MACROPGAHE-SPECIFIC NANOPARTICLE DELIVERY OF MICRORNAS TO MITIGATE VENTILATOR-INDUCED LUNG INJURY

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The acute respiratory distress syndrome (ARDS) is a life-threatening condition that requires life-support therapy with mechanical ventilation (MV). However, MV generates mechanical forces that can exacerbate lung injury, known as ventilator-induced lung injury (VILI) [1]. These forces can damage the alveolar-capillary barrier and trigger the release of proinflammatory mediators which further damage the barrier. Recently, our laboratory demonstrated that alveolar macrophages (AMs), the resident immune cells of the lung, respond to mechanical forces by upregulating an anti-inflammatory microRNA, miR-146a, but that this native mechanotransduction response is insufficient to mitigate VILI [2]. In addition, we have demonstrated that overexpression of miR-146a in-vivo using non-targeted lipid nanoparticles (LNPs) mitigates cytokine release and barrier disruption following injurious ventilation [2]. However, the in-vivo nanoparticle distribution data showed that ~40% of nanoparticles are distributed in non-AMs cells (primarily epithelial cells) [2]. Therefore, in this study we aim to develop mannosylated LNP (M-LNPs) that can deliver miR-146a to only AMs. We hypothesize that this AM-specific delivery of miR-146a can more potently mitigate lung injury and dampen inflammatory signaling pathways during ARDS/VILI. We use an in vitro pneumocyte-AM co-culture system to evaluate the targeting efficiency of M-LNPs. We find that M-LNPs preferably deliver miR146a to AMs at higher extent than LNP delivery. To evaluate the therapeutic potential to mitigate lung injury during mechanical ventilation, we use an in vitro barotrauma model and measure pro-inflammatory cytokine release. Our results indicate that the M-LNPs can more potently dampen pro-inflammatory cytokine release in response to barotrauma.

References: [1] Carrasco Loza, et al., (2015) *Open Respir Med J*, 9:112-9 [2] *Bobba, *Fei, et al., (2021) *Nat Commun,* 12, 289.