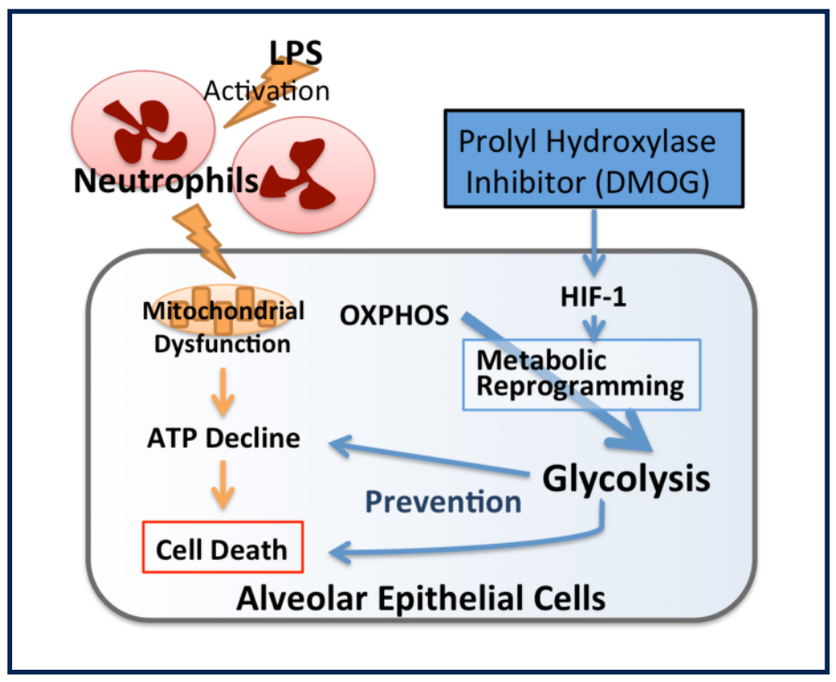
Metabolic reprogramming by inhibition of prolyl hydroxylases protects alveolar epithelial cells from LPS-neutrophil-induced energy derangements and cell death



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Summary

- LPS-activated neutrophils cause ATP decline and alveolar epithelial cell death.
- Pharmacological inhibition of a cellular oxygen sensor, prolyl hydroxylases (PHDs) causes HIF-1 mediated metabolic reprogramming from oxidative phosphorylation (OXPHOS) to glycolysis.
- PHD inhibition protected alveolar epithelial cells from neutrophil-LPS-induced ATP decline and cell death via HIF-1-mediated metabolic reprogramming.

