Biology of chemokine receptors: not just for leukocyte trafficking

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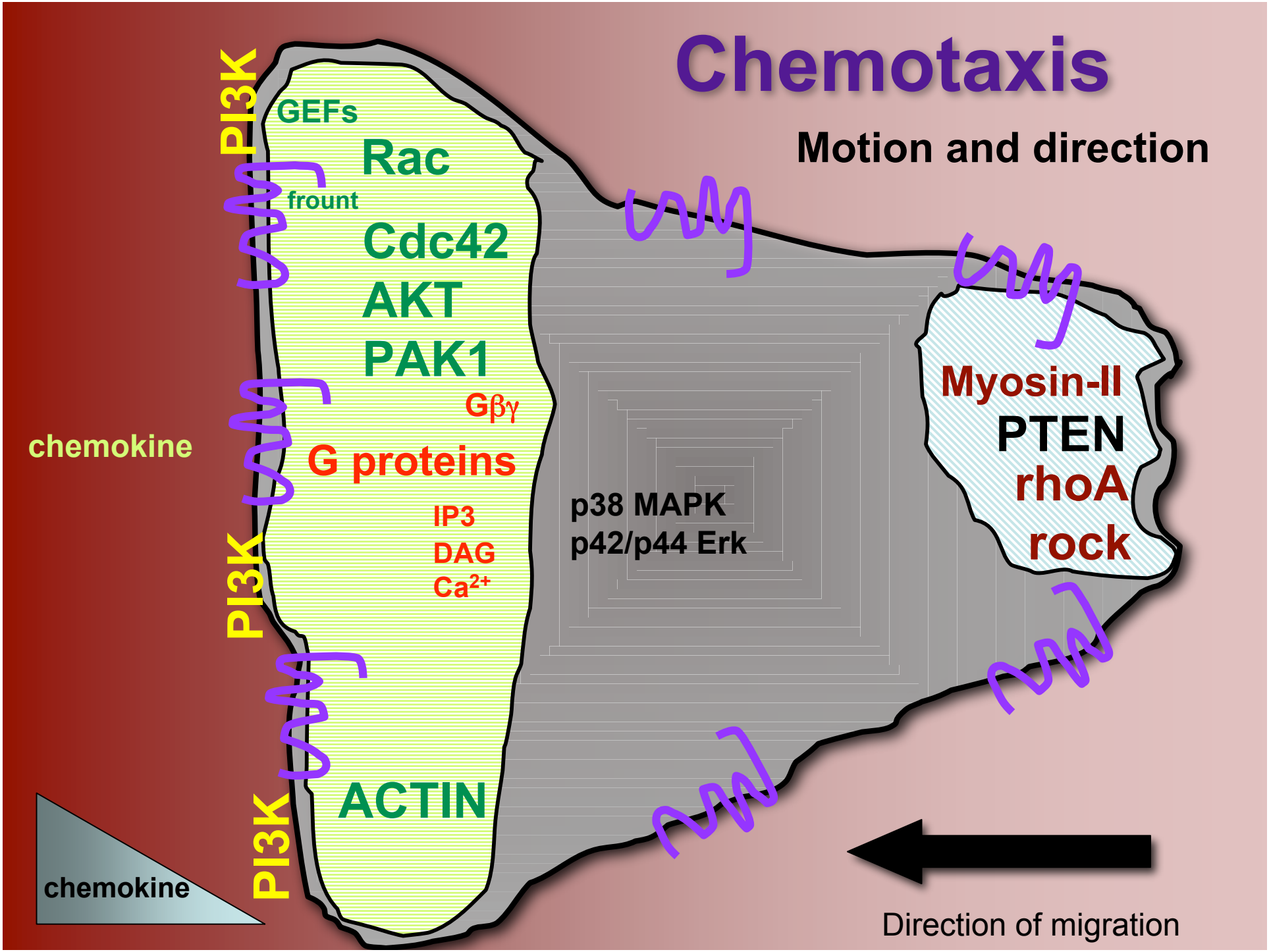
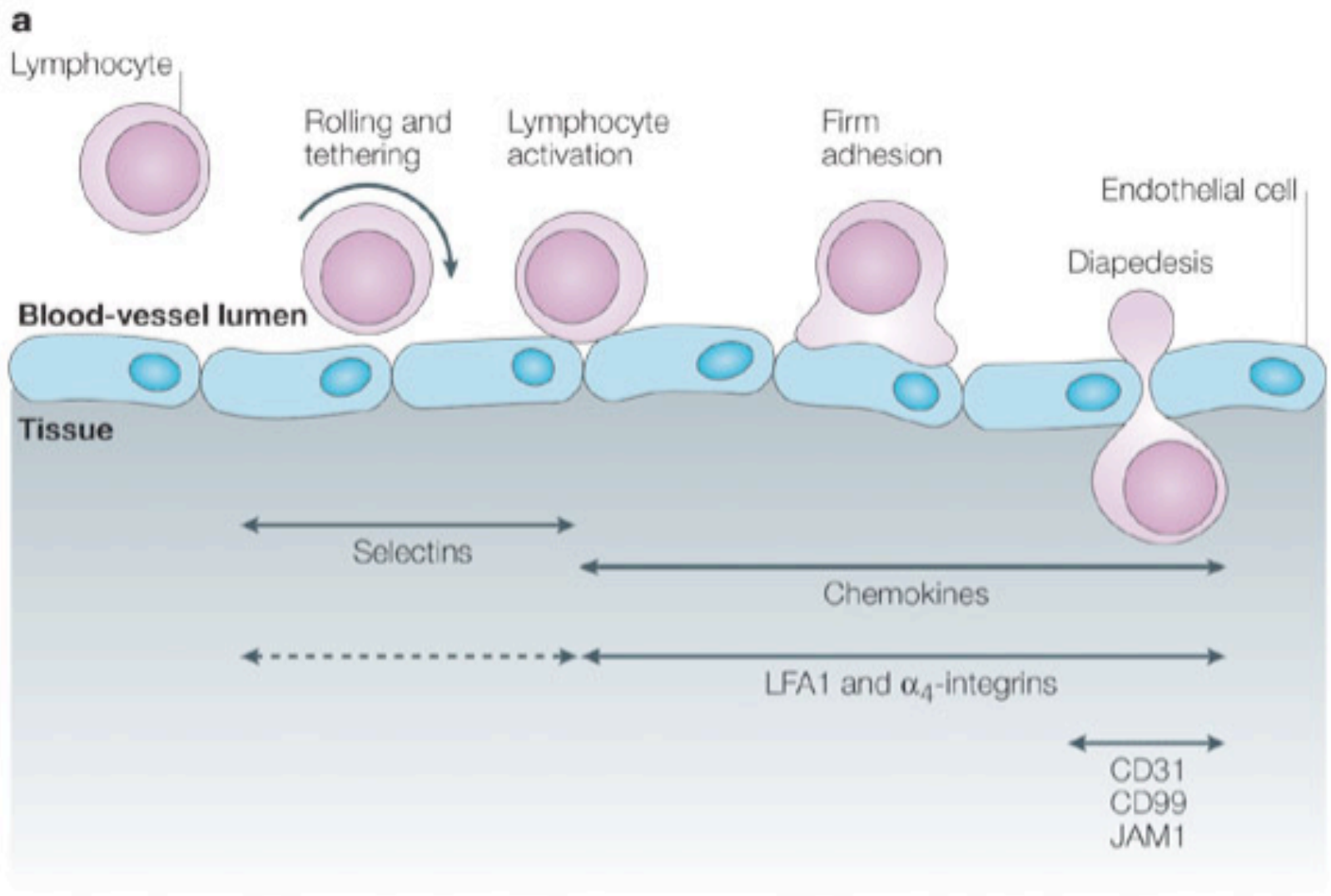
Chemokines and chemokine receptors

