10.09 The innate and adaptive immune responses following Mesenchymal Stromal Cell administration before 'second hit' injury in rodent pneumonia models.

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Background: In ventilated ARDS patients secondary, opportunistic infection is often a result of a depressed immune system due to prolonged primary infection and overuse of antibiotics. Here we aimed to develop a clinically-relevant, 2-hit model by first establishing *K.pneumoniae* infection and then administering a subsequent lipopolysaccharide (LPS) injury to mimic secondary injury. Mesenchymal stromal cells (MSCs) were administered during the acute phase of pneumonia to examine a possible protective effect toward a later 'second hit' injury.

Methods: A clinically-isolated, antimicrobial-resistant (AMR) *K.pneumoniae* bacteria was administered to rats to induce pneumonia. MSCs or control (PBS) was administered 1h later. After 72h, a bolus of *E.coli* LPS was administered, and injury allowed to develop during ventilation for 4h. Blood and BAL were collected and analysed post-mortem for leukocyte numbers, differential cell counts, and inflammatory cytokine levels to determine MSC mechanism of action *in vivo*.

Results: MSCs increased survival compared to control animals. Total white cell counts in the lung were decreased by MSCs after LPS injury (Fig1A) and neutrophil fraction was also reduced (Fig1B). Circulating white cell populations were notably different at baseline in non-survivors of 2nd hit and/or prolonged ventilation, MSCs appeared to stabilise this (Fig1C&D).

Conclusion: MSCs attenuated secondary injury and decreased mortality in pneumonia and appeared to be mediated by circulating and local immune populations.

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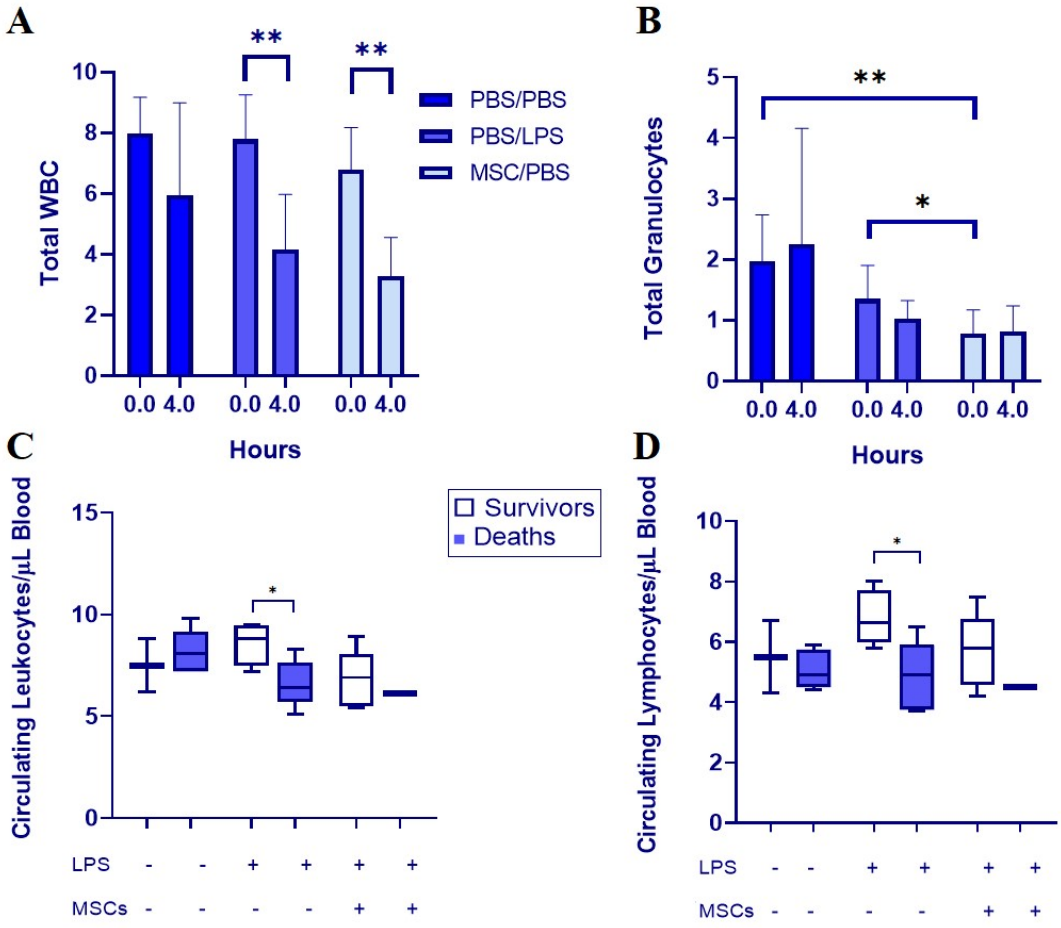

Figure 1: Local and Circulating white blood cell populations are altered by MSC administration and survival is dependent on baseline levels. LPS administration decreased the circulating levels of WBCs at 4h (A). Granulocytes were decreased by MSC administration at baseline and retained at low levels (B). Animals who did not survive the 4h protocol had significantly lower levels of WBCs and lymphocytes at baseline (C,D).