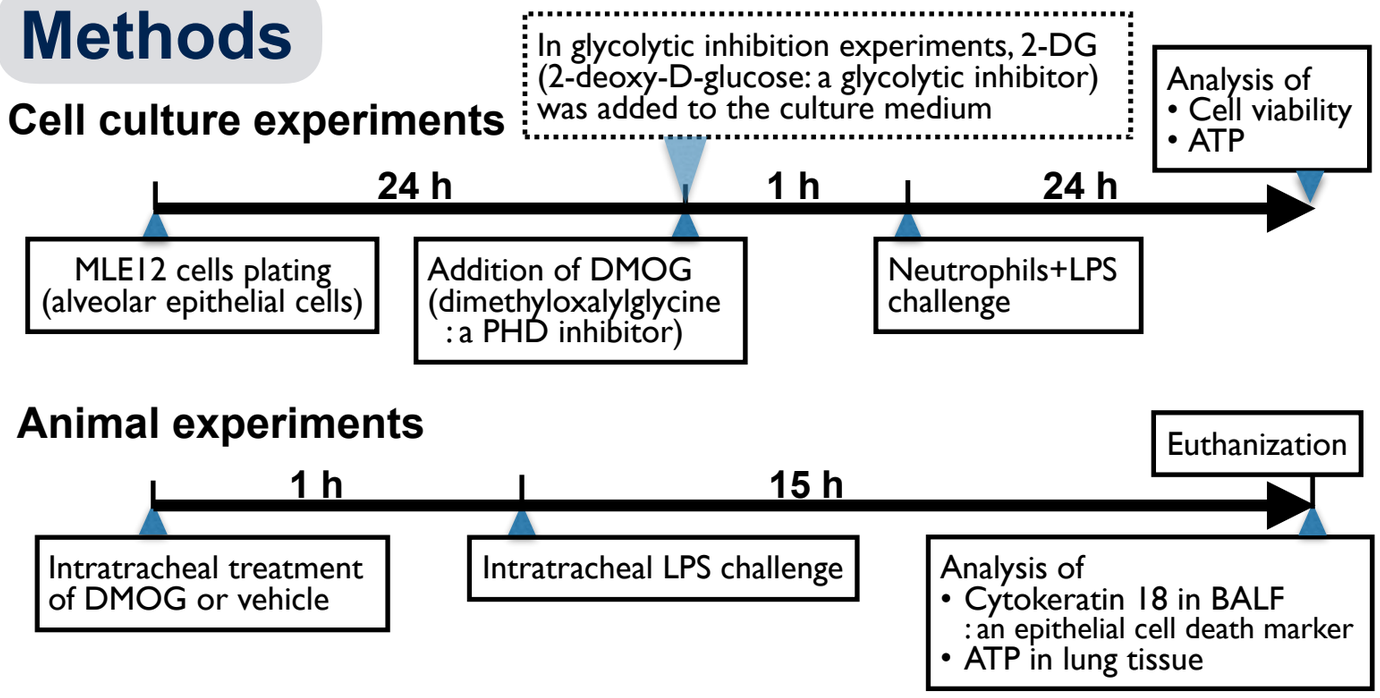
Background

- **Neutrophil-mediated alveolar epithelial injury** is a hallmark of acute respiratory distress syndrome (ARDS).
- Cellular **energy derangement due to mitochondrial dysfunction** underlies the alveolar epithelial injury.
- Therefore, **metabolic reprogramming** shifting bioenergetic activity from mitochondria-dependent OXPHOS to glycolysis may protect alveolar epithelial cells from ARDS.

Hypothesis

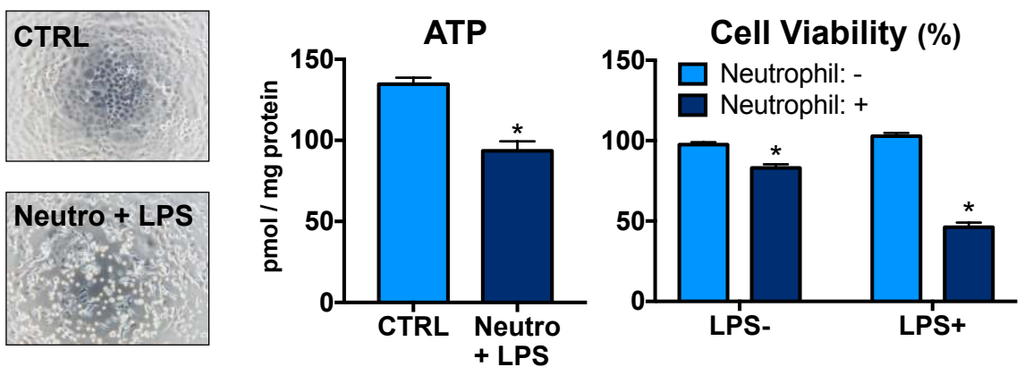
Metabolic reprogramming by pharmacological inhibition of a cellular oxygen sensor, prolyl hydroxylases (PHDs) may protect alveolar epithelial cells from lung injury.

