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Potential therapeutic targets for lung repair during human *ex vivo* lung perfusion

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ABSTRACT

Introduction: The *ex vivo* lung perfusion (EVLP) technique has been developed to assess the function of marginal donor lungs and has significantly increased donor lung utilisation. EVLP has also been explored as a platform for donor lung repair through injury-specific treatments such as antibiotics or fibrinolytics. We hypothesised that actively expressed pathways shared between transplantation and EVLP may reveal common mechanisms of injury and potential therapeutic targets for lung repair prior to transplantation.

Materials and methods: Retrospective transcriptomics analyses were performed with peripheral tissue biopsies from "donation after brain death" lungs, with 46 pre-/post-transplant pairs and 49 pre-/post-EVLP pairs. Pathway analysis was used to identify and compare the responses of donor lungs to transplantation and to EVLP.

Results: 22 pathways were enriched predominantly in transplantation, including upregulation of lymphocyte activation and cell death and downregulation of metabolism. Eight pathways were enriched predominantly in EVLP, including downregulation of leukocyte functions and upregulation of vascular processes. 27 pathways were commonly enriched, including activation of innate inflammation, cell death, heat stress and downregulation of metabolism and protein synthesis. Of the inflammatory clusters, Toll-like receptor/innate immune signal transduction adaptor signalling had the greatest number of nodes and was central to inflammation. These mechanisms have been previously speculated as major mechanisms of acute lung injury in animal models.

Conclusion: EVLP and transplantation share common molecular features of injury including innate inflammation and cell death. Blocking these pathways during EVLP may allow for lung repair prior to transplantation.