- 50 chemokines and 20 GPCR chemokine receptors have been identified
  - most chemokine receptors have > 1 ligand
  - some chemokines activate > 1 receptor
- These molecules direct the migration of leukocytes throughout the body
- Through this process they play a critical role in innate and acquired immunity
- Chemokines and their receptors are important in many disease processes

Chemokine and chemokine receptors

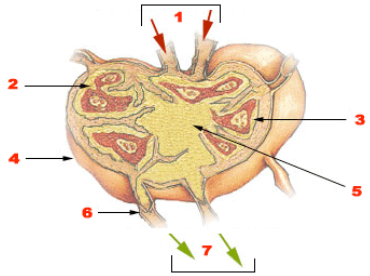
- Chemokine receptors in leukocyte trafficking
- Chemokine receptors in leukocyte regulation
- CCR5 and CXCR4
- Potential unexpected toxicities of chemokine receptor antagonism


Chemotaxis
Motion and direction
PI3K
GEFs
Rac
frount
Cdc42
AKT
PAK1
Gβγ
G proteins
IP3
DAG
Ca2+
chemokine
PI3K
PI3K
ACTIN
p38 MAPK
p42/p44 Erk
Myosin-II
PTEN
rhoA
rock
chemokine
Direction of migration



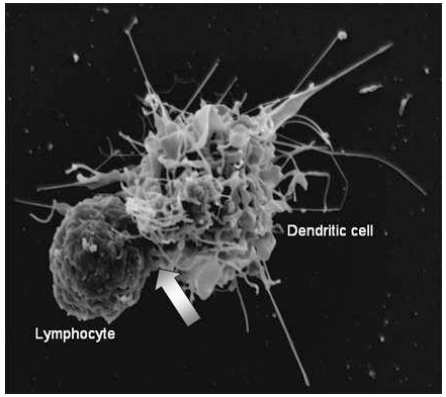
Nature Reviews Immunology **5**, 546-559 (2005)