Methods



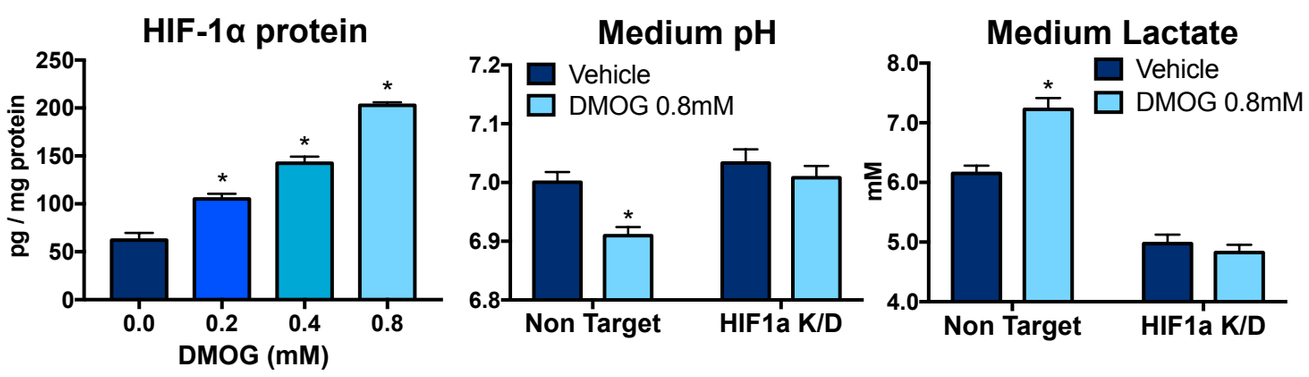
Results and Discussion

Neutrophils + LPS induces ATP-decline and alveolar epithelial cell death



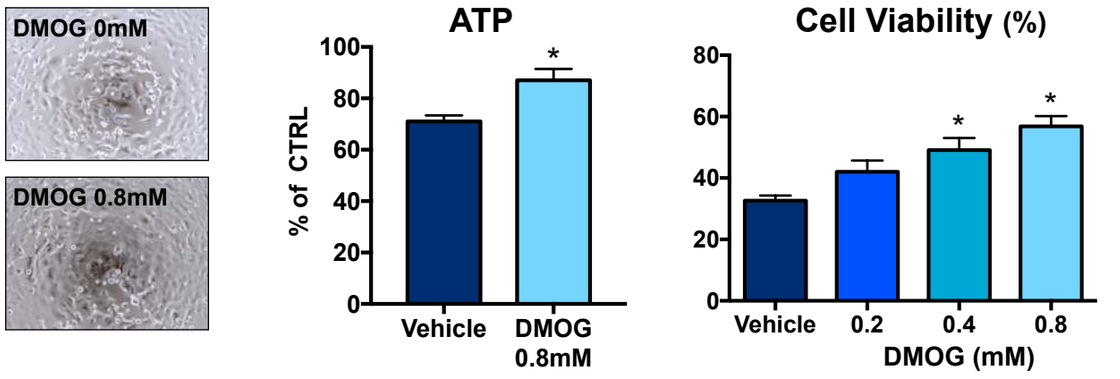
Neutrophil-LPS challenges induced ATP decline in MLE12 cells; an alveolar epithelial cell line. Concomitantly, cell viability was significantly decreased by neutrophil-LPS challenge. The cell death was not suppressed by caspase 3/7 inhibitor (data not shown). * p<0.05 *vs.* control.

Pharmacological inhibition of PHDs by DMOG causes HIF-1 mediated metabolic reprogramming



A PHD inhibitor, DMOG increased HIF-1α protein in MLE12 cells, however not HIF-2α (data not shown). Moreover, DMOG increased indicators of glycolytic activity; medium acidification and lactate production, which were abolished by HIF-1α knock-down. * p<0.05 *vs.* vehicle group.

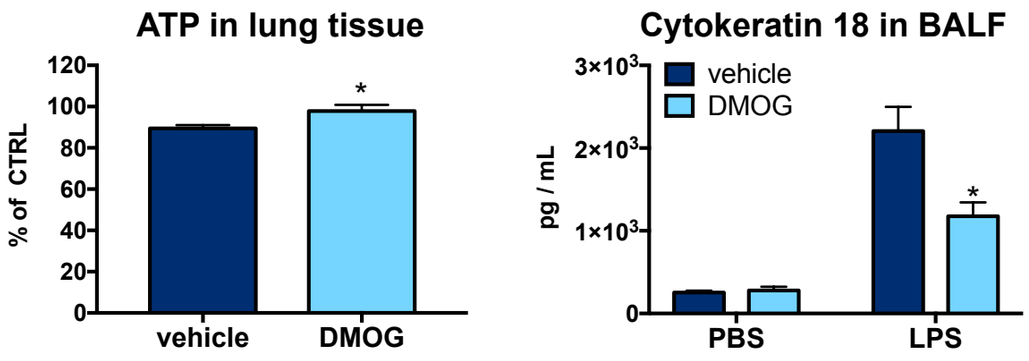
DMOG protects alveolar epithelial cell through HIF-1-mediated metabolic reprogramming from OXPHOS to glycolysis.



DMOG treatment attenuated the neutrophil-LPS-induced ATP decline and cell death in dose-dependent manner. * p<0.05 *vs.* vehicle group

HIF-1α knock-down abolished the protective effects of DMOG. Furthermore, glycolytic inhibition by 2-DG reversed the effects of DMOG. * p<0.05 *vs.* vehicle group

Intratracheal DMOG treatment attenuates alveolar epithelial cell death and ATP decline in LPS-induced lung injury mice



Intratracheal LPS-instillation-induced ATP decline in lung tissues and increased an epithelial cell death marker; cytokeratin 18 in BALF. Intratracheal DMOG treatment attenuated these changes. * p<0.05 *vs.* vehicle group.

Conclusion

- **Pharmacological inhibition of PHDs protected alveolar epithelial cells from LPS-neutrophil-induced ATP decline and cell death via HIF-1-mediated metabolic reprogramming.**
- **Metabolic reprogramming from OXPHOS to glycolysis may be a novel approach to protect alveolar epithelial cells from ARDS.**

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