ADCC antibodies against diverse influenza strains: Implications for universal vaccination

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What are ADCC antibodies?

• Note: ADCC process can both kill virus infected cells AND result in liberation of cytokines/chemokines that induce an antiviral state (non-cytolytic mechanism)

Acknowledgement

Sinth Jegaskanda PhD

Work on influenza ADCC antibodies

• 1977-1984 Greenberg et al, Hashimoto et al. First describes Flu-specific ADCC

• 1984-2004 – nothing!

• 2004: Jegerlehner et al. ADCC to extracellular portion of M2 protein may help control influenza infection in mice.

• 2011: Corti et al. Reduced protection of mice when neutralizing antibody mutated to remove Fc receptor binding.

• 2014: DeLillo et al: Anti-stem broadly neutralizing antibodies effective in mice in part related to Fc receptor presence/ADCC activity

• 2012-4: Jegaskanda/Kent: ADCC induced by infection recognizes broad range of influenza strains in humans and macaques
Outline

- Ability of influenza infection to induce cross reactive ADCC
  - Macaques
  - Humans
    - Individuals pre and post 2009 of different ages
    - Pooled IVIG made pre and post 2009
- Ability of vaccines to induce cross reactive ADCC in macaques
  - TIV
  - Whole inactivated virus with adjuvant
  - MVA vectored vaccine

Do ADCC antibodies induced by influenza infection cross react with other strains?

Seasonal H1N1 infection induced cross-reactive antibodies to 2009-pandemic HA protein

- Anamnestic ADCC response after subsequent H1N1pdm infection was faster than CTLs or Nabs
- Associated with protection from high levels of influenza virus recovery

Why did older subjects have less mortality during the H1N1pdm pandemic?


Jowell et al. (2009) NEJM
Older individuals (>45 years) had pre-existing H1N1pdm-specific ADCC

Intravenous Ig (IVIG)

- Pooled polyclonal IgG extracted from plasma from over 100-400,000 donors
- Used to treat immunodeficiencies and autoimmune diseases
- Provides a "snap-shot" of herd immunity towards influenza viruses
- Could have therapeutic benefits against new pandemic influenza viruses if it contains cross-reactive antibodies

IVIG manufactured pre-2009 and post-2009

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IVIG made prior to 2009 contains cross-reactive 2009 H1N1pdm-specific ADCC mediating antibodies

- Studied recombinant influenza HA proteins from either the 2009 H1N1 pandemic (CA/09), seasonal H1N1 (SI/06, NC/99, BR/07) or HIV gp140 (negative control)

Kindly provided by Steve Rockman at bioCSL
How cross-reactive is IVIG to different influenza subtypes?

IVIG can recognise a broad range of influenza subtypes

* Tested recombinant influenza HA proteins from either H1N1 (A/California/04/2009), H2N2 (A/Japan/305/1957), H3N2 (A/Brisbane/10/2007), H4N6 (A/Swine/Ontario/01911-1/1999), H5N1 (A/Vietnam/1203/2004) and H7N7 (A/Chicken/Netherlands/03/2003) or gp140 negative control

Is broadly-reactive ADCC induced by current protein vaccine strategies?

Stimulated with H3N1 pdm HA protein
Gated on NK cells

No ADCC induced by TIV in macaques

Jegaskanda et al. (2013) J Virol
No ADCC induced by TIV in macaques

**Summary**

- ADCC antibodies that cross react to diverse influenza strains are induced by influenza infection in both macaques and humans
  - May have played a role in reduced mortality of elderly during H1N1pdm pandemic
  - Are present in IVIG, even prior to epidemics
- Modest or no induction of ADCC by current protein vaccines without adjuvant in macaques (and humans)
- Improved vaccine strategies needed to induce ADCC
  - Will broadly reactive ADCC antibodies induced by a “universal influenza vaccine” offer partially protection from disease following infection with divergent strains?

**Much still to learn.**

**A few key research priorities**

- Difficult to measure ADCC responses in mice and ferrets
  - Mice: NK cells more resistant to activation. Use of Fc-knock out mouse models current standard.
  - Ferrets: few immunologic reagents
- Need for passive transfer experiments in larger animal models
  - ADCC “only” antibodies without Nab function
- Need for incisive studies of human vaccinees
  - Pre-existing ADCC from prior influenza infections can make interpretation difficult in adults
  - Analyses of younger children or subjects pre-screened for ADCC needed
  - Need protection studies in humans with vaccines inducing ADCC
- Better understanding of the best antigens to target by ADCC
  - Surface proteins - HA, NA, M2e obvious targets.
  - Further targeting of the most conserved elements of HA and NA.
  - “Internal” proteins also induce ADCC and might be useful – NP, M1.
- Better understanding of role of other Fc-mediated functions
  - Phagocytosis etc.

**Acknowledgements**

**University of Melbourne**
- Sinthujan Jegaskandha
- Pat Reading
- Andrew Brooks
- Matt Parsons
- T. Amarasena
- S. Alcantara
- Wendy Winnall
- Marit Kramski
- Rob De Rose
- Emma Job
- Gamze Isitman
- Ivan Stratov
- Rest of Kent lab

**University of Wisconsin**
- Tom Friedrich
- Jason Weinfurter

**BioCSL Melbourne**
- Steve Rockman

**WHO influenza center Melbourne**
- Karen Laurie
- Aeron Hurt
- Ian Barr
- Anne Kelso

Clinical trial participants, blood donors and funders