Dendritic Cell trafficking



Mature DC

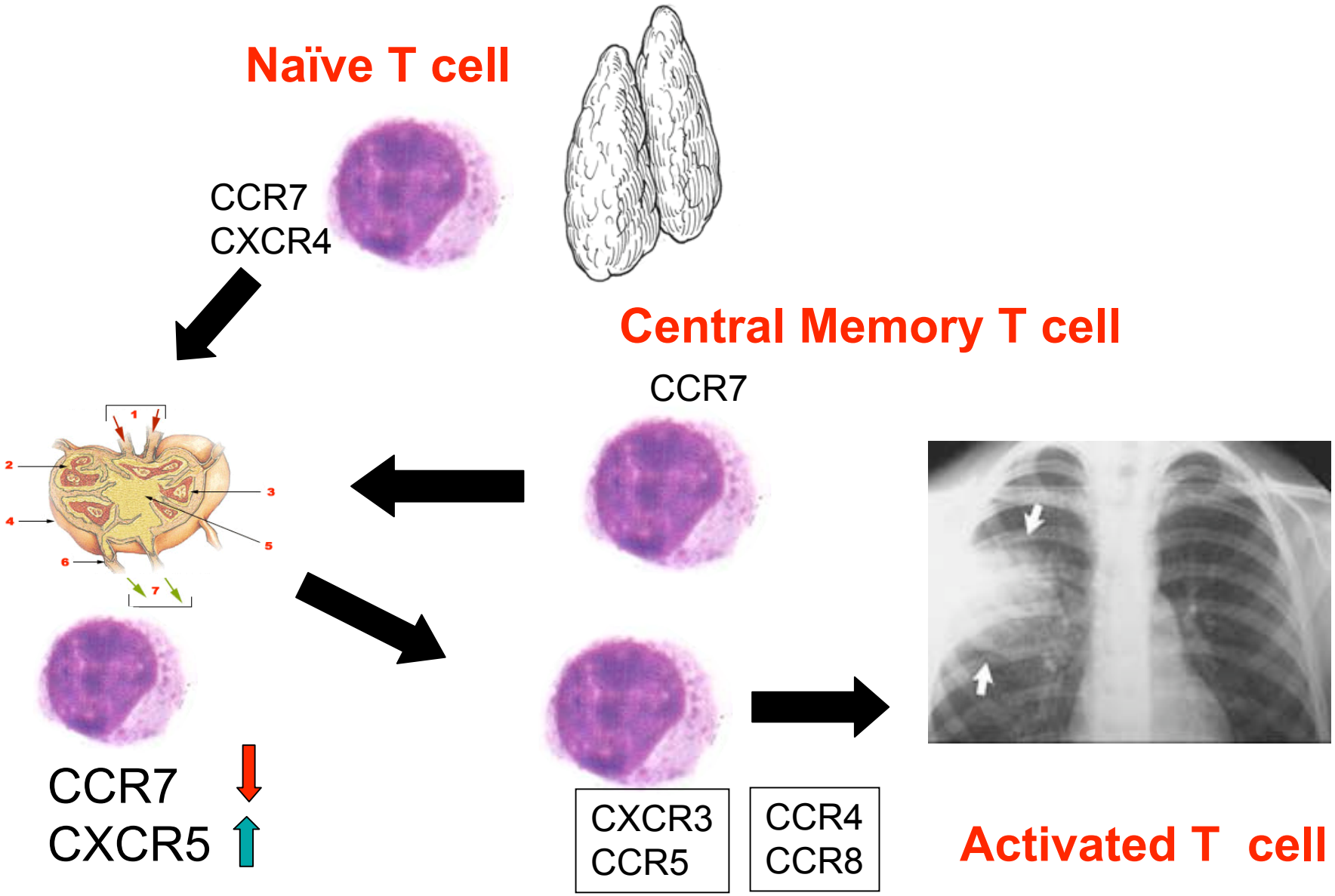
CCR7



CCR1
CCR2
CCR5
CCR6

Immature DC

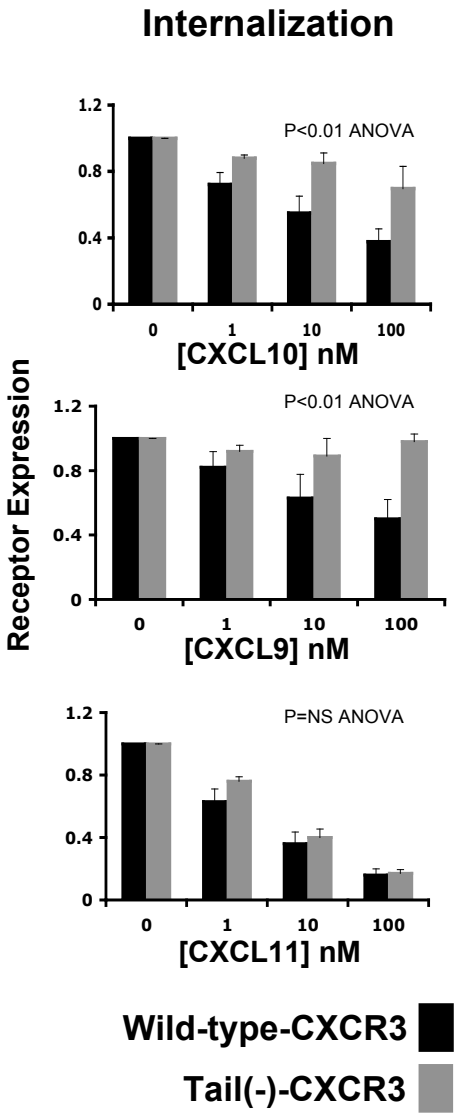
Lymphocyte trafficking



Chemokines and chemokine receptors play functionally non-redundant roles

- CXCL10 has unique roles in allograft rejection and response to Toxoplasmosis infection despite being 1 of 3 ligands for CXCR3
    - expression differences?
        - timing
        - location
    - signaling differences?

