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Title: TNF and IP-10 drive inflammation into hyperinflammation in the murine lung

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Body: The lung is prone to injurious stimuli from two sides: directly via the airways or indirectly via the capillary network. Once the alveolar-capillary barrier is disrupted, pulmonary inflammation is ongoing. Inflammation may proceed without tissue damage until the stressor is removed or may aggravate leading to organ dysfunction as in acute respiratory distress syndrome. We propose that salutary and destructive inflammation (hyperinflammtion) are two distinct modules, activated depending on the severity of injury. This study was designed to examine our hypothesis that TNF and IP-10 drive inflammation into hyperinflammation. C57/BL6 mice were instilled with 50µL HCl pH=2 or saline and then ventilated for 1 hour, before 5µg TNF + 5µg IP-10 in 50µL PBS were aerosolized into the lungs. Control groups received 50µL PBS. Mice were ventilated for a further 6 hours. Lung mechanics, oxygenation and cardiovascular parameters were monitored during ventilation. Pro-inflammatory mediators, leukocyte recruitment, microvascular permeability and histology were examined in the lungs. There was no significant difference between mice instilled with acid pH=2 or saline alone. Inflammatory mediators and neutrophils were found in all ventilated lungs, but oxygenation and lung functions were not impaired. Additional application of TNF+IP-10 led to critical physiological dysfunction only in mice pre-treated with acid pH=2, not in those treated with saline. This indicates that acid pH=2 initiates inflammation and makes the lungs susceptible to hyperinflammation triggered by TNF+IP-10. We conclude that a certain set of mediators, including TNF and IP-10, may be responsible for turning mild inflammation into full-blown hyperinflammation.