World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

HIV-1 and IgA Antibodies: Interactions and implications

Bennani Kenza [1, 2, *], Mahmoud Mustapha [1, 2], Yahyaoui Ghita [1, 2] and Kouara Sara [1, 2]

[1] *Department of Bacteriology-Virology, Central Laboratory of Medical Analysis, CHU Hassan II, Fez, Morocco.*
[2] *Faculty of Medicine, Pharmacy and Dental Medicine of Fes, University of Sidi Mohamed Ben Abdellah, Fez, Morocco.*

World Journal of Advanced Research and Reviews, 2024, 23(02), 126–133

Publication history: Received on 23 June 2024; revised on 31 July 2024; accepted on 02 August 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.23.2.2337

Abstract

Antibodies, particularly Immunoglobulin A (IgA), play a crucial role in mucosal tissues as immune effectors against pathogens and as immunomodulators of the microbiota. During infection with human immunodeficiency virus type 1 (HIV-1), a systemic and mucosal IgA antibody response is triggered. Although naturally produced serum IgA specific to HIV-1 envelope protein are quantitatively and qualitatively lower than their IgG counterparts, they also possess antiviral properties such as neutralization and Fc-dependent effector functions. Neutralizing IgA antibodies can block mucosal transmission of HIV-1 in animal models, suggesting that their induction through vaccination could be pivotal for infection prevention. Recently, broadly neutralizing IgA antibodies have been identified in some individuals living with HIV-1. Given the potential for vaccination to induce these mucosally protective antibodies, research efforts are needed to better understand their development and functions. This review discusses the general roles of IgA antibodies in homeostasis and antimicrobial immunity, and explores their implications in antibody responses during HIV-1 infection.

Keywords: HIV-1; Neutralizing antibodies; IgA; Therapeutic target

1. Introduction

Human Immunodeficiency Virus type 1 (HIV-1) infection is primarily transmitted through sexual contact, involving the virus passing through urogenital or anal mucosae. Mucosae serve as both anatomical and biological barriers that limit pathogen penetration. Several mechanisms have been identified for HIV-1 penetration through these mucosae, including passive diffusion of viral particles, transmigration by infected cells, capture by immune cells, and transcytosis through epithelial cells. Following its passage through mucosae, HIV-1 locally infects target cells such as CD4+T lymphocytes and dendritic cells, , then spreads to the lymph nodes, rapidly disseminating throughout the body via free virions and infected cells [1]. In response to infection, specific IgM, IgG, and IgA antibodies against HIV-1 viral proteins develop, notably in mucosa-associated lymphoid tissues. Neutralizing antibodies against HIV-1 envelope glycoproteins (gp160) play a crucial role in the immune response. They block viral infection by preventing virus binding to cellular receptors and facilitating virus elimination by the immune system [2,3] . Initially, non-neutralizing antibodies against gp41 appear in circulation approximately one week post-infection, followed by anti-gp120 antibodies after three to four weeks. The first neutralizing antibodies against gp120 appear several months after seroconversion [4] . Reflecting selective pressure on viral evolution, around 20% of infected individuals develop heterologous neutralizing antibodies against gp160 capable of neutralizing diverse viral isolates in vitro. Approximately 1% produce broadly neutralizing antibodies (bNAbs) with potent neutralizing activity against hundreds of different viral isolates [1]. These bNAbs have been cloned and extensively characterized, representing a promising avenue for therapeutic strategies and HIV-1 vaccine development. Although IgA antibodies are the most abundant in the human body, their role in the immune response against HIV-1 remains poorly understood. The first neutralizing IgA antibodies against HIV-1 have been

* Corresponding author: Bennani Kenza

identified in some chronically infected individuals, paving the way for further exploration of their potential in infection protection [3,5].

1.1. IgA antibodies

Immunoglobulins A (IgA) are heterodimeric glycoproteins composed of two heavy chains (IgH) and two light chains (IgL), connected by disulfide bridges and non-covalent bonds (Figure 1) [6] .

