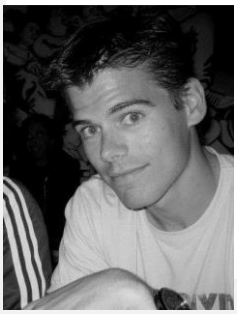
ImmunoTools *special* Award 2014



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Neutrophils in severe RSV-disease: wielding the double edged sword.

In my research I try to characterize the role of neutrophils during severe RSV disease in humans. The human respiratory syncytial virus (RSV) is among the most important respiratory pathogens in children. Infection by RSV causes mild to severe, potentially life threatening acute airway and lung disease, leading worldwide to 200.000 deaths each year. Currently there is no effective treatment.

Neutrophils are by far the most abundant leukocytes in the lungs of children with RSV disease. However, remarkably their precise role, whether pivotal in the host innate anti-viral response or detrimental by causing inflammatory damage, is unclear.

Neutrophils might switch roles (from virus clearing to collateral damage causing) during the disease and my main hypothesis is that as such increased and prolonged activation of neutrophils during the disease course is a key event in the pathogenesis of severe RSV disease.

To unravel these time-related dynamic changes in neutrophil activity I will try to phenotyp the neutrophil in lung-lavage fluid of mechanically ventilated children with RSV using neutrophil markers with flow cytometry during their disease course (CD11b/c, CD14, CD54, CD18, CD62L, CD44, CD45). Using neutrophil activation and inhibition markers we want to visualize different subsets of high and/or low activation. We hypothesize that the balance between activation and inhibition is disturbed later during the disease. As a consequence the subset of highly activated and damaging subgroup will therefore cause more damage in the late phase of the disease. Furthermore I will look for shifts in neutrophil recruitment/activation mediators (e.g. IL-8 and TNF-α) during the RSV disease course, measuring both in lavage fluid and in serum.

Next we will extract neutrophils from human blood and co-culture them with primary bronchial epithelial cells of young children mimicking different clinical situations by adding lung-lavage fluid from children with severe RSV disease and milder RSV disease and recombinant Immunotools cytokines (TNF-a, IL-8, MIP-1a, IL-10, GM-CSF). Results from these in vivo and in vitro studies will increase our insight in neutrophil function and changes during RSV disease. Again flow cytometry will be used to characterize neutrophil subsets.

Third we will look at specific inhibition of neutrophil recruitment in a mice pneumovirus model, to address possible therapeutic options. We will compare the result of early and late inhibition of neutrophils and use flow cytometry to assess neutrophil phenotyps (Gr-1, CD11b, CD49d).

I anticipate that the combined study of humans, animals, in vivo and in vitro models will increase our insight into the role of neutrophils in hRSV disease. I hypothesise that neutrophils have a role as effector cells in the anti-viral response, but may also contribute to the immunopathology when increased and/or prolonged activated. And that interference in this process could lead to, dearly needed, novel therapeutic options.