Inhibitory role of serum IgA upon Fc functions

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RV144 Vaccine Immune Correlates associated plasma gp120 IgA with reduced vaccine efficacy

*gp120 IgA in plasma - reduced vaccine efficacy*

*Haynes et al NEJM 2012*
How did RV144 gp120-IgA reduce vaccine efficacy?
IgA epitope competition reduced IgG ADCC

Tomaras et al. PNAS 2013
Role of IgA in HIV is complex

• **Protective Mucosal IgA:**
  • Passive transfer of **NAb of IgA** in NHP is protective (*Watkins AIDS 2013*)
  • Vaccination in NHP associated **mucosal IgA** with protection (*Bomsel Jimmuno 2011*)
  • **Mucosal ENV-IgA** in HESN associated with protection (*Tudor Mucosal Immuno 2009*)
  • **Dimeric/Polymeric IgA** is highly functional (*Wills Jimmuno 2018, Bakema mAbs 2011*)

Lopez et al ARHR 2018
Role of IgA in HIV is complex

- **PLASMA IgA: Monomeric**
  - Plasma gp120-IgA reduced RV144 vaccine efficacy (*Haynes NEJM 2012*)
  - Plasma gp120-IgA blocks IgG ADCC (*Tomaras PNAS 2013*)

Lopez et al ARHR 2018
Role of IgA in HIV is complex

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  - **Plasma** IgA associated with disease progression (*Fling J Allergy Clin Immuno 1988, Coates J Clin Epi 1992*)
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• **PLASMA IgA:**
  • Plasma gp120-IgA reduced RV144 vaccine efficacy (*Haynes NEJM 2012*)
  • Plasma gp120-IgA blocks IgG ADCC (*Tomaras PNAS 2013*)
  • Plasma IgA associated with disease progression (*Fling J Allergy Clin Immun 1988, Coates J Clin Epi 1992*)
  • Plasma IgA inhibits ADCC in HIV progressor subjects, but not Elite controllers (*Ruiz J Virol 2015*)
Dissecting the role of plasma IgA in HIV infection using Systems Serology

Viremic Controller (VL<2000) vs Progressors (Kelleher-Kirby Institute)

35 Controllers  40 Progressors

Computational Analysis “humoral signatures”

Biophysical Profiling

Functional Profiling

Purified the IgG and IgA
Identifying IgG and IgA humoral signatures associated with HIV viral control

Which features are associated with HIV Control?

HIV Viremic Controllers VL<2000

HIV Progressors
Viremic controllers (VC) and Progressors have very different Ab profiles
IgG mediated Fc effector functions are enhanced in Viremic Controllers

Enhanced IgG Fc functions

Success CV: 80.9%, Combined X Var: 46.7%
Viremic Controllers have enhanced Fc effector functions

Spearman rho

-0.50 0.10 0.70

Neutrophil Phagocytosis

Phago score

% lysis PKH-CFSE

Prereg

Progressors VC

101

102

103

104

105

Viral RNA

IgG gp120

IgG1 gp120

IgG2 gp120

IgG3 gp120

IgG4 gp120

ADNP

RFADCC

CD4

gp120 IgG3 MFI

gp120 IgG3
Plasma IgA markers differentiate Viremic controllers (VC) from Progressors.
Plasma IgA and CD89 (FcaR) engagement differentiate Viremic controllers (VC) from Progressors.

Progressor total plasma (monomeric) IgA1 bind with higher affinity to FcaR.

Viremic controller IgA have weaker binding to FcaR.

What does this mean?!
Different Forms of IgA: monomeric IgA

- bind FcAR-lower affinity
- Fc inhibition (ITAMI)
- inhibits ADCC and Fc functions
- secretes inhibitory cytokines
  (Pasquier Immunity 2005)

Lopez et al ARHR 2018
Ben Mkaddem Autoimmunity Reviews 2013
Plasma IgA can inhibit IgG Fc effector functions – via FcAR inhibitory signaling

Neutrophil Phagocytosis
HIV + IgA

Neutrophil Phagocytosis
HIV neg IgA
Plasma IgA can inhibit IgG Fc effector functions via FcaR (CD89) inhibitory signaling

Progressor plasma IgA inhibits Fc functions

VC total IgA weakly inhibits Fc functions

Matthew Worley
Ester Lopez
Multiple mechanisms of IgA inhibition in HIV infection

**RV144**
- epitope competition

**Progressors**
- Strong inhibition
- Lower ADCC

**Viremic controllers**
- Weaker inhibition
- Higher ADCC
Fc effector functions may be important for enhancing broadly neutralizing Abs

Antibody and TLR7 agonist delay viral rebound in SHIV-infected monkeys

Erica N. Bordiučchi1,6, Jinyan Liu1,6, Joseph P. Nikolola1,6, Anthony M. Cadena1,6, Wen-Han Yu2, Stephanie Flechinger2, Thomas Broge3, Peter Abbink1, Noe B. Mercado1, Abishek Chandrashekar1, David Jetton1, Lauren Peter1, Katherine McMahan1, Edward T. Mosley3, Elena Bekerman1, Joseph Hesselgesser4, Wenjun Li5, Mark G. Lewis5, Galt Alter1, Roman Ghezzi1,2, & Dan H. Burton5,6

ARTICLE

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Corrections are redundant to efficacy body PGT121 in macaques

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Summary

• Multiple mechanisms by which IgA can inhibit Fc Functions
  • Epitope competition
  • IgA-FcaR inhibitory signaling

• HIV progressors have enhanced IgA-FcaR inhibition
• Viremic Controllers may have enhanced IgA
• IgA can also reduce Fc functional capacity of bNAb responses *in vitro*
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Volunteers!!!!!!