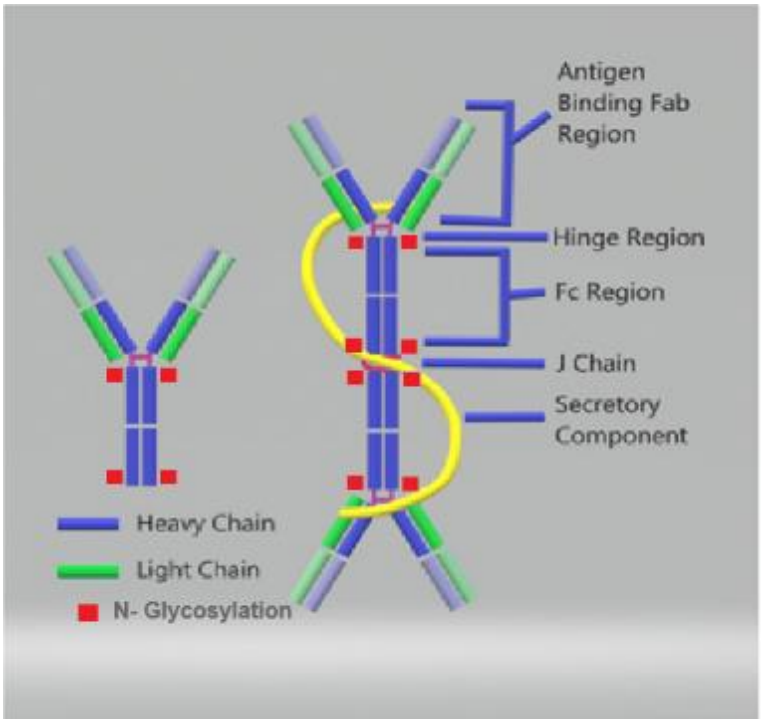

Figure 1 Structure of IgA antibody

In humans, IgA is divided into two subclasses, IgA1 and IgA2, resulting from class switching in B lymphocytes of mucosa-associated lymphoid tissues (MALT) [6] . IgA1 is more susceptible to cleavage by bacterial proteases due to its longer and more flexible hinge region, which includes O-glycosylated glycans [7] .

IgA exists in various molecular forms, including monomeric (IgAm), dimeric (IgAd), polymeric (IgAp), and secretory (S-IgA), with the latter stabilized by a Joining chain (J chain) and a secretory component (SC) covalently attached by the polymeric immunoglobulin receptor (pIgR) [8] . S-IgA is abundant in mucosal secretions, providing resistance against bacterial and proteolytic degradation [7] .

IgA is the most abundantly produced antibody class in the human body, particularly in mucosal tissues, with estimated intestinal production of about 3 g/adult/day [9]. The proportions of IgA1 and IgA2 vary across mucosal sites, e.g., 80-90% IgA1 in nasal and genital secretions, and 60% IgA2 in the colon [7]. In individuals infected with HIV-1, IgA anti-HIV-1 antibodies predominate in the intestine as S-IgA, while IgG anti-HIV-1 antibodies are more prevalent in serum and other secretions [10, 11].

IgA possess a specific receptor, FcαRI (CD89), found on monocytes, neutrophils, eosinophils, macrophages like Kupffer cells, and dendritic cells in various lymphoid tissues [12]. CD89 binding is well-documented, alongside other IgA receptors including transferrin receptor CD71, Dectin-1, and DC-SIGN [13] . Structurally, CD89 comprises two extracellular domains (EC1-EC2), a transmembrane region, and a short cytoplasmic tail [14] . IgA monomers bind to two FcαRI molecules simultaneously (2:1 stoichiometry), enhancing binding avidity [15] . IgA1 and dimeric IgA2 exhibit differential affinities for FcαRI and DC-SIGN, respectively [16] . CD89 plays a pivotal role in immune modulation, influencing pro- or anti-inflammatory responses depending on IgA subclass and glycosylation [16,17] . Additionally, the polymeric Ig receptor (pIgR, 83 kDa) facilitates IgA and IgM transport across epithelial cells via transcytosis, crucial for mucosal immunity [18] .

1.2. The antiviral functions of IgA against HIV-1

1.2.1. Protection of mucosal surfaces

Immunoglobulins of type A (IgA) play a crucial role in defending mucosal surfaces against pathogens by acting through the polymeric IgA receptor (pIgR) [19] . At the luminal level of organs, they prevent adhesion and invasion of microorganisms, as well as neutralize toxins through mechanisms of agglutination and immobilization. Within the epithelium, IgA can intracellularly neutralize viruses such as Sendai virus, rotavirus, and HIV-1. Moreover, in the lamina propria, they facilitate the excretion of antigens and microorganisms into the lumen, thereby contributing to immune exclusion [20] . Secretory IgA (S-IgA) antibodies play a crucial role in trapping pathogens in mucus by binding to mucins [21] . Additionally, glycosylated IgA can interfere with bacterial pili, preventing microorganisms from attaching to mucosal surfaces [7]. Finally, high-affinity IgA can immediately agglutinate "daughter" bacteria after their division, a process known as "chained growth," thereby disarming or eliminating potentially invasive bacterial species from the intestinal lumen [22].

