Inhibitory role of serum IgA upon Fc functions in HIV infection and anti-HIV broadly neutralizing antibodies

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Background:
The importance of Fc antibody functions was highlighted by the RV144 vaccine trial, however, serum IgA was associated with reduced vaccine efficacy and inhibition of Fc functions. Elucidating how IgA modulates Fc responses is pertinent. Furthermore, certain passive transfer studies of anti-HIV broadly neutralizing antibodies (bnAbs) suggest a vital role for Fc functions in control or protection of HIV. Here we sought to assess if serum IgA could inhibit the Fc capacity of IgG from HIV individuals or bnAbs.

Methods:
IgG and IgA were purified from plasma of 33 Viremic Controllers (VC) and 41 progressor ART naïve individuals and profiled for HIV-specific IgG1, IgG2, IgG3, IgG4, IgA1, IgA2 levels. Purified IgA and IgG from both cohorts, along with a range of HIV-bnAb IgG were assessed for their ability to mediate Fc functions. The influence of IgA upon IgG was assessed by adding pooled HIV-specific IgA, HIV-negative IgA, IgA1 or IgA2 to respective functional assays.

Results:
VCs were associated with higher IgG mediated Fc functions (p<0.001) and enhanced gp120-specific IgG3 (p=0.003), which inversely correlated with viral load (r=-0.42, p<0.0001). When HIV-specific IgA was added to IgG, upto 50% (range 10-50%) decrease in Fc functions was observed for VC, Progressor and bnAb IgG. Intriguingly, inhibition was also observed when HIV-negative IgA was added, suggesting a non-HIV epitope inhibitory mechanism. Addition of FcαR block to these assays was capable of reconstituting Fc functions, suggesting that IgA inhibition is mediated through IgA-FcαR binding.

Conclusion:
Serum IgA can inhibit Fc functions of IgG purified from VC, progressors and bnAbs. Both HIV-specific and HIV negative serum IgA reduced the functional capacity of IgG, suggesting both epitope competition and IgA-FcαR mediated inhibitory mechanisms. Understanding the mechanisms behind why IgA inhibit Fc responses could lead to improved future HIV vaccine design and educate passive transfer monoclonal antibody therapies.

Disclosure of Interest Statement:
No disclosures