Expansion of ancestral strain-specific AIM positive CD4 cell subpopulations in vaccinated individuals with breakthrough infections with SARS-CoV-2 variants

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Background: Breakthrough infections with SARS-CoV-2 variants are increasingly common in vaccinated individuals. Immune imprinting, whereby prior exposure to one virus strain limits the development of immunity against new variant strains of the virus, while boosting responses to the original strain, has been observed in antibody responses to SARS-CoV-2. We sought to investigate whether antigen (Ag)-driven CD4 cells, reflected in frequencies of activation-induced markers (AIM) positive CD4 cell subpopulations sensitised to the ancestral vaccine strain, are expanded after breakthrough infections in vaccinated individuals.

Methods: Pre- and post-infection peripheral blood mononuclear cells (PBMCs) from 8 individuals during a period of Omicron transmission who received either an adenovirus-vectored (n=4) or mRNA COVID-19 vaccine (n=4) (containing Spike protein from the ancestral strain of SARS-CoV-2) were stimulated with S-protein peptide pools from the ancestral strain for 24 hours and AIM expressing CD4+ T cells were enumerated. AIM markers included 4-1BB, CD69, OX40, CD107a and IFN-gamma and frequencies were expressed as a percent of the parent CD4+ subpopulation.

Results: The mean frequency of AIM-positive Th1 cell subset expressing 4-1BB and 4-1BB+CD69 increased significantly after infection (p=0.035 and p=0.032, respectively). The median frequency of Th1 cells expressing 4-1BB, 4-1BB+CD69+, 4-1BB+IFN-gamma+, and 4-1BB+OX40+ CD4 cells were also increased after infection. However, no significant differences were observed in the frequency of other subpopulations of CD4+ T cells.

Conclusions: An expansion of AIM-positive CD4 cell subpopulations, particularly Th1 cells expressing 4-1BB and 4-1BB+CD69 was observed in response to the ancestral strain Ags in vaccinated individuals who had subsequent breakthrough infections with SARS-CoV-2 variants. These findings are consistent with an expansion of T cells sensitised to the vaccine (ancestral) strain that cross-react with variant Ags. Further studies are ongoing to determine whether this expansion is indicative of immune imprinting.