Romulus and Remus of Inflammation: The Conflicting Roles of MAP2K1 and MAP2K2 in Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by pulmonary edema due to excessive alveolocapillary permeability that causes a progressive decline in blood oxygen concentrations. Its prevalence is ∼10% of ICU patients and up to 23% of all ventilated patients. Given its multiple causes, manifestations, and responses to treatment, ARDS is a heterogeneous clinical entity (1). The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic setting has resulted in a further increase in ARDS incidence. Management of ARDS focuses on symptomatic therapy by providing cardiac and advanced respiratory support. To this day, no pharmacologic treatment has proven effective in attenuating the lung injury in ARDS.

The molecular mechanisms of lung injury in ARDS are complex and not fully understood. The initial exudative phase is governed by an alteration of the epithelial-endothelial barrier integrity, excessive inflammatory cell recruitment, and activation of neutrophils and monocytes. The subsequent release of signaling molecules mediates inflammation and can contribute to the pathophysiology of ARDS. Different cellular signals have been explored because of their potential role in the pathogenesis of ARDS. Recruitment of inflammatory cells to the lung is often maintained and amplified by the presence of local and systemic inflammatory cytokines and growth factors (2).

Accordingly, there is dysregulated signaling during chronic inflammation that results in the perpetuation of inflammation, resulting in tissue damage. Early induction of many inflammatory transcripts depends on transcription factor networks, including the master regulator of inflammation, NF-κB (3). However, the net production of the corresponding cytokines is regulated by MAPK (mitogen-activated protein kinase) signaling pathways, which are activated by various inflammatory signals. The MAPKs are a family of serine-threonine kinases that are activated by phosphorylation. The MAP2K/ERK signaling pathway can activate cytoplasmatic and nuclear targets that promote the expression of various cytokines that amplify the inflammatory response, thereby perpetuating and aggravating lung injury.

Those pathways have been studied using preclinical animal models involving the activation of stimulus-induced acute lung injury (ALI). The role of MAP2K1/MAP2K2 during inflammation has been controversial. Although these MAP kinases share 80% homology, the regulation of the MAP2K/ERK pathway involves the suppression of MAP2K2 by MAP2K1, but not vice versa. Consequently, MAP2K1 deletion leads to prolonged MAP2K2-ERK1/2 activation, resulting in sustained inflammatory responses. Using murine models, *MEK1* repletion has been shown to perpetuate the inflammation, contrary to what happens after *MEK2* depletion, which results in a rapid resolution of the inflammation (4). This suggests a regulatory effect of MAP2K1 on MAP2K2 and subsequent ERK activation, which has led several groups to propose using MAP2K2/ERK inhibitors to control inflammation. The conflicting relationship between MAP2K2 and MAP2K1 is reminiscent of the mythology story of the brothers Romulus and Remus. Romulus killed (suppressed) his twin Remus, which led to a dominant role of Romulus in the foundation of Rome and the Roman Kingdom.

In this issue of the *Journal*, Gong and colleagues (pp. 555–563) report that MAP2K2 inhibition has a deleterious effect on recovery from ALI (5). The authors present evidence that the mice deficient in MAP2K2 exhibit faster recovery after being challenged with *Pseudomonas aeruginosa* than the wild-type mice, faster clearance of bacteria, and decreased neutrophil counts in BAL. Also, they confirm that MAP2K2 is necessary for ERK activation, and its deletion does not affect the activity of MAP2K1. Functional enrichment analysis of the gene expression data suggested that MAP2K2 is associated with inflammation and interferon-related processes, and its deactivation drives the expression of genes toward reparative programs. Given the threat of increased ARDS cases due to new variants of SARS-CoV-2 or other viruses, this work is important for understanding the molecular mechanisms involved in the resolution of ALI. It opens the door for the development of much more selective drugs.

Finally, the authors found an SNP in *MAP2K2* (rs350912A) associated with an increased risk of death in ARDS. However, the effects of this genetic variation on the protein structure and how it affects its function remain to be determined. It could be assumed that it would have an alteration on the regulatory subunit that results in a sustained proinflammatory effect over time, triggering a higher mortality rate. However, this is still unknown, and it underscores the importance of identifying how the MEK/ERK pathway is regulated and how it alters the pulmonary macrophage inflammatory responses. ■

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