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**Title:** Marginated monocytes play a central role in lung ischaemia–reperfusion injury in mice: Implications for lung transplantation

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**Body:** Background: Lung transplantation success is limited by donor lung inflammation, which exacerbates ischaemia-reperfusion (IR) injury leading to primary graft dysfunction. Alveolar macrophages within the donor lung and recipient neutrophils have been implicated in this process. Recent evidence suggests that lung-marginated inflammatory subset monocytes play a key role in the progression of acute lung injury. We hypothesised that donor lung-marginated monocytes are important contributors to the IR injury in lung transplantation. Methods: Isolated mouse lungs were flushed for 5min with RPMI/4%BSA buffer, and then underwent 2hrs of ischaemia and 2hrs of recirculating perfusion (40ml/kg/min). Results: Compared to perfusion-only controls, IR produced much higher levels of BALF protein and lung wet:dry ratios (Table 1). A substantial number of Ly-6C$^{high}$ monocytes still remained after reperfusion (4.8 x10$^5$) and exhibited activation as measured by L-selectin shedding. Monocyte depletion (by pretreating mice with iv clodronate) resulted in a significant reduction in IR-induced injury (Table 1), with reduced lung neutrophil CD11b expression.

Lung Injury

| | Perfusion | IR | Clodronate IR |
|---|---|---|---|
| BALF Protein mg/ml | 0.34±0.15* | 0.83±0.61 | 0.24±0.06** |
| Wet:Dry Ratio | 4.7±0.3** | 6.0±0.3 | 5.5±0.1** |

Mean±SD,* p<0.05, **p<0.01 vs IR

Discussion: We have demonstrated that significant numbers of monocytes are still retained within the buffer-flushed lungs, and that these monocytes play a central role in the evolution of IR injury. Our findings indicate that lung-marginated donor-derived leukocytes, in particular monocytes, can be an important novel target for prevention of post-transplantation lung injury.