See Article page e113.

Commentary: To die or not to die—rescuing lung cells from ischemia–reperfusion injury

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For those with end-stage lung disease, lung transplantation is truly a lifesaving therapy. With improved methods of organ donor management and lung assessment within the last decade, the number of transplants performed annually has nearly doubled and continues to increase.¹ Despite continuing research efforts, lung transplantation is still associated with the lowest survival rates among all solid-organ transplants.² The development of severe primary graft dysfunction (PGD) is a major cause of this unfavorable prognosis, leading to high mortality within the first month after transplantation.^{3,4} Although the pathophysiology of PGD is still being investigated, the mechanism seems to be multifactorial based on injuries sustained to the graft during the transplantation process.⁵ One of the major contributors toward the development of PGD is lung ischemia–reperfusion injury (LIRI), a pathologic process occurring shortly after graft reperfusion involving the production of reactive oxygen species, the activation of immune and coagulation systems, endothelial dysfunction, and cell death.⁵ Despite ongoing investigations, no effective clinical treatment for LIRI is currently available.

In an attempt to unveil a therapeutic target to decrease the pathologic burden of LIRI, Ueda and colleagues⁶ from

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CENTRAL MESSAGE

Inhibition of necroptosis through the use of necrosulfonamide may protect against lung ischemia–reperfusion injury, alleviating the pathologic burden commonly seen in post-transplant recipients.

Kyoto University administered necrosulfonamide (NSA) to rats within a previously validated in vivo hilar clamping model of LIRI. The concept of administering NSA as a LIRI prophylactic stems from addressing a recently described mechanism of necrotic cell death, necroptosis. Previously defined as an uncontrolled process, necroptosis is a caspase-dependent regulated form of necrosis composed of a series of cellular signals.⁷ NSA works to effectively inhibit a downstream signaling protein in this pathway (mixed kinase domain-like protein), thus, reducing necroptosis.

Within the authors' evaluation, administration of NSA significantly reduced the number of necroptotic cells within the lung tissue after reperfusion compared with vehicle. This reduction was associated with significantly greater lung oxygenation, better lung compliances, lower airway pressures, less lung edema, and the presence of less inflammatory cytokines in animals treated with NSA. The authors' work brings forth the importance of targeting cell death-specific pathways during LIRI and, most importantly, demonstrates the role of necroptosis in the development of lung injury after lung reperfusion. Furthermore, the work of Ueda and colleagues has broad implications in the setting of different types of acute lung injuries that are dominated by necrotic cell death. Administration of NSA after prolonged warm ischemic injury or as an additive to the

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ex vivo lung perfusion perfusate during the recovery of severely injured lungs may also prove to result in positive outcomes.

Despite the promising findings of their study, further examination of this therapeutic drug needs to be performed in different animal models (preferably a large animal transplant model) to evaluate its preclinical potential within a more translational setting. Furthermore, although the dosing of NSA was arbitrarily set based on previously published literature, the optimal dose and timing of administration are the next step toward optimizing this therapeutic strategy.

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See Article page e113.

Commentary: A journey of a thousand miles begins with a single step

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Ischemia-reperfusion injury (IRI) remains the leading cause of primary graft dysfunction in lung transplantation and is considered the most important risk factor in early morbidity and mortality.¹ One of the prevailing features of IRI is necroptosis, a recently recognized category of cell death. Traditionally, cell death has been divided into controlled, programmed cell death (apoptosis), and accidental cell death (necrosis). Necroptosis displays features of both: the initiation of necroptosis is tightly regulated, and necroptotic cells trigger a strong inflammatory response.

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CENTRAL MESSAGE

Necroptosis is a promising new therapeutic target for reducing ischemia-reperfusion injury in lung transplantation.

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Necroptosis has been described as a relevant factor in a variety of diseases.^{2,3}

In this issue of the *Journal*, Ueda and colleagues⁴ report on the efficacy of necrosulfonamide, a mixed-lineage kinase domain-like protein inhibitor, in a rat pulmonary ischemia-reperfusion injury model. The number of