1.3. Inhibition of viral transcytosis: (Figure 2)

Regarding viral transcytosis, a crucial process in HIV-1 infection through mucosal surfaces, it occurs across polarized epithelial cells from the apical to the basal pole [23] . Despite its low efficiency with less than 0.02% of the initial inoculum, this process demonstrates that the genital epithelium acts as an effective barrier against HIV-1 [24] . Mucosal epithelial cells lack the conventional CD4 receptor; therefore, HIV-1 attachment and entry occur through alternative receptors such as glycosphingolipids and heparan sulfate proteoglycans [25] . Anti-HIV-1 IgA has been shown to inhibit HIV-1 transport through in vitro transcytosis models using human mucosal epithelia [26] . Conversely, recombinant IgG or IgA bNAb antibodies, while capable of neutralizing transcytosed HIV-1 virions, do not directly block transcytosis [5].

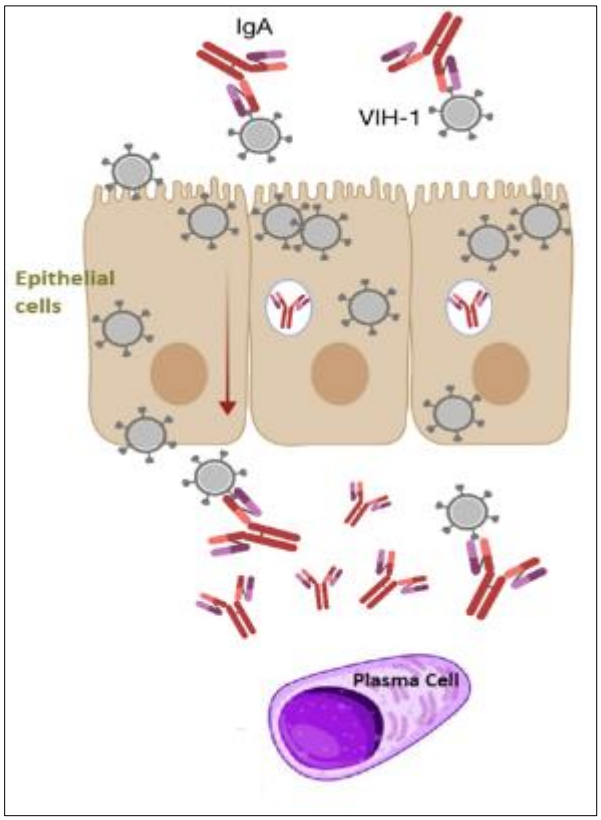

Figure 2 Inhibition of viral transcytosis

1.4. Neutralisation virale

Neutralization involves inhibiting the interactions of HIV-1 with its cellular receptors (CD4) and co-receptors (CCR5 or CXCR4) by binding of neutralizing antibodies (nAbs) to viral envelope glycoproteins. This not only blocks viral entry but also triggers Fc-dependent effector functions, leading to the elimination of infected cells and thereby preventing viral spread [27] (Figure 3).

