Modeling homeostatic T cells responses

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T cell homeostasis: keeping the immune system the right size.
The homeostatic T cell response to lymphopenia

Activated/Effector T cells

Naïve T cell pool

Memory

INPUT

Ag

Lymphopenia

- Infection, stress, HIV
- Thymectomy/old age
- Clinical intervention (chemo and radio therapy)
Different signals for different subsets

**Naïve T cells**
Cytokines + TCR

- CD4
- IL-7
- Stromal cell

- CD8
- IL-7
- IL-15

**Memory T cells**
Cytokines

- (s)pMHC
- dc

- IL-7 - survival
- IL-15- proliferation

More division but more death also
Measuring homeostatic T cell responses in vivo

**Lymphopenia Induced Proliferation (LIP)**

1. Proliferation (CFSE)
2. Survival (cell recovery)
Heterogeneous LIP response of polyclonal CD8 T cells

Day 6:
- Naive: 59%
- Memory/effecter: 41%

Day 13:
- Naive: 9%
- Memory/effecter: 91%
Proliferative responses by different clones are heterogeneous.

F5 - low avidity

OT1- high avidity

CD44

CD122

CFSE

CFSE

CFSE

CFSE
Antigen and homeostatic induced proliferation

**Foreign**
- pMHC
- TCR signal
- IL-2
- IL-2R
- γc cytokine growth factor proliferative

**Homeostatic**
- Self-pMHC
- IL-7R
- IL-7

IL-2R
Trying to understand cell cycle control during LIP

- Flu

+ Flu

Flu specific F5 TCR transgenic T cells

How can modeling help understand LIP?

Define cellular events underlying the response.

Does LIP follow the same rules as antigen responses?

Are they governed by the same biological programme?

Creating successful models can identify key parameters that can help understand the biological processes.
Autopilot *divisions model*

Probability density of first mitosis occurring at time $t$

No divisions possible before time $t = T$
**Stochastic divisions**

**A-phase**
(non-dividing, $G_0/G_1$)

**B-phase**
(actively dividing, $S,G_2,M$)

Stochastic trigger

All cells in A-phase have equal probability ($\lambda$) per unit time of receiving trigger to divide and entering B-phase, regardless of division history.

Cells in B-phase take a time $\Delta$ to divide.

Once divided, cells return to A-phase and have equal chance of undergoing further divisions.
Generating time series data to model

\[ d_3 \]
\[ d_7 \]
\[ d_{11} \]
\[ d_{14} \]

\[ 210 \]
\[ 43210 \]
\[ >66543210 \]
\[ >66543210 \]

\[ d_0 = 91\% \]
\[ d_0 = 31\% \]
\[ d_0 = 12\% \]
\[ d_0 = 7\% \]
Time series data for F5 TCR transgenic T cells
Cell division + cell survival = expansion

Predicted expansion from CFSE

Observed expansion

no/little cell death
Comparing the Autopilot and Single divisions models - mean divisions
Comparing the Autopilot and Single divisions models - mean divisions

Time dependent reduction in $\lambda - \mu$

$$\lambda(t) = \lambda_0 \exp(-\mu t)$$
Comparing the Autopilot and Single divisions models - CFSE profiles

- Gett-Hodgkin model with Weibull-distributed times to first division
- Smith-Martin model with exponentially declining division rate

Frequency of cells in each division

- Observed
- Model prediction
Parameters for model

**Autopilot**

*Weibull distribution*

\[ T \text{ (lagtime)} = 0 \]

\[ \Delta = 2.88 \, \text{d} \]

**Single divisions**

**Const \( \lambda \):**

\[ T = 2.03 \, \text{d} \]

\[ \lambda = 0.21 \]

\[ \Delta = 6.65 \, \text{h} \]

**Reducing \( \lambda \):**

\[ T = 2.44 \, \text{d} \]

\[ \lambda_0 = 0.455 \, \text{day}^{-1} \]

\[ \Delta = 6.19 \, \text{h} \]

\[ \mu = 0.115 \]
Testing the model

- Parameter values are biological reasonable

- Important predictions of the model:
  - *Single stochastic divisions*
  - *Lag time ~ 2 days to division onset*
  - *Slowing in division rate*
‘Autopilot’ antigen induced proliferation

Naïve T cells

TCR signal

IL-2 - γc cytokine
- growth factor
- proliferative

Autocrine loop
**TCR signal**

**IL-7** - \( \gamma \)c cytokine
- growth factor
- proliferative

Triggered by Self-pMHC

Naïve T cells competition

IL-7
Acknowledgements

Andrew Yates,
Emory University, Atlanta, U.S.

Robin Callard
Institute for Child Health, UCL

Rodolphe Thiébaut
INSERM U875, Université Bordeaux

Mark Coles
Department of Biology and HYMS
University of York, U.K.

Present:
Georgina Cornish
Claire Pearson
Manoj Saini
Charles Sinclair
Sim Tung

Past:
Anne Mathiot