IL-4 RECEPTOR SIGNALING REGULATES LUNG MACROPHAGES DURING HELMINTH COINFECTION RESULTING IN ENHANCED GAMMAHERPESVIRUS PERMISSIVENESS

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Helminth infection conditions lung macrophages in the long term, but little is known about how helminths affect lung macrophage responses to respiratory viral coinfection. Experimental helminth infection of BALB/c and C57BL/6 mice revealed an increased type 2 airway inflammation in C57BL/6 mice that was associated with pronounced phenotypic changes in lung macrophages. These changes consist of a disappearance reaction of SiglecF+ alveolar macrophages (AlvMs) and a concomitant recruitment of monocyte-derived macrophages. Monocyte-derived macrophages replenish macrophages in the airways and lung, as shown with Ms4a3TdT reporter mice, and have a distinct profile to tissue resident macrophages. Competent IL-4Rα responsiveness or intra-tracheal instillation of recombinant IL-4 or IL-13 reproduced the contraction of AlvMs and recruitment of monocyte-derived macrophages, while anti-IL13 antibody treatment impaired the phenotypic changes post helminth infection. Helminth infection of C57BL/6 mice resulted in enhanced permissiveness to subsequent infection with murid gammaherpesvirus 4 (MuHV-4) during the acute stage of the infection in vivo with viral early tropism mainly restricted to AlvMs. AlvMs isolated from helminth-infected C57BL/6 mice appear more permissive ex vivo to MuHV-4. This enhanced permissiveness of AlvMs after helminth infection was dependent on direct IL-4Rα signalling. Thus macrophages-specific IL-4Ra signalling is required for the observed macrophage phenotypic changes and renders AlvMs more permissive to gammaherpesvirus infection.