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Epstein-Barr Virus (EBV)-lytic Cross-reactive Influenza-A (IAV) Memory CD8 T-cells in EBV Sero-negative Middle-aged Adults

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Epstein-Barr virus (EBV)-lytic cross-reactive Influenza-A (IAV) memory CD8 T-cells in EBV sero-negative middle-aged adults

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EBV is a common human pathogen, which infects ~90% of people and establishes a life-long chronic infection. The clinical outcomes of acute infection can range from asymptomatic to severe immunopathology such as infectious mononucleosis (IM). However, for unknown reasons 5-10% of middle-aged adults (>35 years) remain EBV-seronegative (EBV-SN) when the virus infects the vast majority of people, and is actively shed at high titers during chronic infection. Here we show that EBV-SN (ASN) HLA-A2+ middle-aged adults possess a unique IAV-M1-GIL$_{58-66}$ memory CD8 T-cell response that cross-reacts with EBV lytic epitopes that differs from teenage EBV-SN (TSN) (18-19 years) and EBV-seropositive (EBV-SP) adult donors. The five tested HLA-A2+ EBV-SN middle-aged adults had a significantly increased IAV-M1$_{58-66}$-GIL tetramer+ CD8 frequency compared to EBV-SP donors. Upon exposure to EBV antigens in vitro both IAV-M1$_{58-66}$GIL/EBV-BMLF1$_{280-288}$-GLC and IAV-M1$_{58-66}$-GIL/EBV-BRLF1$_{109-117}$-YVL, functionally cross-reactive CD8+ responses could be detected in the peripheral blood of middle-aged EBV-SN donors, while only IAV-M1/EBV-YVL cross-reactive responses were detected in some teenage EBV-SN or EBV-seropositive people . Surprisingly, these IAV-M1-GIL-specific CD8 T-cells in middle-aged EBV-SN adults expanded dramatically to EBV lytic antigens and produced cytokines at high functional avidity. They lysed EBV-infected targets and showed potential (by CD103 expression) to enter mucosal epithelial tissue where infection initiates. Additionally, these cross-reactive cells had an oligo-clonal T-cell receptor repertoire different than EBV-SP donors. Taken together these data suggest that an altered cross-reactive T cell repertoire could mediate protective immunity against viral infection. Our results imply that sero-negative adults might have the ability to resist viral infection via heterologous immunity. (NIH-AI49320).

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