinal ischemia/reperfusion-induced indirect ALI (11). However, the relevance of immune cells may differ in direct ALI, because, in a recent study, IL-1 β and IL-18 levels in bronchial alveolar fluid were significantly higher in patients with direct ARDS than in patients with indirect ARDS, and inflammasome inhibition with tetracycline reduced the production of these cytokines originating from alveolar leukocytes from patients with direct ARDS (12). Moreover, for therapeutic aspects, deleterious effects of Nur77 signaling on the antigen-specific immune response need to be taken into account in the future as well, as for any immunosuppressant. In this regard, upregulation of Nur77 has been found in response to TCR and CD28 stimulation in thymocytes, leading to their apoptosis (13).

Independently from the exact mechanism and target cell type, Nur77 may qualify as a promising new target for treatment of ALI. Although Nur77 has hitherto been regarded as an orphan receptor with no endogenous ligands identified, the accumulating evidence suggests that small molecules, such as cytosporone B11, *N*-pentyl 2-[3,5-dihydroxy-2-(1-nonanoyl)-phenyl]acetate 12, and specific unsaturated fatty acids (such as docosahexaenoic acid), can interact with the Nur77 receptor and modulate its activity (4). In particular, celastrol, extracted from the Chinese herb *Tripterygium wilfordii*, was reported to control

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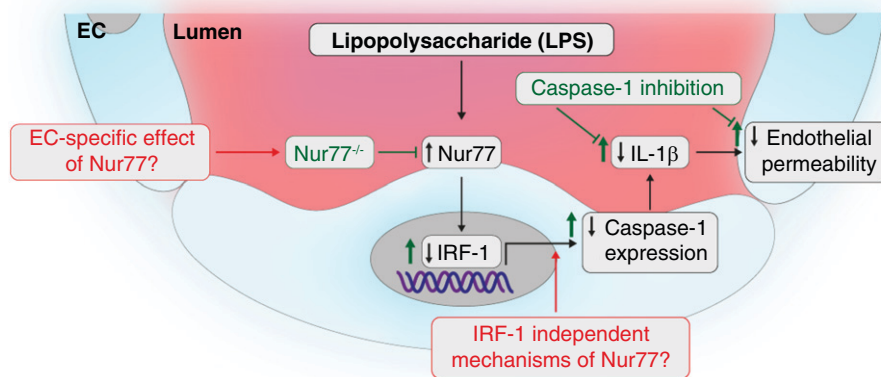


Figure 1. Overview of the antiinflammatory signaling pathway of the orphan nuclear receptor Nur77 in EC. LPS induces an increase of Nur77 expression that negatively regulates endothelial inflammasome activation, subsequent IL-1 β secretion, and endothelial permeability through transcriptional inhibition of caspase-1 expression by IFN regulatory factor-1 (IRF-1). The authors demonstrate that global Nur77 knockout (Nur77^{-/-}) decreases the effect of the Nur77-mediated antiinflammatory signaling. EC-specific effects of Nur77^{-/-} and IRF-1/caspase-1-independent mechanisms of Nur77 should be investigated in the future. The text in green indicates the findings of the authors. The text in red indicates unanswered questions. EC = endothelial cells.

lung inflammation by targeting Nur77 (14). Thus, addressing the Nur77–inflammasome axis in ARDS may hold promise for the development of future ALI therapeutics. ■

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