The 3 CXCR3 ligands induce different pathways of receptor internalization



Colvin, et al., JBC 2004

CCR5

- CCR5 is an inflammatory chemokine receptor expressed on
  - monocytes/macrophages
  - dendritic cells
  - T cells
    - memory $CD4^+$ and CD8 cells $^+$
    - $CD8^+$ CTL
- CCR5 has 3 ligands: MIP-1α (CCL3), MIP-1β (CCL4), and RANTES (CCL5)
- CCR5 is expressed on infiltrating cells during graft rejection, autoimmune disease, and response to infection
- CCR5 may play a <u>regulatory role</u> in monocyte and lymphocyte function
  - CCR5 down-regulates T cell-dependent immune responses as exhibited by enhanced DTH responses

Chemokines/Chemokine receptors affect T cell differentiation

- CCL3 (MIP1α) acting through CCR5 can polarize T_H1 responses
  - upregulates IL-12 and IFN-γ expression

  Karpus et al., *Journal of Immunology* 158:4129 (1997).

- CCR5 activation after Toxo infection induces IL-12 expression
  - induced by soluble Toxo antigen

  Aliberti et al., *Nature Immunology* 1:83 (2000).

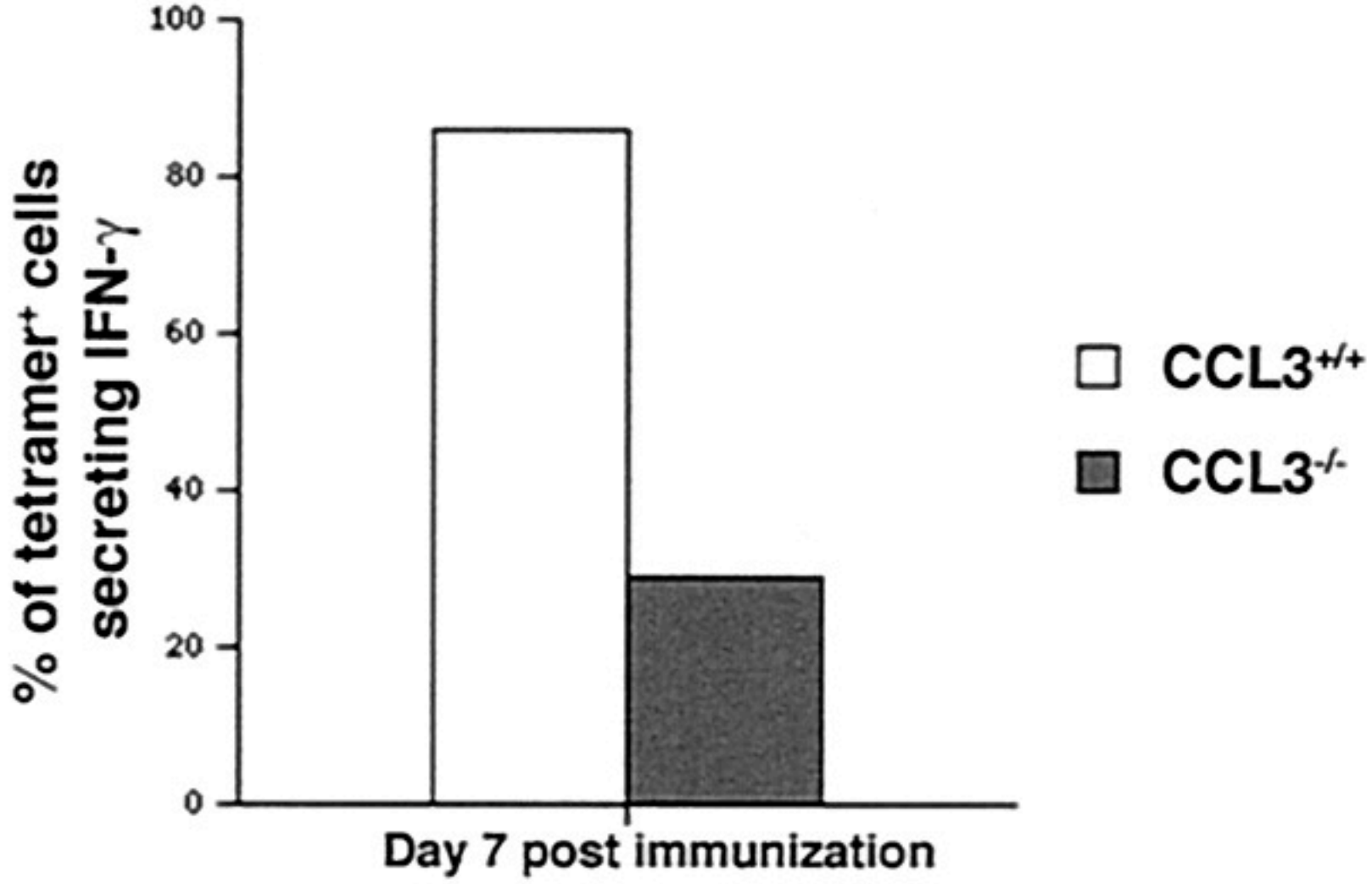
- CCL2 (MCP-1) acting through CCR2 can polarize T_H2 responses
  - suppresses IL-12 and upregulates IL-4 expression

