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Keyword 1: ALI (Acute Lung Injury) **Keyword 2:** Monocyte / Macrophage **Keyword 3:** Epithelial cell

Title: Resident alveolar macrophages mediate early alveolar epithelial death signaling and dysfunction

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Body: Acute lung injury (ALI) is characterized by alveolar epithelial dysfunction. We previously showed that early epithelial dysfunction was specifically mediated through tumor necrosis factor (TNF) p55 receptor signaling [1]. This study examined the contribution of resident alveolar macrophages (AM) to this phenomenon following acid aspiration. C57Bl6 mice were treated intratracheally with liposomes containing either clodronate or PBS. After 48 hours, they underwent intratracheal instillation of hydrochloric acid followed by mechanical ventilation to assess respiratory parameters. Oxygenation, respiratory elastance, alveolar TNF concentration, lung caspase-8 activity and alveolar fluid clearance (AFC) were measured at 90 minutes after acid instillation. Clodronate liposomes produced an 80% depletion of AMs. AM depletion significantly improved the deterioration in respiratory elastance ($cmH_2O/\mu l$: PBS=0.06±0.008; CLOD=0.05±0.004; $p<0.05$) and PaO_2:FiO_2 (PBS=304±113; CLOD=426±41; $P<0.05$) induced by acid instillation. Additionally, alveolar TNF was significantly reduced (pg/ml: PBS=46.5±25.8; CLOD=15.5±2.7; $P<0.05$), along with attenuated lung caspase-8 activity (arbitrary units: PBS=14763±5466; CLOD=7135±372; $P<0.01$), and improved AFC (%/30min: PBS=3.8±2.6; CLOD=7.1±2.4; $P<0.05$). Caspase-8 activity showed an inverse correlation to AFC (Pearson $r=-0.766$; $P<0.0001$) implying epithelial death receptor activation. These data suggests that during ALI induced by acid aspiration, epithelial dysfunction and hypoxemia are a result of epithelial cell death receptor activation by alveolar macrophage-derived TNF. [1] Patel et al. Intensive Care Med. 2011;37(Supplement):S205 Supported by Wellcome Trust, UK.