Migration of Tumor-Specific T Cells

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Migration of Tumor-Specific T Cells

• non-random
• determined by characteristics of T cells and the specific microenvironment
• tumor cells exploit similar mechanisms as leukocytes
Migration of leukocytes

Multi-step process of adhesion:
- Selectins: Tethering of T cells on the endothelium
- Chemokine receptors: activation of integrins
- Integrins: firm adhesion.

Lymph node homing
- L-Selectin
- CCR7 activated by CCL19/21
- LFA-1
Chemokines and Chemokine receptors

- >50 chemokines identified (small cytokine-like proteins)
- appr. 20 chemokine-receptors identified
Chemokines and Chemokine receptors

Homeostatic chemokines/ - receptors
• mucosa: TECK - CCR9

Inflammatory chemokines/ - receptors
• Mig - CXCR3
Chemokine receptor expression during T cell differentiation

- **Naive**: CCR7+, CCR5-
- **Central Memory**: CCR7+, CCR5-
- **Effector Memory**: CCR7-, CCR5+
  - **Effector**: CCR7-, CCR5+

- **Type 1**: CXCR3+
  - **Central Memory**: CCR7+, CCR5-
  - **Effector**: CCR7-, CCR5+

- **Type 2**: CCR3+
  - **Naive**: CCR7+,
  - **Effector**: CCR7-, CCR5+
Distribution of vaccine-induced T cells depends on T cell differentiation

Peripheral blood

Bone marrow

Tyrosinase-specific CD8+ IFNγ+ T cells

Tyrosinase-specific CD8+ IFNγ+ T cells

Tn      Tcm    Tem    Teff

Tn      Tcm    Tem    Teff

CCR7+    CCR7-   CCR7+    CCR7-
Accumulation of T cells in tissues

- Migration (entry)
- Increased proliferation/ reduced apoptosis
- Reduced exit
Targets of T cells in immunotherapy

Therapeutic vaccination/adoptive transfer:
• ability to migrate into the tumor

Adjuvant vaccination:
• ability to migrate into many compartments
Methodological approach to assess migration of T cells

- Migratory phenotype
  Chemokine receptor/Adhesion antigen expression

- Migratory potential
  Chemokine receptor function

- Migration/Accumulation in vivo
  Detection of specific T cells in tumor and specific compartments
Analysis of migratory potential of T cells

Indirect
- CCR expression and function
  - Ca-flux
  - Receptor downregulation
  - Actin Polymerization

Direct
- Transwell migration assay
Chemokine receptors of importance for T cell migration in immunotherapy

<table>
<thead>
<tr>
<th>Chemokine</th>
<th>Ligand</th>
<th>Expression</th>
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</thead>
<tbody>
<tr>
<td>CXCR4</td>
<td>SDF-1</td>
<td>multiple</td>
</tr>
<tr>
<td>CCR4</td>
<td>TARC</td>
<td>skin</td>
</tr>
<tr>
<td>CCR7</td>
<td>SLC, ELC</td>
<td>lymph node</td>
</tr>
<tr>
<td>CXCR3</td>
<td>MIG, IP10</td>
<td>inflammation/tumor</td>
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</table>
Expression of chemokine receptors on specific T cells:
Tyrosinase-reactive T cells are CXCR4+
(ligand SDF-1: bone marrow, ln, liver, lung)

However, CCRs are often not functional (Rabin et al., JI, 1999)
Functional analysis of CXCR4 expression on CD3+ CD8+ tyrosinase reactive T cells by Ca-flux

CXCR4 expressed on tyrosinase-specific T cells is functional in response to the specific ligand SDF-1

+Tyr peptide

CD8

IFN γ

+Ionomycin

Fluo -3

Time

+SDF-1

+Ionomycin
Migration of tyrosinase-specific vaccine-induced T cells into the bone marrow
Migration of T cells in immunotherapy

Breakout session topics

To discuss:
• current knowledge
• methodological approach and
• modulation by adjuvants/vaccination route
of migration/migratory potential of tumor-specific T cells in immunotherapy.
Migration of Tumor-Specific T Cells - SBT 3.11.04

Participants

- Sam Hwang, NCI
- Stefan Martin, Univ. of Freiburg
- David Mullins, Univ. of Virginia
- John Bender, Favrille
- William Carson, Univ. of Ohio
- Alan Epstein, Univ. of South. Calif.
- Heidi Hoerig, Columbia Univ.
- Julian Kim, Cleveland
- Gregory Plautz, Cleveland
- Christian Poehlein, Earle A. Chiles Research Institute
- Per Thor Straten, Danish Cancer Center
- Natalie Dubois-Stringfellow, XOMA
Migration of leukocytes and tumor cells