Immunity to invasive *Salmonella* infections: lessons from animal models and man

Pietro Mastroeni

University of Cambridge
Lessons from mice
Systemic infections progress in distinct phases

Bacterial numbers in target organs

Innate resistance
- Resident MΦ
- PMNs
- ROS
- Complement
- scla11a

Adaptive response ("inflammation")
- inflammatory MΦ
- NK cells
- RNI
- ROS
- TLR4
- Myd88
- TNFα
- IFNγ (NK cells)
- STAT-1
- IL12
- IL18
- IL15

T-cell dependent acquired immunity
- α/β TCR+ CD4+ cells
- H-2 genes

Secondary infections
- CD4+ cells
- CD8+ cells
- Antibody, FcR

Carrier state
- nu/nu mice
- rag1−/− mice
- scid mice
- α/β TCR−/− mice
- Some H-2 haplotypes

Days p.i.
1
5-7
15-40
variable
Like a “castle of cards”

- Resident MΦ
- PMNs
- Complement

- Inflammatory MΦ
- MΦ activation
- Cytokine networks

- Antibody
- T-cells

Level 1: Innate immunity
Level 2: Adaptive immunity
Level 3: Antigen-specific acquired immunity
Dynamics of the *in vivo* infection process, immunity and vaccination

Molecularly tagged, fluorescent *Salmonella* subpopulations

Tag analysis (PCR or sequencing):
- presence
- absence
- relative proportions
- population heterogeneity

- location
- intracellular numbers
Dispersive infections with intracellular and extracellular phases

- Resting phagocyte
- Infected phagocyte
- BMD-inflammatory macrophages
- IL-12
- TNF
- IL-18
- ROI
- RNI
- Lysosomal fusion
- IFN

Multicellular lesion with inflammatory phagocytes being activated

Fully activated lesion

Bacteria escape from lesions to infect new resting cells

New lesions develop from individually infected cells

Control of intracellular growth

Resting phagocyte
- Infected phagocyte
- Intracellular bacterial growth

Opsonization by antibodies

Uptake by FcγRI, increase in the number of infected cells and enhancement of antimicrobial functions of phagocytes by ROIs
Lessons from humans: genetic immunodeficiencies/associations


**Humoral/antibody**
- Complement deficiencies

**T-cell mediated immunity**
- Variants in cytokine-inducible Src-homology-2-containing (CISH)
  - HLA-\(DRB1^{*04:05}\); HLA-\(DRB1\) (rs7765379)

**Phagocyte antimicrobial functions**
- CGD- X-linked and autosomal recessive deficiencies
- β-thalassaemia/HbE disease
  - TLR4 rs4986790
  - \(IKBKG\) (encoding NEMO) mutations
  - \(NFKBIA\) (encoding \(I\kappa B\alpha\)) mutations
  - MyD88-defects
  - TIRAP missense variant (rs8177374)

**Signalling**
- IL12/IL23p40 deficiency
- IL12R\(\beta1\) deficiency
- Anti-IFN\(\gamma\) autoantibodies
- IFNR1 deficiency
- STAT1 deficiency
- TNFα (protective MHC class III haplotype \(DDX39B, LTA, TNF\))
Lessons from humans: epidemiological risk factors/comorbidities in endemic areas

Antibody functions
- absence of anti-\textit{Salmonella} antibodies in young children
- dysregulated antibody responses in HIV patients

Phagocyte functions
- malaria
- HIV

T-cell mediated immunity
- malnutrition
- anaemia
Vaccines

Are we making the most of the lessons that we have learnt from mice and man?
Lessons from mice
How can we affect the infection with external intervention?

Antibody

- unaltered growth
- resurgence of bacteraemia
- unrestrained bacterial spread
If we are going to use vaccines whose efficacy is based on antibody responses, we must strive to increase the efficacy of these responses to eliminate the infection in the early stages.
Time post infection

Bacterial numbers

Antibody

.................or to lower the infection load to a level that will allow an unprimed cellular immunity to cope with the disease
Optimise the antibody response: isotypes and effector functions

Mouse V<sub>H/K</sub>
Human Fc

IgG<sub>1</sub>  IgG<sub>2</sub>  IgG<sub>3</sub>  IgG<sub>4</sub>

TSSPSAD :: OmpA

Log<sub>10</sub> Viable bacterial counts

Control  IgG<sub>1</sub>  IgG<sub>2</sub>  IgG<sub>3</sub>  IgG<sub>4</sub>

Intracellular bacterial count

Human phagocyte
“Quality” and effector functions of mouse antibodies \textit{in vivo}
Should we also push forward research on live attenuated vaccines as an additional/alternative option?

Cell-mediated immunity

- Suppression of growth and spread
- Enhanced killing
- Suppression of bacteraemia
To decide on a **rational** path for vaccination in **endemic areas** we need to better understand the immunological **determinants of resistance/susceptibility** to typhoid and iNTS disease **in the context of predisposing factors**.
Epidemiological risk factors
(e.g. age, co-morbidities, genetic)

Susceptibility to disease

Immunological signatures

Functional defects of immune effectors
Resident MΦ
PMNs
Complement
Inflammatory MΦ
MΦ activation
Cytokine networks

Level 1
Innate immunity

Level 2
Adaptive immunity

Level 3
Antigen specific acquired immunity

Antibody
T-cells

Highest level of resistance
A lot has been done, but much remains to be done
Andrew Grant
Chris Coward
Richard Dybowski
Mark Sheppard
Gemma Foster
Olivier Restif
Yun Shan Goh
Mike Clark
Duncan Maskell
Pietro Mastroeni

Gordon Dougan
Simon Clare
Chris Hale
George Vassilou
Cal MacLennan

Allan Saul
Simona Rondini
Francesca Micoli

David Gray
Tom Barr

Sjef Verbeek

Ferric Fang

Andres Vazquez-Torres

University of Colorado
Denver | Anschutz Medical Campus