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Novel imaging-supported trisomic mouse model of RSV-infection for immunological studies of respiratory infections in the context of Down syndrome.

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Introduction

Individuals with Down syndrome (DS) are particularly prone to severe and recurrent lower respiratory tract infections (LRTI) with RSV [1]. The DS-related structural and functional anomalies in the respiratory system, as well as altered immune constitution, may contribute to the severity of RSV infection. Towards studying LRTI and its treatment options in the context of DS, we characterized a model of RSV infection and its associated pathology in the Ts65Dn mouse model of DS, supported by multimodal, longitudinal non-invasive imaging.

Methods

Five to six-week-old Ts65Dn mice and their euploid littermates were intranasally challenged with a recombinant luciferase encoding RSV strain (rhRSV-Luc) or PBS [2]. Mice were followed up daily by weighing, bioluminescence imaging (BLI), and micro-computed tomography (µCT). An in-house trained U-shaped convolutional neural network was used to segment the lungs and extract the total (TLV), aerated, and non-aerated lung volumes and corresponding mean densities. At predefined endpoints (4 and 7 days post-infection), we invasively tested lung function and airway hyperresponsiveness, followed by bronchoalveolar lavage, spleen, and lung collection to assess immunological response and viral load.

Results/Discussion

BLI localized rhRSV-Luc infection to the nose, and lower respiratory tract of mice (Fig. 1), similar to the course of human infection. The establishment of LRTI was supported by the viral load at endpoints. Moreover, BLI indicated that Ts65Dn mice less efficiently clear the virus, which we could link to increased CD4+:CD8+ T-cell ratios in the lungs and spleens of infected Ts65Dn mice (Fig. 1&2). Overall spleen cell counts demonstrated lower splenocyte numbers and the absence of systemic monocyte upregulation and humoral response in Ts65Dn mice. Regardless of rhRSV-Luc infection in the presence of an altered immune response, µCT analysis revealed no signs of pneumonia or bronchiolitis in mice following infection, consisted with the absence of altered lung functions or neutrophil counts in the lungs and airways upon

infection of Ts65Dn mice.

Conclusions

We here report and characterize the first multimodal imaging-supported model to study LRTI in the context of DS. Challenging Ts65Dn mice with RSV resulted in an LRTI followed by less efficient viral clearing and the absence of a humoral response. This model can be applied to study passive immunization and vaccination strategies against LRTI in the context of DS.

Disclosure

- a) I or one of my co-authors have **no financial interest** or **relationship** to disclose regarding the subject matter of this presentation.

Affix

References

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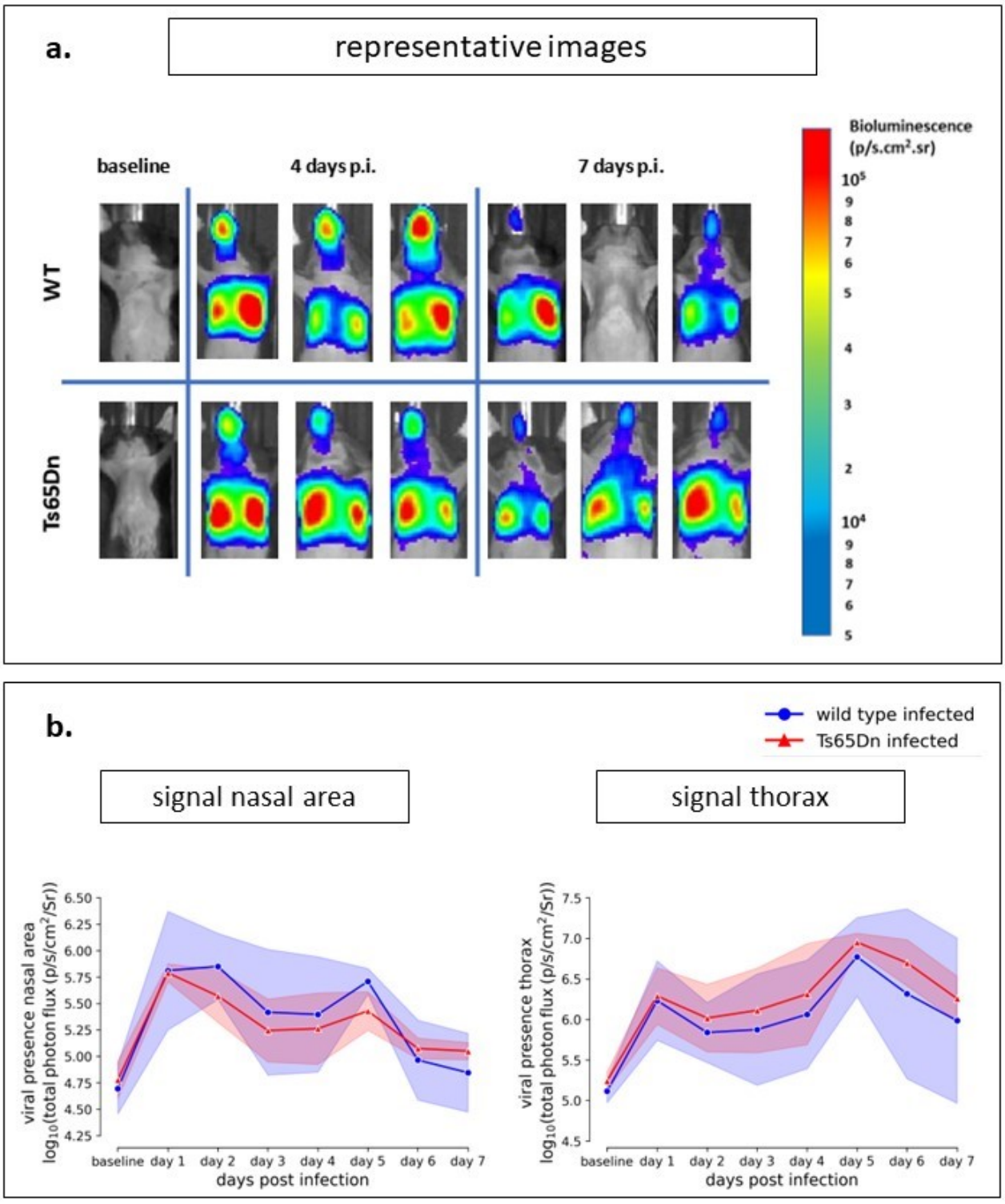

