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Commentary: Every detail counts—different c-Jun N-terminal kinase isoforms perform different functions

Victor van Berkel, MD, PhD

Primary graft dysfunction (PGD) is one of the leading contributors to both short-term and long-term outcomes for lung transplantation. Despite improvements in surgical technique and donor preservation, the incidence of early PGD remains at approximately 30% of patients, with 15% to 20% of patients having severe (grade 3) PGD at 72 hours.¹ Although PGD is a multifactorial problem—dependent on donor, recipient, and operative factors—ischemia–reperfusion injury has been demonstrated to be central to the pathogenesis of PGD.² As such, an extensive body of research exists attempting to elucidate the molecular mechanisms of ischemia–reperfusion injury, in an effort to identify a means to ameliorate PGD.

c-Jun N-terminal kinases (JNKs) are part of the mitogen-activated protein kinase family and mediate multiple cellular effects in response to stress stimuli. To describe the role of JNKs within cells as complicated would be a gross understatement; the pathway has been under study for more than 20 years, with hundreds of interactions identified.³ For those of us who have purged most of molecular biology from our memories, a useful approximation is that inflammatory signals can activate JNKs, which can in turn, via interactions including activation and inhibition of other small molecules, regulate several important cellular functions, including cell growth, differentiation, survival, and apoptosis. It is perhaps not surprising, therefore, that ischemia–reperfusion stimulates the JNK pathway, and that blockade of this pathway improves ischemia–reperfusion injury.⁴

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CENTRAL MESSAGE

Different isoforms of JNK have different effects on ischemia–reperfusion.

In an effort to define more closely what components of the JNK pathway are impacting ischemia–reperfusion, Jing Tan and colleagues⁵ describe in this issue of the *Journal* an elegant series of both in vitro and in vivo experiments looking at 2 isoforms of JNK—JNK1 and JNK2. The authors used small interfering RNAs to block the activity of JNK1 and JNK2 independently and demonstrated in various in vitro studies the effectiveness of their blockades, as well as the impacts on inflammation, cell-cycle progression, and cell injury. Across these various cellular processes, results were consistent—blockade of JNK1 led to improved health of the cells (less inflammation, active progression, less cell injury), whereas blockade of JNK2 led to more damage to the cells. Finally, they build on these data by blocking the expression of JNK1 in an in vivo rat lung transplant model, which led to improved oxygenation, with less inflammation and graft injury.

The more precise our knowledge about these molecular pathways become, the more hope we have of developing effective treatments for disease processes. Although these data have no immediate impact on the clinical course of our patients, as there is no isoform-specific JNK blockade available, it is basic science research like this that helps focus future therapeutic efforts.

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Commentary: A tale of two isoforms in lung ischemia reperfusion injury: One is bad, two is good

Jonathan D'Cunha, MD, PhD

In the spring of 1987, I was attending a lecture for Biocore Semester 2 at the University of Wisconsin introducing the concept of differential regulation of second messenger systems within the cell. Yes, I know I am dating myself, but this historical context is important for introducing the point of the decades of research into these pathways. At that time, cAMP was all the rage, and we were taught that understanding the signaling mechanisms within a cell and the downstream consequences of various stimuli would lead to better understanding of biological effects at higher levels. The molecular events leading to these cellular events humble clinicians, especially cardiothoracic surgeons, when treating a patient with hypoxia and systemic inflammation.

For patients with advanced lung disease, lung transplantation (LT) is a key therapeutic option. LT can indeed extend and improve the quality of life, but one of the major obstacles for successful long-term outcome is primary graft dysfunction (PGD) around the time of transplantation. PGD affects approximately 10% to 15% of all LT recipients and is associated with increased risks of chronic rejection and mortality.¹ Characterized clinically and radiographically by

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CENTRAL MESSAGE

The isoforms of c-Jun N-terminal kinase 1 and 2 have different functional impacts on ischemia/reperfusion injury in a lung transplantation model.

hypoxemia and pulmonary infiltrates (ie, edema) with diffuse alveolar damage, PGD is a severe form of ischemia/reperfusion (I/R) lung injury with inflammation occurring within the first 72 hours after lung transplantation.

I/R injury (IRI) is multifactorial, complex, and highly integrated, leading to perturbation induced by ischemia and severe damage to cellular structures during reperfusion. These events lead to cell death and severe injury to transplanted organs.¹ The incidence of I/R injury is much higher, such that it would be reasonable to postulate that it exists along a spectrum of severity. Despite considerable progress during the past decade, the molecular mechanisms responsible for IRI/PGD remain poorly understood. Consequently, identifying new molecular targets and preventive measures for IRI is critical for improved outcomes.

In this issue of the *Journal*, Tan and colleagues² investigate the role of the c-Jun N terminal kinase (JNK) pathway and its role in IRI injury in a rat model of LT. JNK is a member of the mitogen-activated protein kinase (MAPK) family of signaling pathways within the cell that respond to stressful stimuli. Activated JNK exerts its influence through the AP1 family of transcription factors to regulate numerous cellular events, including proliferation, differentiation, inflammation, and survival. JNK is a

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