Useful References

Overview of the presentation

◆ Lymphocyte recirculation is essential for normal immune function

◆ Cells with different functions recirculate differently

◆ Controlling recirculation helps optimise immune responses

◆ Cellular localisation influences disease pathology

◆ Common activating signals have cell type specific effects on trafficking
The mechanisms of cell trafficking

A multi-step process:

Both common mechanisms and selective expression of specific ligands plays a role

von Andrian & Mackay
NEJM 343:1020 (2000)
The challenges of immunosurveillance

- To bring antigen in contact with the rare cells that can respond to it

- To expand antigen specific cells efficiently and distribute these cells to all tissues

- To do this as fast as possible
A seminal observation in cellular immunology

- Rapid small lymphocyte recirculation was essential for normal immune function

- Experiments started because of the inscrutable nature of small lymphocyte function

- Depended on being able to canulate the thoracic duct of the rat

The lymphocyte -- a disgraceful gap in medical knowledge


First dose

5 days: $2 \times 10^9$ small lymphocytes

Second dose

5 days: $2 \times 10^9$ small lymphocytes

![Graph showing hemagglutination levels over time after receiving tetanus toxoid.](chart.png)
Subdividing the immune system

Small lymphocytes initiate immune responses

- B cells (humoral)
- T cells (DTH)

T cells (DTH)

- Cytotoxic cells (CD8)
- Helper cells (CD4)

1960-64

1975-79

1986-present

- Natural
- Induced
- Treg

- Th3
- Th17
- Th2
- Th1
- Naive cells

Effector and Memory cells
Optimisation of cell trafficking

- By cell type (naive vs memory)
- By target tissue (imprinting allows memory cells to return to site of antigen production)
- By effector phenotype (influence of T cell phenotype on trafficking patterns)
Tissue dependent lymphocyte phenotype

Data from canulation of the popliteal lymph node of sheep
Controlling recirculation helps optimise immune responses

- FTY720 antagonises S1P receptors
- It’s an effective immunosuppressant
- Administration leads to the retention of lymphocytes in 2° lymphoid tissue
- Lymphocytes express S1P$_1$ and S1P$_4$
S1P₁ is essential for efficient lymphocyte egress from 2° lymphoid tissue.

Animals reconstituted with equal amounts of S1P₁ positive and S1P₁ negative thymocytes.

CD69 contributes to lymphocyte retention in 2º lymphoid tissue

Local concentration of antigen specific and antigen presenting cells

- Activation of immune response
  - Upregulation of CD69:S1P₁ signalling inhibited
  - Activated lymphocytes trapped in lymph node with APCs
    - Several rounds of division before release to the circulation
Cellular localisation influences disease pathology

Periphery $\rightarrow$ Blood Brain Barrier $\rightarrow$ CNS

CFA

Experimental autoimmune encephalomyelitis (EAE)
Experimental autoimmune encephalomyelitis (EAE)

Antigen presenting cell

MOG35-55 typical EAE
MOG79-90 typical EAE
MOG97-114 atypical EAE
Clinical disease correlates with pattern of target organ localisation

Clinical disease correlates with pattern of target organ localisation

Pathology reflects T cell phenotype

- Antigen influences T cell phenotype
- T cell phenotype influences target organ infiltration
- Target organ inflammation influences pathology
- Different pattern of autoimmune disease
Common activating signals have cell type specific effects on trafficking

- Target organ inflammation encompasses a mixture of different leukocytes

- The composition of this mixture may have an effect on disease
EAU analysis protocol

Peptide with complete Freund’s adjuvant (CFA) s.c.

HISTOLOGY, TEFI and FLOW CYTOMETRY

d0  d5  d13  d18  d21  d25  d32

Clinical disease

Copland et al. IOVS 49, 5458 (2008)
EAU analysis protocol

Peptide with complete Freund’s adjuvant (CFA) s.c.

HISTOLOGY, TEFI and FLOW CYTOMETRY

Normal   Primary Peak   Secondary Regulation

d0   d5   d13   d18   d21   d25   d32

Clinical disease

Copland et al. IOVS 49, 5458 (2008)
**EAU analysis protocol**

Peptide with complete Freund’s adjuvant (CFA) s.c.

Clinical disease

HISTOLOGY, TEFI and FLOW CYTOMETRY

Copland et al. IOVS 49, 5458 (2008)
Counting cells in EAU

Kerr et al. J.Autoimm 31, 354-361
TNFR1 knockout mice are resistant to EAU

Raveney et al. J. Immunol (in press)
Macrophages but not T cells depend on TNFR1 for recruitment

TNFR1 ko → TNFR1 ko
WT → WT
TNFR1:WT → WT

Raveney et al. J. Immunol (in press)