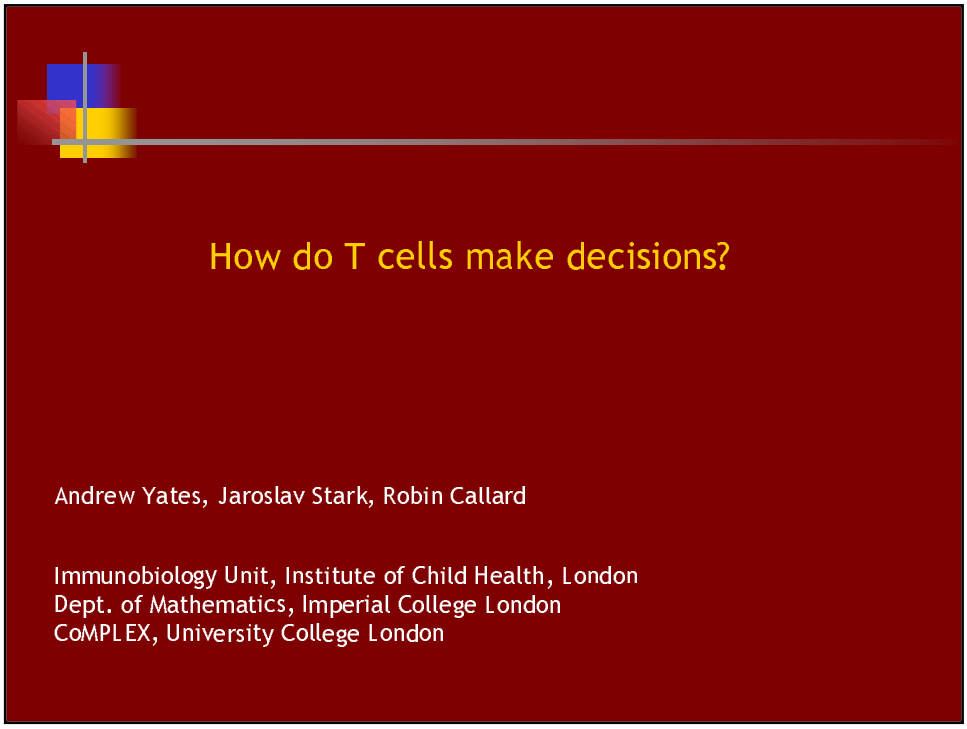
How do T cells make decisions?
Andrew Yates, Jaroslav Stark, Robin Callard
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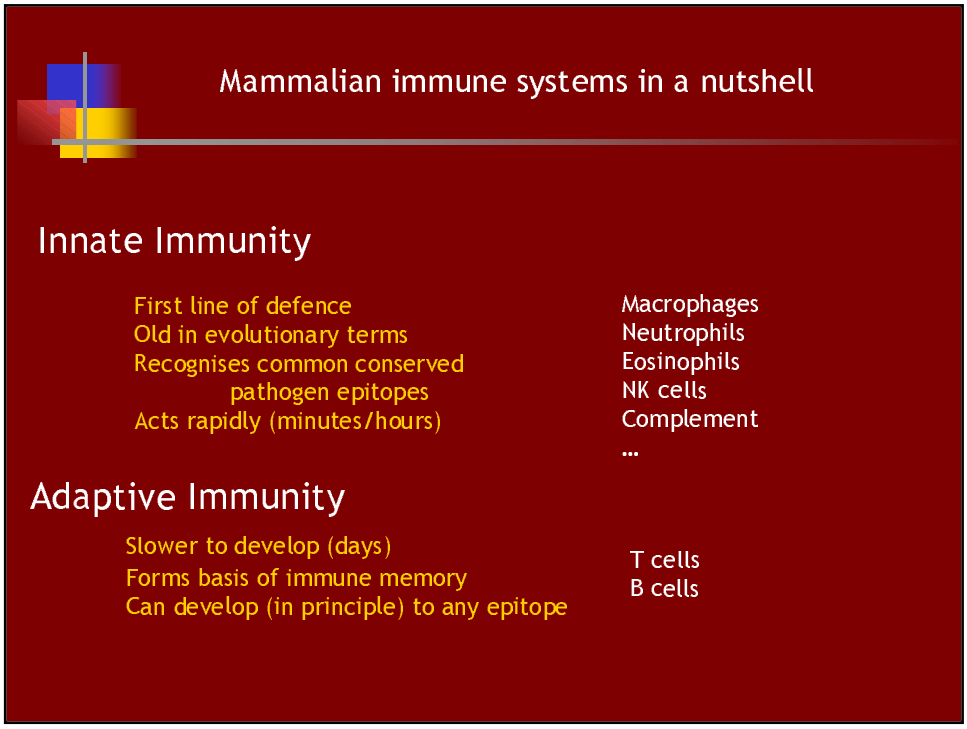
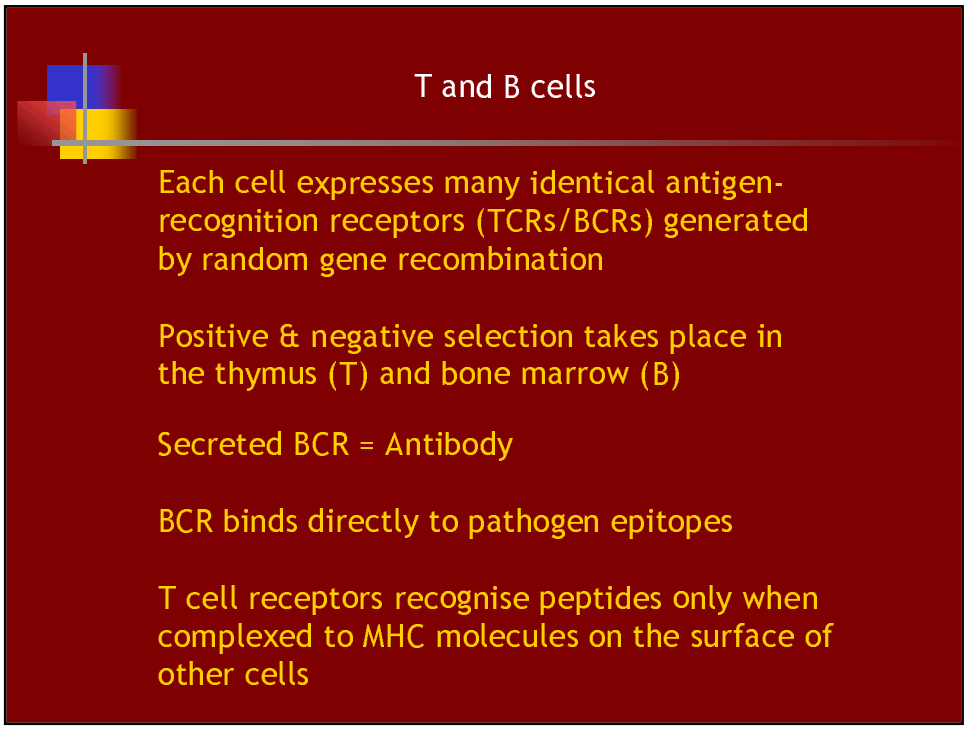
Challenges faced by an immune system
Reliable self/non-self discrimination
To minimise harm to the host -
to be rapid, specific and limited
To select the most appropriate response -
Viruses
Intra/extra-cellular bacteria
Helminths
Protozoa
Self (cancer)