Figure 1: imaging viral development in trisomic mice

a) Representative images of a luciferase recombinant human RSV strain in wild-type (WT) and Ts65Dn mice, a baseline scan (24h before infection) and 3 infected animals at 4 days post-infection (p.i.) and at 7 days p.i., are shown for each genotype. **b)** Viral development over time for the nasal area and the thorax, one-day p.i. a peak in viral presence was observed in the nasal area and 5 days p.i. a peak was observed in the thorax. Graphs indicate the mean and standard deviation. Mixed-effect model analysis was applied no significant differences ($p<.05$) were found.

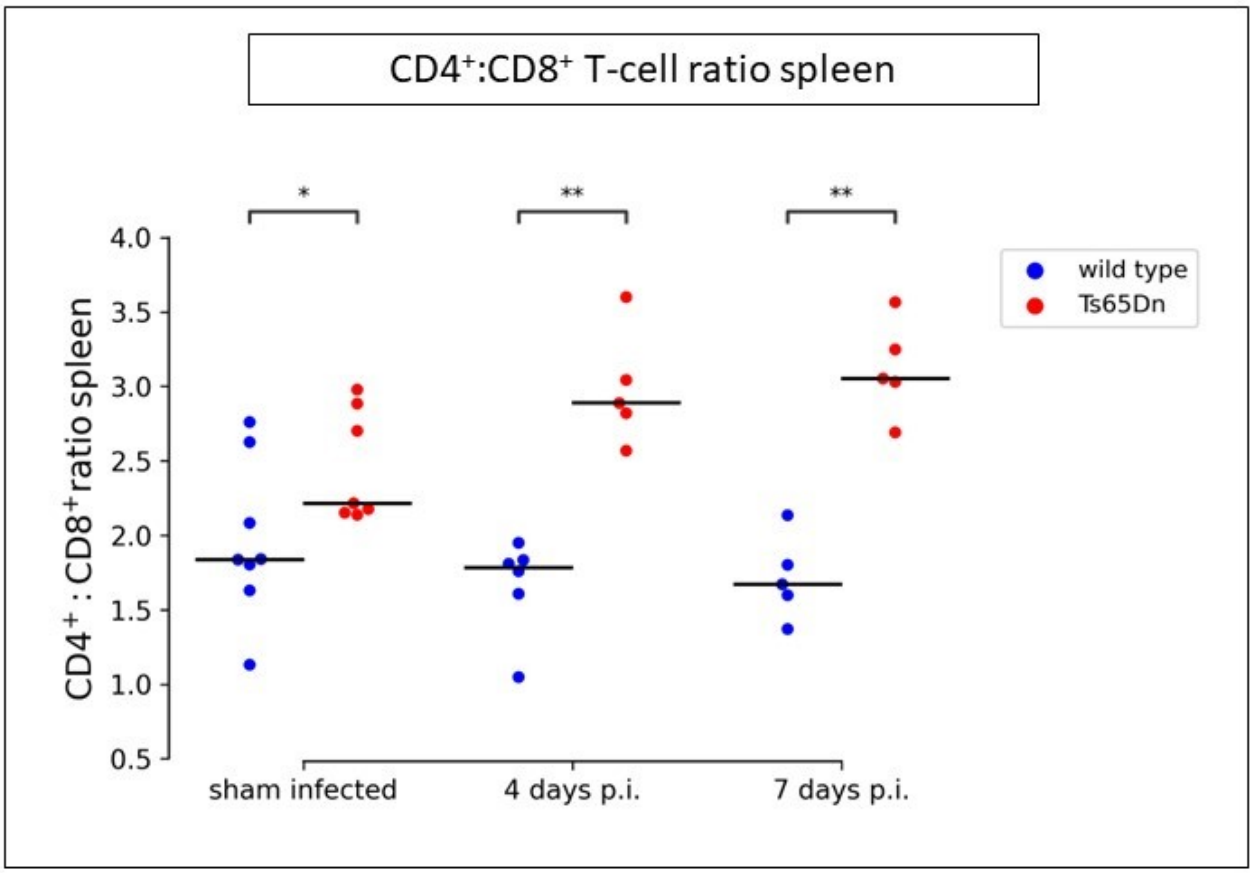

Figure 2: systemic CD4+:CD8+ T-cell ratio in trisomic and wild-type mice
CD4+:CD8+ T-cell ratio in the spleen of trisomic (Ts65Dn) and wild-type (WT) mice. Splenocyte count demonstrated a higher ratio in Ts65Dn mice. Statistical analyses were performed making use of the Kruskal-Wallis test followed by a Mann-Whitney post hoc test with Holm-Bonferroni correction. Lines represent the median. Used significance levels: *p<.05,**p<.01,***p<.001, ****p<.0001.