Neonatal and paediatric immunology relevant to HIV persistence

Deena Gibbons PhD
Peter Gorer Department of Immunobiology
Kings College London
&
Nigel Klein MD PhD
Institute for Child Health
University College London
Neonatal Immunology and HIV

Infant immunology qualitatively/quantitatively different from that in the adult.

- Different immune response to HIV
- Different HIV susceptibility
- Different HIV persistence

unique aspects towards cure.
So what is different in infants?

**Innate immunity**
- Monocytes
- DCs
- PMNs
- TLRs

- pDC: mDC in adult 1:2
- pDC: mDC in infant 3:1

Impaired response to TLR7 (detects ss RNA of HIV) in neonatal monocytes

So what is different in infants?

Adaptive immunity
- T follicular helper cells
- T cells
- B cells

Development of TFH in newborn mice defective compared to adults
- major reservoir of HIV

T memory stem cell (TSCM)?
- HIV reservoir

Majority are naïve in infant (less susceptible to HIV?)
Much higher CD4:CD8 ratio

Increased replication of HIV in CB mononuclear cells

3x increased replication of HIV in cord blood T cells

9x increased replication of HIV in cord blood monocytes

Differential expression of host factors determine this susceptibility

→ Contributes to faster disease progression in neonates

Neonatal T cell Function

Although under optimal circumstances, lymphocytes from neonates can mount robust responses, the responses in neonates, particularly Th1 responses, are sub-optimal / almost non-existent, conventionally explained as a way to maintain tolerance.

Birkholz et al, Human Immunology 75 584 (2014)
Infants do make immune responses to HIV

Does the T cell function influence HIV viraemia in children?

- Tolerogenic environment
- Decreased type 1 IFNs
- Decreased levels of Th1 cytokines (IL12/IFNγ), some bias towards Th2 and extracellular pathogen clearance
- Low magnitude (or non existent) CD4 and CD8 responses with narrow specificity

Contributes to faster disease progression in neonates?

Log$_{10}$ HIV-1 RNA plotted against age in untreated HIV-infected children

But... neonatal CD4 are not inert.. just different

Adult

Baby

.....they make CXCL8
% of CD4 making CXCL8 decreases with age

R^2 = 0.5759
CXCL8

- Mainly produced by epithelia, macrophages, fibroblasts
- Two forms 77aa/72aa
- Recruits neutrophils to phagocytose antigen
- Human PMNs can’t respond to IL17
- Binds CXCR1 & CXCR2
- Levels of receptors are tightly controlled
CXCL8 receptors

- CXCR1+ve CD8 defines a highly cytotoxic CD8 T cell

- Does CXCR1 define a “rapid-responder” subset of CD8 T cells that bridges the gap between the innate and acquired immune responses.

- Interestingly, significant expression of CXCR1 on HIV-1–specific CD8 T cells in individuals on HAART was restricted to persons who were able to control HIV-1 replication when taken off HAART.

Summary I

• Human neonatal immune system is not just an immature version of the adult

• Neonates have different responses - not sub-optimal.

• Classic adult HIV reservoirs may not be the same in infants
Thymic Output is a key difference

• Vital for a diverse T-cell repertoire
• High thymopoiesis in infancy, declining with age
• Difficult to measure / complex interplay

Bains et al Blood 2009
Sangaard et al AIDS 28.209 2014
Increased Thymic output leads to a different pattern of Immune Reconstitution

Sefe et al Paeds and Child Health 17:121. 2007
Bunupuradah et al AIDS 27:579 2013
The decline in Thymic Output has an important influence on eventual CD4 count.

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Robbins et al CID 48.350 2009
Walker AS Manuscript in preparation from Arrow Trial
HIV Reservoirs may be different in children and can be influenced by the balance between tolerogenic environment and drivers of immune activation.
Cells more permissive to HIV infection are present in newborns and early childhood

- Targets in Gut and LNs found in neonates
- More memory cells and activation in Africa

Bunders et al Immunobiology 120:4383 2012
Lawrie et al SAMJ 105:589 2015
Drivers of immune activation may exceed immune tolerance

Doyle et al submitted
Mold et al Science 322:1562 2008
Majority of infants treated early don’t seroconvert

Butler et al PIDJ 34:3 2015
New initiatives to understand immunological responses associated with viral control

**On ART** (acute phase)

- slow suppressor
- rapid suppressor
- rapid rebounder
- slow rebounder

**Off-ART** (interruption/low adherence)

Birth/perinatal HIV infection

HIV RNA

50 cp/mL

time

EPPICC
IMPAACT 1115
CHER
CHERUB-UK
NEVEREST
CHANGES
Thai Cohort

IMPAACT 1115
CHER
PENTA11
Elite controllers

Palma P. et al. J. Viral Eradic 2015
Summary II

- Children have much higher Thymic Output with better immune reconstitution
- Infants do not seroconvert to HIV if ART started early which affords unique opportunities for immune modulation to HIV
- The balance between immune tolerance and activation may be key to the future Cure agenda for children