Mammalian immune systems in a nutshell
Innate Immunity
First line of defence
Old in evolutionary terms
Recognises common conserved pathogen epitopes
Acts rapidly (minutes/hours)
Macrophages
Neutrophils
Eosinophils
NK cells
Complement
...
Adaptive Immunity
Slower to develop (days)
Forms basis of immune memory
Can develop (in principle) to any epitope
T cells
B cells


T and B cells
Each cell expresses many identical antigen-recognition receptors (TCRs/BCRs) generated by random gene recombination
Positive & negative selection takes place in the thymus (T) and bone marrow (B)
Secreted BCR = Antibody
BCR binds directly to pathogen epitopes
T cell receptors recognise peptides only when complexed to MHC molecules on the surface of other cells

Dendritic Cells (DCs)

A bridge between innate and adaptive immunity

- Recognise 'danger' and browse the site of infection
- Digest and process pathogen fragments
- Migrate to lymph nodes
- Present foreign peptides to T cells on MHC I/II

Carry information to T cells regarding the nature of the pathogen, through 'contextual signals' -

COSTIMULATION

Triggering T cells

A successful (mid- to high-affinity) interaction between a DC and a T cell leads to

- Activation
- Proliferation/clonal expansion
- Differentiation from naïve into 'effector' (Th1/2) status

of the T cell

This requires TCR-MHC/peptide binding AND costimulation

e.g. B7.1/B7.2 - CD28
OX40-OX40L
IL12

T cell subtypes

Roughly constant in number
~10^{11} in healthy adult human

Large repertoire
~10^{8}- 10^{9} different TCR sequences

Two main subclasses:

Cytotoxic T lymphocytes ($CD8^+$ CTL)
- recognise MHC I + peptide (7-8 aa)
- MHC I expressed on all cell types
- can kill infected host cells

T helper cells ($CD4^+$)

T helper cells

Recognise MHCII + peptide (10-13 aa)

Give B cell help (optimal antibody production) + CTL help

Fall broadly into two subclasses:

Th1	Viruses, intracellular bacteria
Th2	Extracellular bacteria, parasites, worms, allergy

Effector status characterised by cytokine secretion patterns:

Th1	IFNg, TNFa
Th2	IL4, 5, 10, 13

T helper cell differentiation

How do T helper cells make the right choice?

- Costimulation

  e.g. IL12 from DCs induces IFNγ production in Th cells

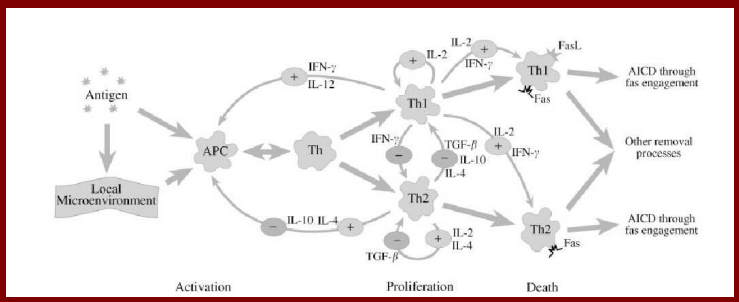
- Cytokine signalling

  Th cells interact through a very complex network of cytokine signals, starting very rapidly (mins-hours) after activation

Th1/2 choice is reversible at the single cell level until 4-5 divisions

Effector phenotype is subsequently irreversible

A question



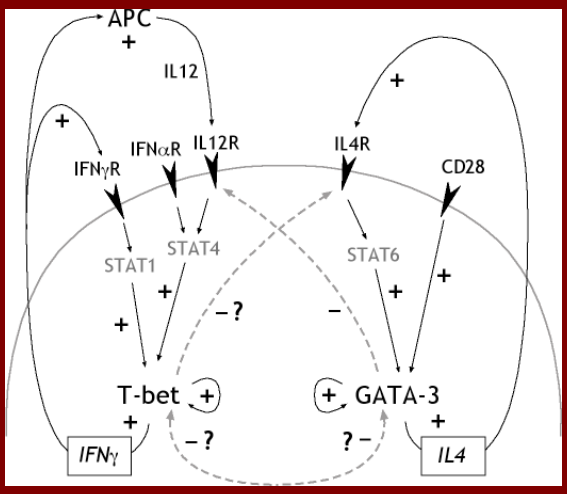
Why do T cells communicate via cytokines at all, if all the information they require for activation and differentiation comes from the DC?

Intracellular processes controlling Th1/Th2 differentiation

↕

Cytokine communication between cells

T-bet /GATA-3 interactions



TCR signalling also briefly induces rapid transcription of both T-bet and GATA-3 through NFκB

T-bet /GATA-3 dynamics

x_1=[T-bet], x_2=[GATA-3]

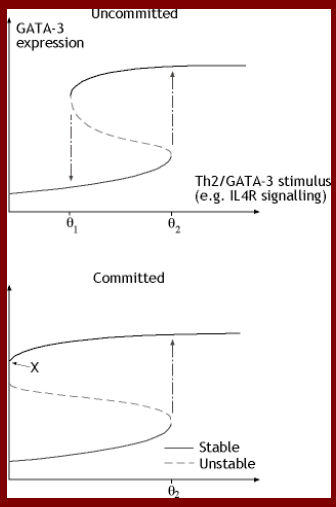
Levels of pro-Th1/2 signal sources in extracellular medium= S_1 and S_2

