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Title: Acid sphingomyelinase deficiency improves lung function in allergen-induced asthma in mice

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Body: Introduction: ASM deficiency causes lipid storage disorders, including hereditary Niemann-Pick-disease (NPD). NPD-patients are susceptible to respiratory failures like chronic obstructive pulmonary disease, cystic fibrosis and acute lung injury. The influence of ASM on TH2-directed diseases has not been investigated. Thus, we examined the role of ASM-deficiency in a murine model of ovalbumin-induced asthma. Method: Male C57BL/6 (WT) and ASM-deficient (ASM-KO) mice were sensitized with ovalbumin (OVA) followed by aerosol challenges (1% OVA). On day 35, lung function parameters were measured and airway hyperresponsiveness (AHR) was provoked by acetylcholine (Ach). Inflammatory responses in BAL and tissue were evaluated by cell counts, cytokine- and IgE-measurements as well as by rt-qPCR analysis. Results: Untreated ASM-KO mice showed no relevant differences in lung function parameters compared to WT. After OVA-sensitization, ASM-KO mice showed improved airway resistance (69%), a higher compliance (141%) and decreased elastance (67%) compared to WT (100%). Concordantly, TH2-responses were clearly down-regulated in ASM-KO mice after OVA-treatment. Levels of IL-4, IL-5 and IL-13 in BAL and IgE in serum were nearly halved in sensitized ASM-KO compared to WT. Vice versa, ASM-KO mice showed higher levels of TH1-cytokines, higher numbers of neutrophils in BAL and stronger apoptosis. Conclusion: ASM-deficiency in mice leads to the typical characteristics of NPD together with an enhanced TH1-directed phenotype. The diminished TH2-response explains the attenuated allergic phenotype in mice lacking ASM. Our findings suggest that ASM is required to skew the adaptive immune system towards a TH2-response.