  Gu et al., *Nature* 404:407 (2000).

- CCL19 (ELC) acting through CCR7 can augment IL-10 expression
  - dampers T_H1 responses

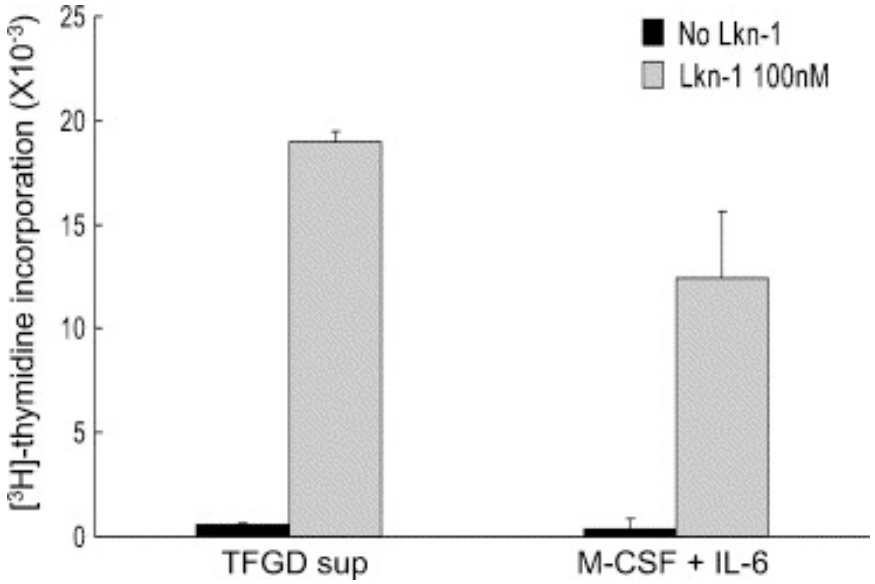
  Byrnes et al., *Journal of Immunology* 163:4715 (1999).