Autoactivation | Extracellular signalling | Cross-suppression

$$f_1 = \frac{dx_1}{dt} = -\mu x_1 + \left(\alpha_1 \frac{x_1^n}{\kappa_1^n + x_1^n} + \sigma_1 \frac{S_1}{\rho_1 + S_1} \right) \frac{1}{(1 + x_2/\gamma_2)} + \beta_1$$

$$f_2 = \frac{dx_2}{dt} = -\mu x_2 + \left(\alpha_2 \frac{x_2^n}{\kappa_2^n + x_2^n} + \sigma_2 \frac{S_2}{\rho_2 + S_2} \right) \frac{1}{(1 + x_1/\gamma_1)} + \beta_2$$

T-bet /GATA-3 interactions



-Bistable, mutually exclusive expression of T-bet and GATA-3

- Attainment of high states of expression requires transient DC signals; sustained by cytokine signalling

- Blocking of cytokine signalling within first 4-5 divisions returns cells to low expression (Th0) state

Heritable Th1/2 commitment can occur through:

2-fold decrease in T-bet/GATA-3 cleavage rate
OR
2-fold increase in T-bet/GATA-3 transcription rates
OR
progressive chromatin remodelling of IFNγ/IL4 loci

Exploring cross-inhibition - predictions

Exogenous cytokines can modify a developing or chronic response
- potential therapy (e.g. leprosy)

If mutual inhibition of T-bet and GATA-3 is both direct and indirect, an ongoing Th2 response can be switched to Th1 by addition of excess IL12

If inhibition is indirect only:
Th2-Th1 switch requires BOTH blocking of IL4 AND excess IL12

Why do T helper cells communicate with each other?

Structured population model

Levels of cytokines/signals in extracellular medium; S_1 and S_2

Cells have continuous internal variables x_1, x_2 with dynamics $dx_i/dt = f_i(\boldsymbol{x}, \boldsymbol{S})$

Cell population density $\phi(x_1, x_2; t)$

Master equation:

$$g(x_1, x_2, S_1, S_2)\phi = \frac{\partial \phi}{\partial t} + \frac{\partial}{\partial x_1}(f_1\phi) + \frac{\partial}{\partial x_2}(f_2\phi)$$

where $$S_i = \frac{C_i(t) + \int x_i \phi \, dx_1 \, dx_2}{\int \phi \, dx_1 \, dx_2}, \quad i = 1,2$$

$C_i(t)$ = signals from non-T cell sources (e.g. DCs)

Further assumptions

Proliferation and differentiation signals appear to be decoupled

So division rate g= constant (2-3 day^{-1})

Cells sense cytokine *concentrations* S_i ...

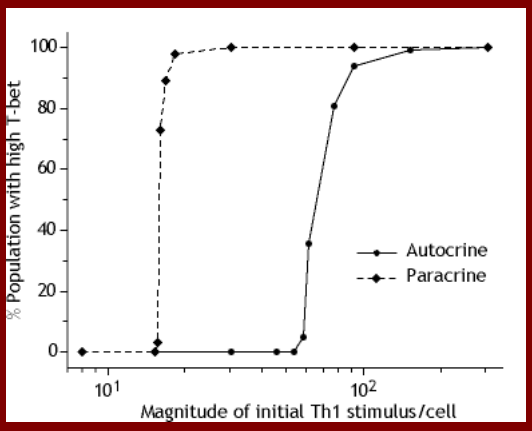
Fast cytokine dynamics (production, absorption, decay)

