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Modulation Of Mechanical Ventilation-Induced Alveolar Epithelial Cell Death Signaling By Underlying Lung Inflammation

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Abstract:
Rationale: Acute respiratory distress syndrome (ARDS) is characterized by alveolar epithelial cell (AEC) dysfunction with alveolar edema formation. This is compounded by mechanical ventilation (MV) through ventilator-induced lung injury (VILI).
Apoptosis is implicated in AEC dysfunction and is activated through initiator caspases-8/-9 and executed via caspase-3. Apoptosis may have distinct roles during different phases/etiologies of ARDS. Caspase activation is associated with early (<3hrs) AEC dysfunction in acid-induced ARDS (**1**) but during later phases (48hrs), caspase activation is associated with resolution (**2,3**). In contrast, at 48hrs, lipopolysaccharide (LPS)-induced ARDS shows no caspase activation but substantial injury (**3**). Furthermore, inhibition of caspase-8 activation can drive necroptotic cell death, the impact of which is less well characterized in ARDS.
Firstly, we sought to characterize the nature of caspase activation and early AEC dysfunction during VILI. Secondly, if caspase signalling is modulated when MV is superimposed onto a model of LPS-induced ARDS. Finally, to investigate if absent caspase activation in LPS-induced ARDS is associated with necroptosis activation.
Methods: To investigate early caspase activation by MV, anaesthetized C57BL/6 mice were exposed to increasing tidal volumes (10; 20; 35ml/kg) for 3hrs (4). To determine if MV induces caspase activation during established lung inflammation, some animals underwent intranasal instillation of 25μg LPS 48hrs prior to 3hrs of 20ml/kg MV. AEC-specific caspase activities were quantified in lung single cell suspensions by flow cytometry using a fluorochrome-conjugated probe (**1**). Finally, mRNA expression of the necroptosis pathway executor MLKL was measured in LPS-instilled lung homogenates using PCR.
Results: Increasing tidal volume provoked an incremental increase in AEC caspase activity associated with increased lung wet:dry ratio. In complete contrast, MV did not promote caspase activation in LPS-pretreated mice.
LPS-induced lung inflammation alone did not lead to caspase activation compared to untreated mice (suggesting that LPS may desensitize these pathways) but upregulated MLKL mRNA at 48 hours (MLKL $\Delta ctx10^5$ compared to 18S; Control:0.89+/-0.32; LPS48hrs:8.20+/-0.68; P=0.003 by *t*-test; N=3-4).
Conclusion: Lung stretch activates early AEC caspase signaling, before substantial injury becomes apparent, but this did not occur in the presence of established LPS-induced lung inflammation. In contrast, our data suggests that in the presence of LPS, necroptosis seems to be the predominant cell death pathway possibly as a result of caspase-8 inactivation. The pathophysiological interplay between apoptosis and necroptosis in ARDS and VILI merits further investigation.
References:
1. *J Immunol*, 2013;190(8):4274-82. 2. ERJ, 2012;39(5):1162-70.

	Uninjured (n=5)	TV10 (n=5)	TV20 (n=5)	TV35 (n=5)
Wet/Dry weight ratio	4.55±0.32	4.33±0.27	4.67±0.44	6.22±0.4##
Caspase activity in AEC identified as CD45- CD31-EPCAM-T1a+ (Median Fluorescent Intensity)				
Caspase 8	73.79±42.52	116.16±58.29	139.69±30.73	142.29±48.36#
Caspase 9	58.53±26.14	98.84±65.07	78.95±21.89	161.21±32.43#
Caspase 3	83.01±26.33	68.04±36.84	101.96±30.13	128.21±24.79#
TV10; tidal volume 10ml/kg , TV20; TV 20ml/kg, TV35; 35ml/kg				
Mean±SD, #P<0.05, ##P<0.001 vs uninjured by one-way ANOVA + Bonferroni's multiple comparison				

	Uninjured (n=5)	TV20 (n=5)	LPS 25ug (n=5)	LPS25ug+TV20 (n=4)
Wet/Dry weight ratio	4.55±0.32	4.67±0.44	4.42±0.32	4.87±0.48
Caspase activity in AEC identified as CD45- CD31-EPCAM-T1a+ (Median Fluorescent Intensity)				
Caspase 8	73.79±42.52	136.69±30.73#	78.85±28.51	81±35.53
Caspase 9	58.53±26.14	78.95±21.89	36.43±24.91	53.02±27.38
Caspase 3	83.01±26.33	101.96±30.13	76.57±19.08	76.55±25.12
Mean±SD, #P<0.05 vs uninjured by *T*-test				

3. AJRCCM 2017;195:A4325 4. Crit Care Med 2012;40(10);2850-57
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