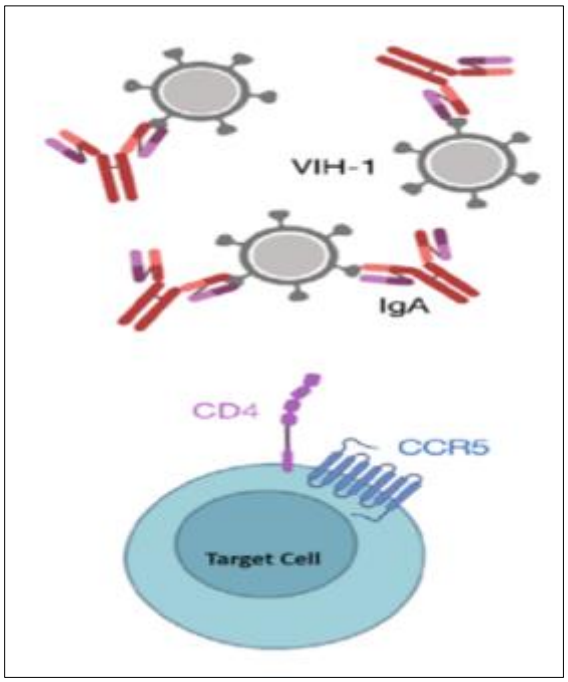

Figure 3 Viral neutralization

The protective capacity of IgG1 antibodies compared to IgA2, whether neutralizing or non-neutralizing (nnAbs) but capable of inducing antibody-dependent cellular cytotoxicity (ADCC), has been extensively studied. In various in vitro models of HIV-1 infection, ex vivo using human tissue explants, and in vivo in non-human primates (NHPs) exposed to S-HIV administered rectally, nAbs provide superior mucosal protection compared to nnAbs, even when used in combination. IgG1 nAbs consistently demonstrated greater protective efficacy than IgA2 in these studies [28] . Our research focused on evaluating the impact of representative IgG1 and IgA1/IgA2 bNAbs targeting different epitopes of Env on HIV-1 transcytosis in an in vitro model. We showed that bNAbs, whether IgG or IgA, do not interfere with the transcytosis of free virus or cell-associated virus but effectively inhibit the infectivity of transcytosed virions. Confocal microscopy of epithelial cell monolayers confirmed the presence of immune complexes formed by bNAbs and virions inside cells, suggesting that neutralization capacity, regardless of antibody class, is critical for mucosal protection against HIV-1 transmission. However, comparative studies of IgG and IgA antibodies isolated from cervicovaginal and rectal lavages of HIV-1-infected women have shown a predominance of IgG subtype nAbs over IgA nAbs, highlighting variability in antibody detection sensitivity depending on sample collection, processing, and storage methods [28].

1.4.1. IgA Fc-dependent effector functions

Complete protection in vivo likely requires polyfunctional anti-HIV-1 antibodies capable of various antiviral activities, including neutralization and Fc-mediated effector functions [27]. Effector functions mediated by the Fc region of antibodies involve the formation of a tripartite complex consisting of the Fab region binding to the viral protein expressed on the surface of infected cells, and the Fc region binding to Fc receptors on innate immune effector cells (such as NK cells, monocytes/macrophages, and neutrophils) or complement molecules [12]. Unlike nAbs, nnAbs may not block the initial entry of HIV-1 into cells but possess effector functions that eliminate infected cells. These antiviral activities reduce viremia and slow viral replication but do not conclusively prevent new infection in NHP models [27].

IgA antibodies have the potential to induce the destruction of HIV-1-infected cells through antibody-dependent cellular cytotoxicity (ADCC). For instance, the anti-gp41 antibody 2F5-IgG1, when expressed as IgA2, binds to FcαRI on monocytes, leading to the lysis of HIV-1-infected cells via ADCC. Furthermore, cooperative action between 2F5-IgA2 and other IgG antibodies like 10E8-IgG enhances the lysis of target cells by ADCC, with similar efficacy observed in NK cells and reduced efficacy in neutrophils [29]. IgA antibodies also promote antibody-dependent cellular phagocytosis (ADCP) of HIV-1 virions or infected cells [30]. Studies have shown that non-neutralizing antibodies (nnAbs) against HIV-1, such as HG129 and HG130 isolated from RV144 vaccinees, induce ADCP in vitro when expressed as dimeric or polymeric IgA [31] . Additionally, IgA antibodies targeting Env induce the internalization of infectious HIV-1 virions by primary monocytes, albeit less effectively than IgG1 antibodies [32].

Furthermore, IgA antibodies can induce complement-dependent cytotoxicity (CDC) through the alternative pathway by recruiting C3 molecules, although they cannot activate the classical pathway due to their inability to bind to C1q [33]. Studies on polyclonal IgA antibodies from RV144 vaccinees have shown their ability to induce complement deposition on gp120-coated beads, phagocytosis by neutrophils, and degranulation of NK cells, highlighting their potential role in antiviral immune responses [34]. The capacity of monoclonal IgA antibodies against HIV-1, including IgA bNAbs, to induce CDC of infected cells remains to be investigated.

