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Transcriptomic investigation reveals donor-specific gene signatures in human lung transplants

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ABSTRACT

Introduction: Transplantation of lungs from donation after circulatory death (DCD) in addition to donation after brain death (DBD) became routine worldwide to address the global organ shortage. The development of *ex vivo* lung perfusion (EVLP) for donor lung assessment and repair contributed to the increased use of DCD lungs. We hypothesise that a better understanding of the differences between lungs from DBD and DCD donors, and between EVLP and directly transplanted (non-EVLP) lungs, will lead to the discovery of the injury-specific targets for donor lung repair and reconditioning.

Methods: Tissue biopsies from human DBD (n=177) and DCD (n=65) donor lungs, assessed with or without EVLP, were collected at the end of cold ischaemic time. All samples were processed with microarray assays. Gene expression, network and pathway analyses were performed using R, Ingenuity Pathway Analysis and STRING. Results were validated with protein assays, multiple logistic regression and 10-fold cross-validation.

Results: Our analyses showed that lungs from DBD donors have upregulation of inflammatory cytokines and pathways. In contrast, DCD lungs display a transcriptome signature of pathways associated with cell death, apoptosis and necrosis. Network centrality revealed specific drug targets to rehabilitate DBD lungs. Moreover, in DBD lungs, tumour necrosis factor receptor-1/2 signalling pathways and macrophage migration inhibitory factor-associated pathways were activated in the EVLP group. A panel of genes that differentiate the EVLP from the non-EVLP group in DBD lungs was identified.

Conclusion: The examination of gene expression profiling indicates that DBD and DCD lungs have distinguishable biological transcriptome signatures.