Investigating the Role of Human γδ T Cells in Cytomegalovirus Infection

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Viral immunity remains a contentious issue in a post-COVID19 environment, with much of global research focus narrowing on conventional T cells and antibody-mediated protection. Believed to be a member of both adaptive and innate immunity, the γδ T cell subset remains largely overlooked in viral defence. Considering the extensive diversity of γδ T cell function, recent studies have implicated γδ T cells in immunity against human cytomegalovirus infection (CMV), with activation upon exposure. CMV is a pathogen associated with complex immune evasion mechanisms that can confound conventional T cell recognition. It is still unclear however, how γδ T cells are recognising and responding to viruses, whether via components on the pathogen itself or via an infected host cell and the nature of this activation, cytolytic or otherwise.

To better understand how $^{+}$γδ T cells respond to viral infection and whether this response shapes their phenotype, we mapped the cytokine profile, changes in frequency and phenotype of Vδ1^{+}γδ T cells in lung transplant patients that developed acute Human Cytomegalovirus (HCMV) infection. Peripheral Blood Mononuclear Cell (PBMC) samples were collected from 27 patients who underwent a lung transplant and contracted or reactivated latent HCMV. Using multiparameter immunophenotyping of longitudinal samples before HCMV infection and post-HCMV, we were able to determine the cytolytic capacity, phenotype alteration and activation of Vδ1^{+}γδ T upon viral infection or reactivation. Notably, we found an increase in CD45RA+, CD27- cells (effector phenotype) Vδ1^{+}γδ T across all samples post-HCMV infection, indicating a shift in Vδ1^{+}γδ T cell cytokine expression as a result of HCMV exposure. Further, the Vδ1^{+}γδ T population in patients experiencing an active HCMV infection, displayed a greater capacity for cytotoxicity, with an increase in granzyme expression, particularly granzyme B. Having discovered a shift in the γδ TCR upon exposure to HCMV, we developed a murine model of MCMV in Black/6 mice over three timepoints, acute (7 days), chronic (21 days) and latent (98 days). Infected mice were exposed to either a wildtype K181 virus, or the mutant Δm157 variant. During acute infection with MCMV, there was a distinct shift in γδ T cell expression, including significant increases in total numbers in the spleen. Moreover, upon infection with the mutant strain, Δm157, there

was a distinct difference in the expression of markers such as CD27, CD62L and KLRG1 between MCMV+ mice at timepoints day 7 and 98.

In summary, HCMV drives Vδ1^{+}γδ T cell activation and subsequent phenotypic changes and our results affirm the potential of Vδ1^{+}γδ T cells to respond to HCMV infection. Additionally, there is scope to investigate the mechanisms of γδ function in multiple tissues during MCMV infection, allowing for parallels to be drawn between peripheral and resident γδ T cells.