CD8 alpha/alpha+ Melan-A/MART-1 specific T-cells in patients with melanoma

Julia Karbach
Elke Jager
Medizinische Klinik II, Hematology / Oncology
Ludwig Institute
Frankfurt, Germany

Chiara Castelli
Instituto Tumori Milano, Milano, Italy

Markus Juelch
Thymed, Mainz, Germany

Isabelle Magalhaes
Nalini Kumar Vudattu
Kirsten Freitag
Markus Maeurer

Department of Medical Microbiology, Mainz, Germany

Zhu Zhu
Abhay Kumar
Kristine Kuus-Reichel

Beckman Coulter, San Diego, CA
Hallmarks of an effective immune response

- **Immediate immunity:**
  activation of specific CD8\(^+\) effector cells

- **Establishment of long-term memory:**
  differentiation into CD8\(^+\) memory cells

→ Clinical outcome, vaccine
Antigen-induced CD8⁺ T cell maturation

- CCR7⁺ CD45RA⁺: precursor
- CCR7⁺ CD45RA⁻: central memory
- CCR7⁻ CD45RA⁻: effector memory
- CCR7⁻ CD45RA⁺: terminally differentiated

Peripheral circulation:
- Density
- Differentiation
- Memory

CD8A TCR CD8B

Extrathymic? ? murine model?
The CD8 coreceptor modulates the avidity

Proof of principle:
Insect cells

% tetramer − staining cells
HLA-A2/ELAGIGILTV
Paradigm: patient with melanoma vaccinated with Melan/MART-1 peptide
CD8AA/CD8A CD8B expression is stable over time
Different maturation in CD8+ T cell subsets

1995 prior to vaccination
T-cell maturation/homing markers in CD8+ T-cells subsets
Differential enrichment of Melan-A/MART-1 in CD8AA / CD8AB + T-cells

1995 prior to vaccination
Melan-A/MART-1 specific T-cells reside in the CD45RA+ CCR7- population.
Differential dynamics of Tet+ T-cells associated with CD8

CD8AA

CD8A CD8B-low

CD8A CD8B-high

<table>
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<th>Year</th>
<th>CD45RA+CCR7+</th>
<th>CD45RA-CCR7-</th>
<th>CD45RA+CCR7-</th>
<th>CD45RA-CCR7+</th>
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Legend:
- CD45RA+CCR7+
- CD45RA-CCR7-
- CD45RA+CCR7-
- CD45RA-CCR7+
T-cells with different avidity reside in individual CD8 T-cells subsets

Avidity maturation of Antigen-specific T-cells over time in CD8+ T-cell subsets?
CD8AA tetramer + T-cells are present in patients with melanoma

Presence of Tet+ T-cells
- CD8AA: ++
- CD8A CD8B-low: +++
- CD8A CD8B-high: +

Maturation
Terminally differentiated

'Avidity'
- CD8AA: ++
- CD8A CD8B-low: +
- CD8A CD8B-high: +

Clinical Relevance
Better understanding of CD8+ T-cell biology, immune monitoring in vaccine trials or development
Hypothesis

TCR+ CD8AA T-cells represent a unique pool of memory T-cells enriched for high avidity T-cells
Different cells express CD8AA

CD8AA cells:
- T-cells αβ TCR+, T-cells γδ TCR+, NK cells, NKT-cells, dendritic cells
CD8AA cells show reduced CD107a expression.