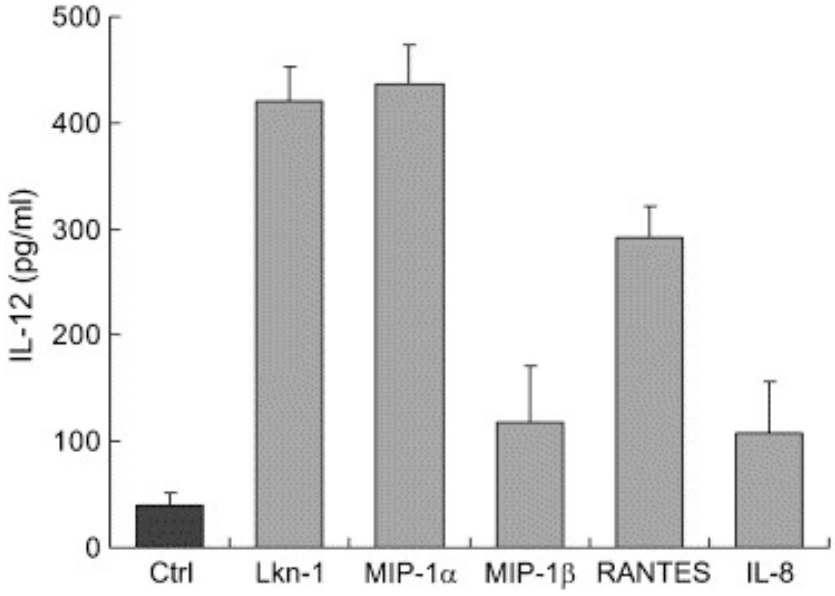
CCL3 significantly enhances the differentiation of primed T cells during MHV infection



Trifilio and Lane, *Journal of Virology*, 2003, 77: 4004-4014

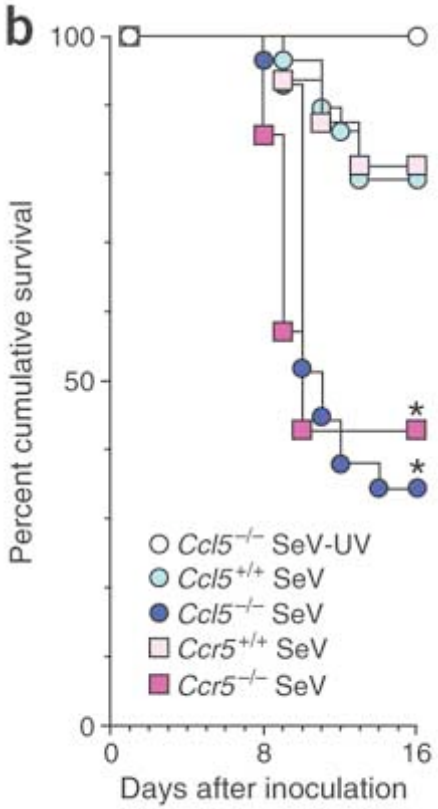
CCL15, CCL3, and CCL5 induce macrophage maturation

