stress-related pathway that is activated by proinflammatory cytokines and growth factors in response to such stimuli as hypoxia with reoxygenation.³ These pathways have been investigated for decades, and much is known about them.

I read this work with great interest because of the intriguing series of experiments and the clarity of the molecular findings.³ Using their previous published experience, the authors dissected their *in vitro* model of IRI to define the isoform response of JNKs with small-interfering RNAs. They found that inhibition of JNK1 was protective of the cells from apoptosis.^{3,4} The opposite was true in experiments with inhibition of JNK2. This work was carried into a rat model of LT with intratracheal injection of JNK1 silencing RNAs. *In vivo*, the authors observed that JNK1 silencing inhibited inflammation and apoptosis, thereby alleviating graft injury. These findings were supported not only functionally, but also histologically. Their work is quite convincing for a damaging role of JNK1 in IRI. Importantly, JNK2 appears to be protective. These are exciting experiments taken from the cell

culture dish to an animal model. Assessing the clinical impact is an area for future studies.

As it relates to IRI and lung transplantation, this work has the potential to be extended into a growing body of literature that seeks to dissect the molecular events and intervene for this complex problem. The application of this molecular understanding will bring hope for potential therapeutics in the donor operating room, *ex vivo* perfusion, and the recipient operating room, with the overall goal of potentially improving the outcomes for this serious, unresolved clinical issue.

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Commentary: Constant dripping wears a stone away

Naoki Ozeki, MD, PhD, and
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Lung transplantation is one of the last treatment options for end-stage respiratory insufficiency. Although postoperative outcomes of lung transplantation have improved over time, pulmonary ischemia-reperfusion injury (IRI) remains a serious concern.^{1,2} Primary graft dysfunction (PGD), a major cause of death in the early period after lung transplantation, is often related to pulmonary IRI. Prevention of PGD is

Toyofumi Fengshi Chen-Yoshikawa, MD, PhD (left), and Naoki Ozeki, MD, PhD (right)

CENTRAL MESSAGE

A mitogen-activated protein kinase, c-Jun N-terminal kinase (JNK), plays a key role in lung ischemia-reperfusion injury. The opposite roles of JNK isoforms are investigated for clinical application.

imperative to achieve long-term graft survival; therefore, minimizing pulmonary IRI is one of the most important tasks related to lung transplantation. In this issue of the *Journal*, Tan and colleagues³ take on this challenging task.

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Mitogen-activated protein kinases, such as c-Jun N-terminal kinase (JNK), are intracellular signaling pathways activated by IRI. JNK controls various cellular processes, including regulation of gene expression and promotion of cell proliferation, death, and migration through phosphorylation of various target molecules. The key role of activated JNK is phosphorylation of transcription factor c-Jun, which forms activator protein-1 (AP-1). Tan and colleagues previously confirmed that the JNK/c-Jun/AP-1 pathway aggravated pulmonary IRI in rat pulmonary microvascular endothelial cells (PMVSCs).⁴ They also showed that the small interfering RNA-mediated silencing of JNK expression led to inactivation of the JNK/c-Jun/AP-1 pathway, alleviating pulmonary IRI. Based on the hypothesis in their established in vitro ischemia-reperfusion model, they now focus on the opposite roles of JNK1 and JNK2 to reveal the mechanisms underlying their effects in pulmonary IRI.⁵ JNK1 plays a detrimental role and JNK2 exerts a protective role in lung IRI, depending on the differential regulation of c-Jun/AP-1 pathway. In addition to in vitro experiments, the authors performed in vivo studies in a rat lung transplantation model. This continuous work of Tan's group should be highly applauded.

This study has some limitations. In vitro experiments were performed only in PMVSCs, but the lung tissue comprises multiple cell types, including type I and type II pneumocytes and alveolar macrophages. The JNK isoform-induced responses in each cell type may vary and remain unknown. Furthermore, the JNK isoform-induced IRI was studied without assessing the early impact of alloimmunity and physiological processes, such as mechanostress. Nonetheless, the authors used a rat lung transplantation model to prove that JNK1 silencing alleviates pulmonary IRI in several aspects.

We congratulate Tan and colleagues on their efforts to develop a novel treatment strategy to alleviate pulmonary IRI following lung transplantation. We believe that their findings open new treatment avenues for clinical lung IRI during transplantation, as has been observed with epidermal growth factor receptor tyrosine kinase inhibitors and immune checkpoint inhibitors against non-small-cell lung cancer with specific features. The authors propose JNK1 inhibition, JNK2 overexpression, and both together as new therapeutic strategies to prevent lung IRI following clinical lung transplantation. Future studies in a large animal model may aid the development of new, innovative, and promising therapies for lung transplantation. In addition, the manipulation of JNK expression may be extended to other organs to prevent IRI.

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