So $S_i \propto$ total expression of x_i

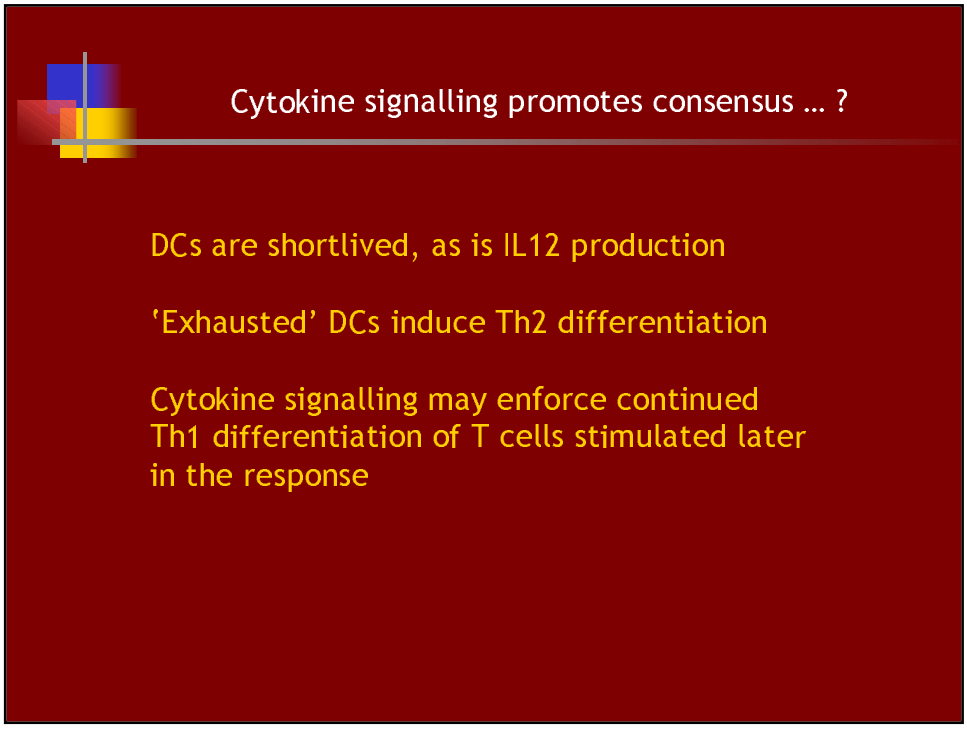
Cytokines diffuse rapidly through a volume $\propto$ cell number

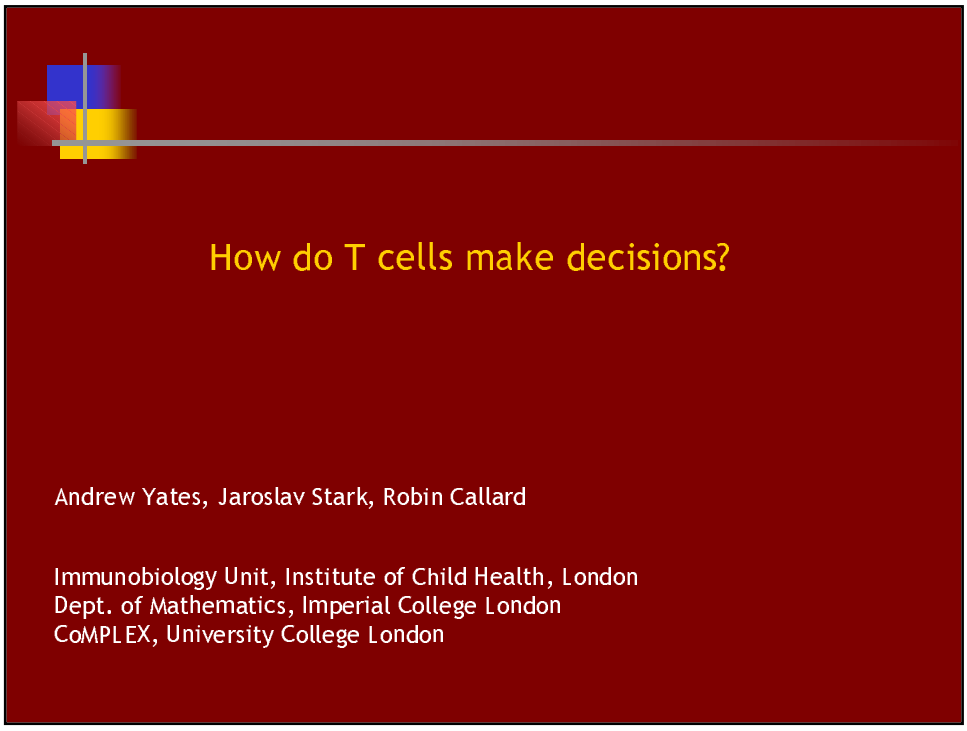
So $S_i \propto$ 1/cell number

Cytokines amplify DC signals



Autocrine - cytokines sensed only by cell that produced them
Paracrine - cytokines shared among population


Cytokine signalling promotes consensus … ?
DCs are shortlived, as is IL12 production
'Exhausted' DCs induce Th2 differentiation
Cytokine signalling may enforce continued Th1 differentiation of T cells stimulated later in the response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