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Subnormothermic ex-vivo lung perfusion protects against ischemia-reperfusion injury via the mTORC–HIF-1α pathway

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Introduction: *Ex-vivo* lung perfusion is a useful technique for evaluating and repairing donor lungs for transplantation. However, studies examining the effects of perfusate temperature on graft function are limited. This study aimed to examine the effects of subnormothermic perfusate temperature during *ex-vivo* lung perfusion on ischemic reperfusion injury of the donor lung.

Methods: Twenty-four male Sprague-Dawley rats were randomly divided into three groups, namely no treatment (sham group, n=8), normothermic EVLP (37 C, normoEVLP, n=8), and subnormothermic EVLP (30 C, subnormoEVLP, n=8). Lung function analyses, in terms of oxygen capacity, compliance, and pulmonary vascular resistance, were performed. The expression levels of inflammatory cytokines were evaluated. Metabolome analysis was performed on lung tissues from each group using capillary electrophoresis time-of-flight mass spectrometry.

Results: Functional parameters such as oxygen capacity, compliance during ex-vivo lung perfusion and subsequent histologic results were significantly superior in the subnormoEVLP than in the normoEVLP. Expression levels of inflammatory cytokines were significantly lower in the subnormoEVLP than in the normoEVLP. Metabolome analysis showed glycolysis to be significantly decreased in the subnormoEVLP than in the normoEVLP. Expression levels of mTORC, HIF-1, NLRP3, and its effector caspase-1 were significantly lower in the subnormoEVLP than in the normoEVLP.

Conclusion: Compared to normothermic EVLP, subnormothermic EVLP improves lung graft function by decreasing the expression of pro-inflammatory cytokines and suppressing glycolytic activity. This can be explained by inhibition of the mTORC-HIF-1*a* pathway in subnormothermic EVLP.