1.4.2. Mucosal IgA response to HIV-1

The IgA Response to HIV-1 at Mucosal Sites: Structural and Functional Differences from Peripheral Immunity [21]. Mucosa-associated lymphoid tissues (MALT) such as GALT play a crucial role as the induction sites for this response [35] . Despite the predominance of IgG in the mucosa of individuals infected with HIV-1 [10,11], IgA is abundant in the intestine, suggesting its role in infection prevention. HIV-1 disrupts the B cell compartment, affecting the production of anti-HIV-1 IgA [36] . In highly exposed seronegative individuals (HESN), the presence of anti-HIV-1 IgA appears to be associated with enhanced protection [37]. These IgA antibodies can block viral transcytosis and neutralize infection of CD4+ T cells [38]. Their action complements circulating IgG, reinforcing mucosal defense against HIV-1 through Fc-dependent effector mechanisms such as ADCC and ADCP [12]. Administration of IgG1 and IgA2d in macaques demonstrates protection against SHIV infection, highlighting the cooperation between IgA and IgG in vivo protection against HIV-1 [39].

1.4.3. Peripheral antibody response and IgA bNAbs against HIV-1

The IgA antibody response to HIV-1 varies significantly among infected populations, including elite controllers with undetectable viremia (1% of HIV-positive individuals), viremic controllers, and individuals on antiretroviral therapy [2,40,41]3, 80, 81, Early in infection, an increase in total serum IgA is observed, attributed to polyclonal activation of non-specific HIV-1 B lymphocytes, and is associated with reduced expression of the CD89 marker, predicting progression to AIDS [8]. Elite controllers are distinguished by unique profiles of anti-Env IgG antibodies characterized by specificity, specific glycosylation, and polyfunctionality, including neutralization, ADCC, ADCP, complement deposition, and NK cell activation [42].

Studies show that anti-gp120 IgA can modulate the magnitude of ADCC responses induced by IgG during HIV-1 infection [40]. Depletion of IgA in viremic subjects increases IgG-mediated ADCC activity, with peak intensity observed in primary infection, plateauing in chronic phase, and decreasing after initiation of antiretroviral therapy [40]. Elite controllers exhibit robust and frequent IgA responses, including high-avidity IgA against gp41, compared to viremic non-controllers and treated patients [2]. Some serum IgA also demonstrate cross-neutralizing capacity against multiple heterologous variants of HIV-1, highlighting their potential as cross-neutralizing antibodies [43].

Historically, class IgG bNAbs isolated mainly originate from peripheral B lymphocytes or plasmocytes of "Elite Neutralizers," individuals capable of naturally controlling HIV-1 infection [44]. Recently, the first class IgA monoclonal antibodies, such as M4008_N1 and M1214_N1, have been identified in people living with HIV-1. These IgAs show cross-neutralizing activity against various HIV-1 variants, targeting distinct epitopes on gp120 [3]. However, their in vitro effector functions and in vivo protective capacity still require further study. Additionally, new IgA and IgG bNAbs from different memory B cell lineages have been identified in a viremic controller, demonstrating broad neutralizing capabilities and enhanced efficacy for IgA, specifically targeting the N332 supersite on Env [5].

1.4.4. HIV-1 Vaccine Development and IgA Antibodies

The development of an effective vaccine against HIV-1 relies on inducing broad-spectrum neutralizing antibodies (bNAbs) capable of targeting multiple virus variants. IgA responses, particularly at mucosal sites, are considered promising for preventing HIV-1 transmission [45]. Among various vaccine strategies tested since 1987, the RV144 clinical trial is the only one to have shown a significant reduction in infections, with a vaccine efficacy of 31%, using a regimen including ALVAC-HIV and AIDSVAX B/E [46]. Initially, IgA specific to the conserved C1 region of gp120 were associated with an increased infection risk among RV144 vaccinees [47]. However, studies have shown these IgA may block ADCC responses of anti-Env IgG, thereby modulating vaccine efficacy [48] .

More recently, characterization of antibody profiles in RV144 vaccinees revealed that high levels of plasma IgA are associated with enhanced polyfunctionality, including phagocytosis and NK cell degranulation [34]. Fischinger et al. demonstrated that plasma IgA are not inherently deleterious and may even cooperate with IgG bNAbs to enhance protection through their effector functions [34]. Inducing mucosal immunity with functional antibodies and cytotoxic T cells remains crucial for HIV-1 vaccine protection. Strategies such as using combined TLR7/NOD2 agonists as adjuvants

in intranasal vaccines show promise, yet the challenge remains to design an effective vaccine strategy that induces bNAbs, including IgA, at mucosal tissue sites [49].