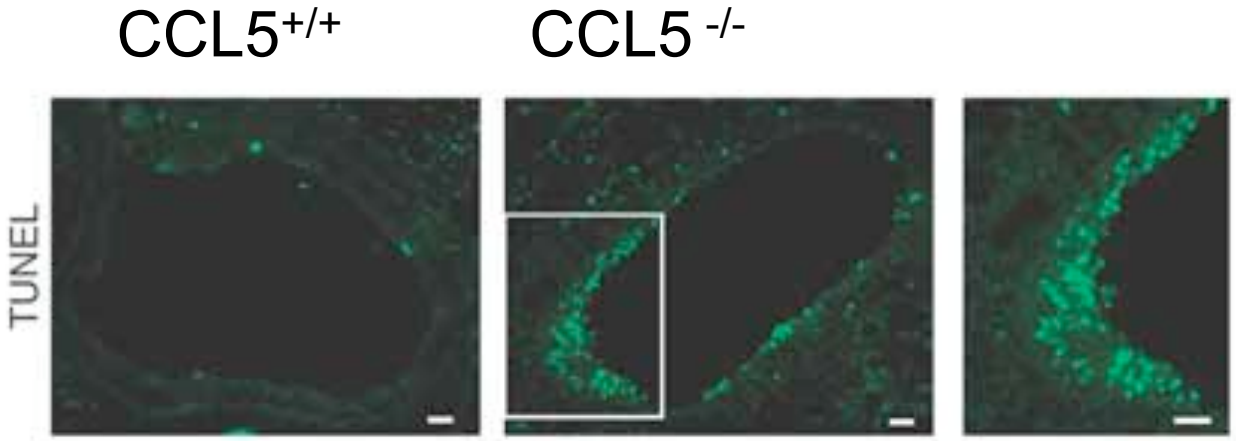




Lee et al., *Cellular Immunology* 234:1 (2005).

CCL5 (RANTES) is required to prevent macrophage apoptosis during parainfluenza infections





Tyner et al., *Nature Medicine* **11,** 1180 - 1187 (2005)

CXCL12 can induce pro- or anti-apoptotic signals

- If induction of p38 MAPK predominates, cells undergo apoptosis

- If induction of AKT predominates, cells are protected from cell death

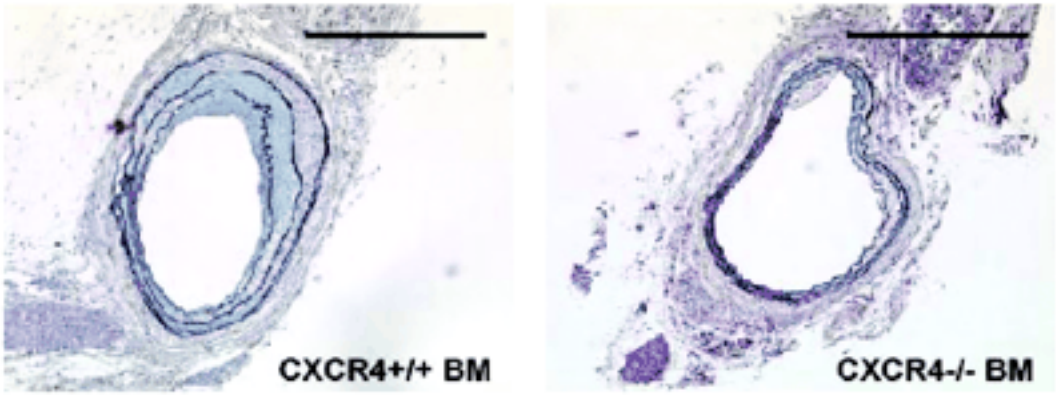
- Vlakakis et al., JI 169:5546 (2002)

CXCL12 is important in development and injury repair

- CXCR4 is required for normal myelopoeisis
- CXCR4 and SDF-1 are required for neuron migration and cerebellar development
- SDF-1/CXCR4 deficiency results in VSD

  - Ma and Springer, *PNAS* 95:9448.

CXCR4 is required in neo-intima formation in mouse carotids following induced injury



- Zernecke et al., *Circulation Research.* 2005;96:784.

Conclusions

- chemokines and chemokine receptors regulate more than leukocyte trafficking
- some of the effects of chemokine/chemokine receptor deficiency are related to their effects on cellular activation, differentiation and/or apoptosis

- the effects of chemokine receptor inhibition in an adult may be different than the effect of genetic deficiency of chemokines/chemokine receptors
- the effects of CCR5 deficiency may be different in immune competent and immune deficient people

Potential toxicities

- susceptibility to infection
  - crypto, toxo
  - Influenza
  - TB
  - HCV
- susceptibility to inflammatory diseases
  - cardiovascular disease
  - Alzheimer's disease
  - inflammatory bowel disease
  - allograft rejection
- susceptibility to autoimmune diseases
- bleeding? wound repair?