TB adaptive immune evasion

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TB infection stages

Mtb exposure → ??%

- infection
  - active TB disease
    - LTBI → ~95%
    - cured TB

BCG vaccination
Co-infections or co-morbidities can:
- enhance incidence of TB disease
- increase severity of TB disease
- complicate TB treatment
- prolong contagious time of TB patients and thereby disease spread
- hamper TB diagnostics
- complicate vaccination strategies

But TB also complicates treatment of the co-infections or co-morbidities!
Adaptive immunity in TB disease

Mycobacterium tuberculosis

TB

T cell

helper

regulatory

B cell

classical

non-classical

activated

memory

atypical
BCG vaccination

Effector response against Mtb ~ protection

Expected response

Observed response

Effector response
No response
Different response
BCG vaccination study

BCG vaccination in healthy, Dutch adult volunteers

A

12 weeks after BCG vaccination:

Vaccinee A:

Vaccinee B:

B

Cumulative scores of skin lesions:

low responders high responders

C

D

Boer et al., Clin Vacc Immunol, 22(7), 778 (2015)
Immune regulation vs effector responses

Low skin inflammation is associated with higher level of CD8 Tregs

Boer et al., Clin Vacc Immunol, 22(7), 778 (2015)
Regulatory T-cells

Identification of a human CD8+ regulatory T cell subset that mediates suppression through the chemokine CC chemokine ligand 4

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Communicated by Johannes van Rood, Europedonor Foundation, Leiden, The Netherlands, March 21, 2007 (received for review November 14, 2006)

CD39 is involved in mediating suppression by Mycobacterium bovis BCG-activated human CD8+CD39+ regulatory T cells

Mardi C. Boer†, Krista E. van Meijgaarden†, Jérémy Bastid2, Tom H.M. Ottenhoff*† and Simone A. Joosten*†

CD8+ Regulatory T Cells, and Not CD4+ T Cells, Dominate Suppressive Phenotype and Function after In Vitro Live Mycobacterium bovis-BCG Activation of Human Cells

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Immune regulation may not be only inhibitory response induced by BCG......
KLRG1 and PD1 following BCG vaccination

TB patients:
PD1 and KLRG1 on CD4\(^+\) T-cells, not on CD8\(^+\) T-cells
Increased frequency in active TB patients, highest in cured TB patients

Boer et al., Tuberculosis, 97:163 (2016)
Adaptive immunity in TB disease

Mycobacterium tuberculosis

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T cell

helper  effector  regulatory

B cell

activated  memory  atypical

classical  non-classical
Unconventional immunity – donor unrestricted T-cells

αβ T-cells

DI Godfrey, AP Uldrich, J McCluskey, J Rossjohn & DB Moody
Nature Immunology 16, 1114–1123 (2015) doi:10.1038/ni.3298
HLA-E

3 alleles,
2 functional proteins,
single amino acid difference:

- HLA-E*0101: position 107 = arginine > E_R
- HLA-E*0103: position 107 = glycine > E_G

E_R and E_G frequencies in population are about equal
No significant differences in crystal structure
E_G has slightly increased cell surface expression
E_G has stronger peptide affinity
E_G has increased thermal stability
Functional significance?

Grimsley et al, Human Immunology, 1997, 52, 33
Hoare, Nat Immunol, 2006, 7(3), 256
**HLA-E in tuberculosis**

Only 2 variants described in humans: single peptides can be presented by most (all) individuals → potentially interesting vaccine target

HLA-E is not down-regulated by HIV-nef, potentially interesting to use HLA-E peptides for post-exposure vaccination against Mtb in HIV⁺ setting

*Cohen et al, Immunity, 1999, 10, 661*

HIV p24 may stabilize HLA-E molecules and thereby even enhance HLA-E surface expression

*Nattermann et al, Antivir Ther, 2005, 10: 95*

HLA-E is enriched within Mtb phagosome compared to HLA-A2, HLA-E may preferentially present phagosomal antigens

*Grotzke, Lewinsohn et al Plos Pathogens, 2009, 5(4): e1000374*
HLA-E restricted T-cell clones can inhibit intracellular growth of MtB


HLA-A2 negative macrophages were infected with live H37Rv and HLA-E restricted CD8+ T cell clones were added (5:1 ratio) for 24 hours. Subsequently cells were lysed and plated to determine the number of colony forming units.
MtB specific HLA-E restricted T-cell clones produce Th2 cytokines

TB patients recognize HLA-E TM strongest before therapy, in contrast HLA-A2 TM are increasingly recognized during treatment.

HLA-E restricted Mtb specific T-cell clones utilize IL-4 to provide B-cell help

Innate immunity

Pathogen

Mφ

HLA-E

CD94

NKG2A

NK cell

Inhibition of NK cell mediated lysis

Adaptive immunity

CD8 T-cell

Specific recognition > T-cell activation

T-cell receptor

HLA-E
Adaptive immunity in TB disease

*Mycobacterium tuberculosis*

TB

- T cell
- B cell
  - activated
  - memory
  - atypical
TB

Th1/Th2
dichotomous
Tregs
HLA-E
terminal differentiation

cross-talk

antibodies
impaired function

recovery
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