2. Conclusion

After decades of intensive research and clinical trials, it is clear that a protective vaccine against HIV-1 must lead to the development of neutralizing antibodies, notably IgA. Although neutralizing IgA antibodies have been shown to be effective in animal models, their precise role in human infection remains to be clarified. The development mechanisms and targets of neutralizing IgA are still poorly understood. The recent identification of IgA bNAbs in infected individuals opens up new prospects for vaccine research. A better understanding of these antibodies is crucial to developing effective vaccines that induce protective IgA responses in mucous membranes, the main entry points for HIV-1.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest.

References

[1] Mouquet H. Antibody B cell responses in HIV-1 infection. Trends Immunol 2014 ; 35 : 549- 61.

[2] Nabi R, Moldoveanu Z, Wei Q, Golub ET, Durkin HG, Greenblatt RM et al. Differences in serum IgA responses to HIV-1 gp41 in elite controllers compared to viral suppressors on highly active antiretroviral therapy. PLoS One 2017 ; 12 : e0180245.

[3] Jia M, Liberatore RA, Guo Y, Chan K-W, Pan R, Lu H et al. VSV-Displayed HIV-1 Envelope Identifies Broadly Neutralizing Antibodies Class-Switched to IgG and IgA. Cell Host Microbe 2020 ; 27 : 963-75.e5.

[4] Frost SDW, Wrin T, Smith DM, Pond SLK, Liu Y, Paxinos E et al. Neutralizing antibody responses drive the evolution of human immunodeficiency virus type 1 envelope during recent HIV infection. Proc Natl Acad Sci U S A 2005 ; 102 : 18514-19.

[5] Lorin V, Fernández I, Masse-Ranson G, Bouvin-Pley M, Molinos-Albert LM, Planchais C et al. Epitope convergence of broadly HIV-1 neutralizing IgA and IgG antibody lineages in a viremic controller. J Exp Med 2022 ; 219 : e20212045.

[6] Cerutti A. The regulation of IgA class switching. Nat Rev Immunol 2008 ; 8 : 421-34

[7] Woof JM, Russell MW. Structure and function relationships in IgA. Mucosal Immunol 2011 ; 4 : 590-7

[8] Lopez E, Shattock RJ, Kent SJ, Chung AW. The Multifaceted Nature of Immunoglobulin A and Its Complex Role in HIV. AIDS Res Hum Retroviruses 2018 ; 34 : 727-38

[9] Conley ME, Delacroix DL. Intravascular and mucosal immunoglobulin A: two separate but related systems of immune defense? Ann Intern Med 1987 ; 106 : 892-9.

[10] Mestecky J. Humoral immune responses to the human immunodeficiency virus type-1 (HIV-1) in the genital tract compared to other mucosal sites. J Reprod Immunol 2007 ; 73 : 86-97.

[11] Mestecky J, Wei Q, Alexander R, Raska M, Novak J, Moldoveanu Z. Humoral immune responses to HIV in the mucosal secretions and sera of HIV-infected women. Am J Reprod Immunol 2014 ; 71 : 600-7

[12] Lu LL, Suscovich TJ, Fortune SM, Alter G. Beyond binding: antibody effector functions in infectious diseases. Nat Rev Immunol 2018 ; 18 : 46-61

[13] Heineke MH, van Egmond M. Immunoglobulin A: magic bullet or Trojan horse? Eur J Clin Invest 2017 ; 47 : 184-92.

[14] [Bakema JE, van Egmond M. The human immunoglobulin A Fc receptor FcαRI: a multifaceted regulator of mucosal immunity. Mucosal Immunol 2011 ; 4 : 612-24

[15] Herr AB, Ballister ER, Bjorkman PJ. Insights into IgA-mediated immune responses from the crystal structures of human FcalphaRI and its complex with IgA1-Fc. Nature 2003 ; 423 : 614-20.

[16] Gayet R, Michaud E, Nicoli F, Chanut B, Paul M, Rochereau N et al. Impact of IgA isoforms on their ability to activate dendritic cells and to prime T cells. Eur J Immunol 2020 ; 50 : 1295-1306.

