Pneumovirus Induced Lung Disease in Mice is Independent of Neutrophil Driven Inflammation

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Introduction

The human pneumovirus: Respiratory Syncytial Virus (hRSV) is the most common cause of lower respiratory tract disease (LRTD) in young children and causes considerable mortality and morbidity. Characteristic features of hRSV-LRTD are:

- Massive neutrophil recruitment in the lungs under influence of IL8
- Viscous DNA-rich mucus plugging obstructing the airways

Neutrophils have been proven damaging during ARDS and sepsis and may play a role in the pathogenesis of pneumovirus infections. One potential damaging effector function of neutrophils is the formation of Neutrophil Extracellular Traps (NETs), which consist of expelled DNA fibers covered with toxic granule proteins which can capture microbes but also damage host tissue.

Hypothesis

We hypothesized that neutrophils are detrimental during severe pneumovirus disease and as such, neutrophil depletion will lead to improved clinical and histopathological outcomes.

Aim

We aim to confirm the detrimental role neutrophils play during severe pneumovirus infection in mice. This could provide new insights in the pathogenesis of pneumovirus infections and lead to anchorpoints for new treatments.

Methods

Animals

- C57Bl6 mice (female, 8wks)
- BALBc mice (female, 8wks)

Virus & Inoculation

- Pneumonia virus of mice (PVM) strain J3666

Neutrophil depletion

- Intraperitoneal injections with anti-Ly6G mAb (500µg, 1A8)

Schedule:

- Day 0: PVM infection
- Day 1: Antibody injection
- Days 1-5: Antibody injection

Figure 1: Significant neutrophil depletion in the 1A8 treated groups

Figure 2: Neutrophil depletion does not result in attenuated disease severity

Figure 3: No increased semi-survival in the 1A8 treated groups.

Figure 4: Neutrophil depletion does not influence viral clearance during severe PVM infection.

Figure 5: Neutrophils increased lung permeability during PVM infection

Figure 6: Increased BAL KC levels in neutrophil depleted mice

Figure 7: NET formation

Conclusion

- Our study shows that neutrophils do not have a major role in modulating disease outcome and viral clearance during PVM infection in mice. As such, this rodent specific pneumovirus model does not support the notion that neutrophils play a key role during severe RSV disease.
- Important differences in neutrophil functions between humans and mice during pneumovirus disease may exist, as shown by the relative absence of NET formation.
- Future studies in humans and possibly other animal models must extend these findings and further address the role of neutrophils in human RSV disease.

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Disclosures

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 Figure 5: Neutrophil depletion does not result in altered lung histopathology

 Figure 6: NET formation

 Figure 8: NET formation