Plasma IgA inhibits HIV-specific IgG Fc functions of viremic controllers and HIV progressors

Authors:
Davis SK[1], Worley M[1], Lopez E[1], Kelleher A[2], Kent SJ[1,3], Chung AW[1]

[1] Department of Microbiology and Immunology, Peter Doherty Institute for Infection and Immunity, University of Melbourne, Melbourne, Victoria, Australia [2] The Kirby Institute, UNSW Australia, Sydney, NSW, Australia, [3] Melbourne Sexual Health Centre, Department of Infectious Diseases, Central Clinical School, Monash University, Melbourne, Victoria, Australia

Background:
The importance of antibody Fc functions was highlighted in the human HIV RV144 vaccine trial, however, plasma IgA reduced vaccine efficacy and antibody Fc functions. Plasma IgA can engage with the Fc alpha receptor (FcαR) to activate or inhibit protective Fc functions. Here we endeavored to determine if plasma IgA influences the Fc capacity of IgG from HIV progressors, viremic controllers (VCs) or bnAbs.

Methods:
IgA and IgG was purified from 33 HIV ART naïve VCs, 41 progressors and 10 healthy individuals. Systems serology approaches including the assessment of HIV-specific antibodies, antibody-dependent neutrophil phagocytosis (ADNP) and FcαR affinity were utilized to determine the effect of plasma IgA on IgG Fc functions. This was further validated by spiking autologous purified IgA with purified IgG from HIV individuals or BnAb PGT121 within respective functional assays.

Results:
Plasma IgA concentrations were significantly elevated in HIV progressors ($p<0.01$). Furthermore, spiking of autologous purified IgA significantly inhibited ADNP (20%) of HIV progressor IgG ($p<0.01$) but not VCs. Intriguingly, inhibition was also observed when HIV-negative IgA was added, suggesting a non-HIV epitope inhibitory mechanism. Similarly, IgA inhibited Fc function of the BnAb PGT121 by 23%. The percentage of IgA-mediated inhibition correlated with FcαR engagement, suggesting inhibition occurs via the FcαR. Addition of FcαR block to these assays reconstituted Fc function, suggesting that IgA inhibition is mediated through IgA-FcαR binding.

Conclusion:
We demonstrate that plasma IgA can reduce the functional capacity of anti-HIV IgG from HIV progressors and to a lesser extent VCs. This inhibition was confirmed to be mediated by IgA-FcαR engagement. Future work aims to assess the acute IgA response within HIV individuals to determine if the inhibitory effect of IgA is inherently present. Understanding the mechanisms behind IgA inhibition of Fc

responses could lead to improved future HIV vaccine design and educate passive transfer monoclonal antibody therapies.

Disclosure of Interest Statement:
This study was supported by the NHMRC and amfAR grants