Introduction into the role of IgA in HIV-1 pathogenesis and vaccination

Major improvements in treatment options for the disease caused by human deficiency virus (HIV) like HAART were achieved in the last three decades. Unfortunately, access to drugs are limited in regions were the HIV epidemic is still ongoing like south Africa and parts of Asia. Therefore, one important goal in HIV research is still unreached: a preventive HIV vaccine[1,2].

As discussed in the essay on RV144 and RV305, RV144 was the first HIV-1 vaccine trial showing some level of protection against HIV acquisition[3]. Even though RV144 did not induce most of the pre-defined mediators of protection, such as high levels of neutralizing or broadly neutralizing or cytotoxic T-cell responses, it mediated protection in vaccinated individuals[4,5]. In conclusion, the dogma that vaccine-induced protection against HIV can be achieved through induction of strong adaptive immune responses, especially neutralizing antibodies has been challenged. The RV144 follow-up analyses showed high levels of IgA against gp120 were correlated with an increased risk of HIV acquisition which indicates that IgA antibodies could interfere with the protective effect of the vaccine[6].
Several papers have investigated the topic surrounding IgA, the correlate of risk in RV144. IgA antibodies against the envelope protein (Env) have been shown to correlate with elevated risk of HIV-infection. However, vaccinees with high Env-specific IgA antibody levels were not at higher risk for infection than placebo recipients. Further analysis revealed that vaccinees with high IgA levels against the first conserved region (C1) of Env gp120 had indeed higher infection rates than participants without C1-specific IgAs[7]. C1-binding IgG monoclonal antibodies (mAbs) originally derived from IgA1 and IgA2 antibodies have been shown to induce ADCC-mediated killing[8]. These conflicting finding has raised the interest in the role if IgA in HIV-1 vaccination and brought up various questions about IgA. Is IgA blocking effector functions, does IgA interfere with the protective IgG antibodies, does IgA make cells more susceptible to viral entry and what is the difference between humoral and mucosal IgA?

It has been known for a long time that IgA plays a major role in immune protection on mucosal surfaces where IgA is the predominant antibody subclass. Whereas IgA is mostly monomeric in the blood, IgA is polymeric in secretions and is considered the first line of protection against pathogens[9]. IgA exists in two subclasses termed IgA1 and IgA2 with the major difference being the extended hinge region in IgA1. Both antibodies bind to the FcyRI (CD86), which is present on a wide range of immune cells including dendritic cells, monocytes and neutrophils[10]. Trough interaction with CD86, IgA can activate the complement system, induce cytokine release by phagocytic cells and influence B-cell maturation[11,12].

Especially in the mucosa, IgA is thought to neutralize HIV or aid in immune exclusion by complexing HIV particles. Mucosal IgA has been implicated in protection in various studies. A recent trial with rhesus macaques has shown that gp41-specific IgAs isolated from vaginal secretions blocked transcytosis of HIV in vitro, depletion of IgA abolished the transcytosis inhibition. These protected individuals also induced plasma IgG antibodies with neutralizing or ADCC inducing activities, implicating a collaboration of plasma IgG and mucosal IgA[13].
After the RV144 outcome stated plasma IgA as a correlate of risk, studies on why IgA in the blood could negatively influence the immune reaction and interfere with protection. One study by Tomaras et al. suggested that IgA is blocking Fc receptors on NK cells and therefore reduces ADCC induction[16]. This was explained by the overlapping recognition of the C1 Env epitope by plasma IgA as well as IgG1 mAbs. Two mAbs CH38 (originally IgA1) and CH29 (originally IgA2) were tested for inhibition of ADCC activity of C1-specific IgG1 mAbs isolated from RV144 vaccinees: only CH38 nut not CH29 inhibited ADCC mediated killing[16].

On the other hand, other published studies indicated a beneficial influence of plasma IgA. A study conducted in rhesus macaques displayed that IgG1 with dimeric IgA2 mAbs given intra-venous protected the animals from high dose intra-rectal SHIV challenge. IgG1 or dimeric IgA2 alone has shown no or only marginal protection[14]. This indicates that plasma IgA1 and IgA2 might contribute differently to immune responses and is one of the few studies implicating protection for plasma IgA. A recent study isolated monoclonal IgA antibodies from RV144 vaccinees and found that they block the binding of Env gp140 glycoprotein to an alternative HIV-1 receptor and induce monocyte-mediated phagocytosis. The authors stated that the high heterogeneity observed among RV144 individuals in the specificities and magnitude of vaccine-elicited IgA might indicate that the vaccine did elicited protective IgA responses in some vaccinees[15].

With our RV144 data set of 300 non-infected vaccinated individuals, we tried to further dissect the network of antibody subclasses and how they influence effector functions. Our main focus was on the protective IgG3 and IgG1 antibodies and how levels of those correlated with functions. In our preliminary RV144 analysis, we confirmed that IgG1 and IgG3, the correlates of protection were correlated with effector functions. Surprisingly, IgA was positively correlated with most effector functions as well, indicating that IgA is not blocking Fc-receptor interaction as stated in the paper by Tomaras et al. Further analysis is need but regarding the controversial literature, IgA might be of interest for vaccine development, especially why IgA was stated as a correlate of risk in RV144 even though is does not seem to block effector functions induced by IgG.

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