[17] Steffen U, Koeleman CA, Sokolova MV, Bang H, Kleyer A, Rech J et al. IgA subclasses have different effector functions associated with distinct glycosylation profiles. Nat Commun 2020 ; 11(1) : 120.

[18] Wei H, Wang JY. Role of Polymeric Immunoglobulin Receptor in IgA and IgM Transcytosis. Int J Mol Sci 2021 ; 22 : 2284.

[19] Macpherson AJ, Yilmaz B, Limenitakis JP, Ganal-Vonarburg SC. IgA Function in Relation to the Intestinal Microbiota. Annu Rev Immunol 2018 ; 36 : 359-81.

[20] Rojas R, Apodaca G. Immunoglobulin transport across polarized epithelial cells. Nat Rev Mol Cell Biol 2002 ; 3 : 944-55.

[21] Macpherson AJ, McCoy KD, Johansen F-E, Brandtzaeg P. The immune geography of IgA induction and function. Mucosal Immunol 2008 ; 1 : 11-22.

[22] Moor K, Diard M, Sellin ME, Felmy B, Wotzka SY, Toska A et al. High-avidity IgA protects the intestine by enchaining growing bacteria. Nature 2017 ; 544 : 498-502.

[23] Gonzalez SM, Aguilar-Jimenez W, Su RC, Rugeles MT. Mucosa: Key Interactions Determining Sexual Transmission of the HIV Infection. Front Immunol 2019 ; 10 : 144.

[24] Bobardt MD, Chatterji U, Selvarajah S, Van der Schueren B, David G, Kahn B et al. Cell-free human immunodeficiency virus type 1 transcytosis through primary genital epithelial cells. J 24 Virol 2007 ; 81 : 395-405

[25] Yasen A, Herrera R, Rosbe K, Lien K, Tugizov SM. HIV internalization into oral and genital epithelial cells by endocytosis and macropinocytosis leads to viral sequestration in the vesicles. Virology 2018 ; 515 : 92-107.

[26] Watkins JD, Sholukh AM, Mukhtar MM, Siddappa NB, Lakhashe SK, Kim M et al. Anti-HIV IgA isotypes: differential virion capture and inhibition of transcytosis are linked to prevention of mucosal R5 SHIV transmission. AIDS 2013 ; 27 : F13-20.

[27] Pegu A, Hessell AJ, Mascola JR, Haigwood NL. Use of broadly neutralizing antibodies for HIV-1 prevention. Immunol Rev 2017 ; 275 : 296-312.

[28] Cheeseman HM, Olejniczak NJ, Rogers PM, Evans AB, King DFL, Ziprin P et al. Broadly Neutralizing Antibodies Display Potential for Prevention of HIV-1 Infection of Mucosal Tissue Superior to That of Nonneutralizing Antibodies. J Virol 2017 ; 91 : e01762-16.

[29] Duchemin M, Khamassi M, Xu L, Tudor D, Bomsel M. IgA Targeting Human Immunodeficiency Virus-1 Envelope gp41 Triggers Antibody-Dependent Cellular Cytotoxicity Cross-Clade and Cooperates with gp41-Specific IgG to Increase Cell Lysis. Front Immunol 2018 ; 9 : 244.

[30] Duchemin M, Tudor D, Cottignies-Calamarte A, Bomsel M. Antibody-Dependent Cellular Phagocytosis of HIV-1-Infected Cells Is Efficiently Triggered by IgA Targeting HIV-1 Envelope Subunit gp41. Front Immunol 2020 ; 11 : 1141.

[31] Wills S, Hwang K-K, Liu P, Dennison SM, Tay MZ, Shen X et al. HIV-1-Specific IgA Monoclonal Antibodies from an HIV-1 Vaccinee Mediate Galactosylceramide Blocking and Phagocytosis. J Virol 2018 ; 92 : e01552-1517.

[32] Tay MZ, Kunz EL, Deal A, Zhang L, Seaton KE, Rountree W et al. Rare Detection of Antiviral Functions of Polyclonal IgA Isolated from Plasma and Breast Milk Compartments in Women Chronically Infected with HIV-1. J Virol 2019 ; 93 : e02084-18.

[33] Janoff EN, Fasching C, Orenstein JM, Rubins JB, Opstad NL, Dalmasso AP. Killing of Streptococcus pneumoniae by capsular polysaccharide-specific polymeric IgA, complement, and phagocytes. J Clin Invest 1999 ; 104 : 1139-47.

[34] Fischinger S, Dolatshahi S, Jennewein MF, Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S et al. IgG3 collaborates with IgG1 and IgA to recruit effector function in RV144 vaccinees. JCI Insight 2020 ; 5 : e140925

[35] Brandtzaeg P. Mucosal immunity: induction, dissemination, and effector functions. Scand J Immunol 2009 ; 70: 505-15

[36] Lopez E, Shattock RJ, Kent SJ, Chung AW. The Multifaceted Nature of Immunoglobulin A and Its Complex Role in HIV. AIDS Res Hum Retroviruses 2018 ; 34 : 727-38

[37] Devito C, Broliden K, Kaul R, Svensson L, Johansen K, Kiama P et al. Mucosal and plasma IgA from HIV-1-exposed uninfected individuals inhibit HIV-1 transcytosis across human epithelial cells. J Immunol 2000 ; 165 : 5170-76.

[38] Tudor D, Derrien M, Diomede L, Drillet A-S, Houimel M, Moog C et al. HIV-1 gp41-specific monoclonal mucosal IgAs derived from highly exposed but IgG-seronegative individuals block HIV-1 epithelial transcytosis and neutralize CD4(+) cell infection: an IgA gene and functional analysis. Mucosal Immunol 2009 ; 2 : 412-26.

[39] Gong S, Lakhashe SK, Hariraju D, Scinto H, Lanzavecchia A, Cameroni E et al. Cooperation Between Systemic IgG1 and Mucosal Dimeric IgA2 Monoclonal Anti-HIV Env Antibodies: Passive Immunization Protects Indian Rhesus Macaques Against Mucosal SHIV Challenges. Front Immunol 2021 ; 12 : 705592

[40] Ruiz MJ, Ghiglione Y, Falivene J, Laufer N, Holgado MP, Socías ME et al. Env-Specific IgA from Viremic HIV-Infected Subjects Compromises Antibody-Dependent Cellular Cytotoxicity. J Virol 2016 ; 90: 670-81.

[41] Fink E, Fuller K, Agan B, Berger EA, Saphire A, Quinnan GV et al. Humoral Antibody Responses to HIV Viral Proteins and to CD4 Among HIV Controllers, Rapid and Typical Progressors in an HIV-Positive Patient Cohort. AIDS Res Hum Retroviruses 2016 ; 32 : 1187-97.

[42] Moris A, Pereira M, Chakrabarti L. A role for antibodies in natural HIV control. Curr Opin HIV AIDS 2019 ; 14 : 265-72

[43] Planque S, Salas M, Mitsuda Y, Sienczyk M, Escobar MA, Mooney JP et al. Neutralization of genetically diverse HIV-1 strains by IgA antibodies to the gp120-CD4-binding site from longterm survivors of HIV infection. AIDS 2010 ; 24 : 875-84

[44] Martin-Gayo E, Gao C, Chen HR, Ouyang Z, Kim D, Kolb KE et al. Immunological Fingerprints of Controllers Developing Neutralizing HIV-1 Antibodies. Cell Rep 2020 ; 30 : 984- 96.e4

[45] van Gool MMJ, van Egmond M. IgA and FcαRI: Versatile Players in Homeostasis, Infection, and Autoimmunity. Immunotargets Ther 2020 ; 9 : 351-72.

[46] Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med 2009 ; 361 : 2209-20.

[47] Haynes BF, Gilbert PB, McElrath MJ, Zolla-Pazner S, Tomaras GD, Alam SM et al. Immunecorrelates analysis of an HIV-1 vaccine efficacy trial. N Engl J Med 2012 ; 366 : 1275-86.

[48] Chung AW, Kumar MP, Arnold KB, Yu WH, Schoen MK, Dunphy LJ et al. Dissecting Polyclonal Vaccine-Induced Humoral Immunity against HIV Using Systems Serology. Cell 2015 ; 163 : 988-98.

[49] Gutjahr A, Papagno L, Vernejoul F, Lioux T, Jospin F, Chanut B et al. New chimeric TLR7/NOD2 agonist is a potent adjuvant to induce mucosal immune responses. EBioMedicine 2020 ; 58 : 102922