Long-term persistence of T cell memory in Italian vaccinees

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What is immunological memory?

Memory is a modification of the frequency and the properties of antigen-specific lymphocytes that persists after antigen is eliminated.

Memory has two properties carried out by different cells:

- Immediate protection
  - Plasma cells and antibodies
  - Effector memory and Terminally differentiated T

- Secondary responses
  - Memory B cells
  - Central memory T

1. How are memory cells generated?
2. How are they maintained for our lifetime?
Lymphoid Tissue

- Central
  - Bone marrow
  - Thymus
- Secondary
  - Spleen
  - Lymph nodes
  - GALT (gut associated lymphatic tissue)
    - Tonsils
    - Peyer’s patches
    - Appendix
LYMPHOCYTES: MEMORY/NAIVE

B LYMPHOCYTES:  Naive: IgM and IgD  
Memory IgG

T LYMPHOCYTES:  Naive: CD45RA/CD62L-  
Memory: CD45RO
Different patterns of co-expression of CCR7 and the isoforms of CD45 allow the differentiation of different subsets of memory and naive cells.
TWO SUBSETS OF MEMORY T LYMPHOCYTES WITH DISTINCT HOMING POTENTIAL AND EFFECTOR FUNCTIONS.


CD4+ and CD8+ T cells.

CCR7+ CD45RA+ T naive

CCR7+ CD45RA- T<sub>CM</sub> central memory

CCR7- CD45RA- T<sub>EM</sub> effector memory

CCR7- CD45RA+ T<sub>TD</sub> terminally differentiated
Naive T
CD45RA+ CCR7+

Primary

APC

Ag

Effector Memory T
CD45RA- CCR7-

High antigen load

Central Memory T
CD45RA- CCR7+

Low antigen load

Secondary

Terminally-differentiated Effectors (TD)
CD45RA+ CCR7-

Effector Memory T
CD45RA- CCR7-
Homeostasis of memory T cells

secondary lymphoid organs

Naïve T

Central memory T

Antigen+ cytokines

peripheral tissues

Effector memory T and Terminally differentiated

persisting antigen
The localization of CCR7+ and CCR7- cells is different

• CCR7+ cells (Naive and CM) are prevalent in lymph nodes
• CCR7- cells (EM and TD) are dominant in tissues and peripheral blood.
Division of labour among memory T cells

**secondary lymphoid organs**

- **Naive T**
  - Home to lymph nodes
  - DC and B cell help
  - Precursors of effectors

- **Ag-cyto**

- **Central memory T**
  - Secondary responses
  - “Protective memory”

- **Effector memory T** and Terminally differentiated
  - Home to non-lymphoid tissues
  - Immediate effector function (cytokines, cytotoxicity)

**peripheral tissues**

- **Ag-cyto**

- **Effector memory T**
  - Immediate protection
  - “Reactive memory”
Human CD8 T cell subsets

**Naive**
- CD45RA⁺ CD27⁺
- CCR7⁺ CD62L⁺

**Central memory**
- CD45RA⁻ CD27⁺
- CCR7⁺ CD62L⁺

**Effector memory**
- CD45RA⁻ CD27⁻
- CCR7⁻ CD62L⁻

**Effector memory RA⁺**
and **Terminally differentiated**
- CD45RA⁺ CD27⁻
- CCR7⁻ CD62L⁻

- **Proliferation**
- **IL-2 production**
- **Cytokine (IFN-γ) production and cytotoxicity**
- **Cytoxicity**
- **Death ?**
Persistence of Anti-HBs Antibody and Immunologic Memory for Hepatitis B Surface Antigen in Two Cohorts of Children Immunised with Hexavalent Vaccines: Implication for Policy and Booster Vaccination – Immunologic study

D. Trabattoni, L. Romanò, M. Pacei, A. Zanetti, M. Clerici
In Europe two vaccines, Hexavac® (Sanofi Pasteur, MSD) and Infanrix®-hexa (GlaxoSmithKline) were licenced for use in October 2000.

Both vaccines protect against diphtheria, tetanus, pertussis, poliomyelitis, Haemophilus influenzae type b and hepatitis B.

In Sept 2005, following the observation of a reduced immunogenicity of the hepatitis B component in the Hexavac® EMA recommended the withdrawal of Hexavac® from the market.
A multicenter study was carried out to investigate whether vaccinated children could respond to a booster dose of hepatitis B vaccine 5 years after primary immunization.

- To evaluate if the decline in antibody titers under protective threshold (10 mIU/ml), observed in children receiving Hexavac®, reflects a loss of immune memory.

- To demonstrate whether T cell memory persist even when serum antibodies decline.
Materials and Methods

- 105 subjects, 65 Hexavac® and 40 Infanrix® were enrolled.

- Antigen specific T cell responses and T memory subsets were evaluated 5 years after HBV vaccination.

Data were analysed comparing:
- Infanrix- vs Hexavac-vaccinated subjects and
- Subdividing children on the base of humoral responses to the vaccines: Responder (anti-HBV Ab titles >10mIU/ml); Non Responder (anti-HBV Ab titles <10mIU/ml).
Results: Naive, Central Memory, Effector Memory and Terminally Differentiated CD4+ T cells

Naive, CM, EM and TD CD4+ T cells were similar in Hexavac- and Infanrix-vaccinated children
Results: Naive, Central Memory, Effector Memory and Terminally Differentiated CD8+ T cells

Naive CD8+ T cells were higher, CM, EM and TD cells were lower in Hexavac- compared to Infanrix-vaccinated children
Results: HBV-specific Naive, Central Memory, Effector Memory and Terminally Differentiated CD8+ T cells

HBV-specific Naive and CM CD8+ T cells were higher, EM and TD were lower in Hexavax- compared to Infanrix-vaccinated children
Results: HBV-specific IFN$\gamma$-secreting CD8+ T cells

HBV-specific IFN$\gamma$-secreting CD8+ T cells were lower in Hexavac-compared to Infanrix-vaccinated children.
Results: Naive, Central Memory, Effector Memory and Terminally Differentiated CD4+ T cells

Naive, CM, EM and TD CD4+ T cells were similar in Responders and Non Responders
Results: Naive, Central Memory, Effector Memory and Terminally Differentiated CD8+ T cells

Naive CD8+ T cells were lower, EM and TD were higher in Responders
Results: HBV-specific Naive, Central Memory, Effector Memory and Terminally Differentiated CD4+ T cells

Naive, CM, EM and TD CD4+ T cells were similar in Responders and Non Responders.
Results: HBV-specific Naive, Central Memory, Effector Memory and Terminally Differentiated CD8+ T cells

Naive cells were lower, CM and EM were higher in Responders
Results: HBV-specific IFNγ-secreting CD8+ T cells

HBV-specific IFNγ-secreting CD8+ T cells were augmented in Responders
Conclusions

• T cell memory is extremely complex and still very unclear.
• HBV specific memory T cells are detected in peripheral blood >5 years after vaccination.
• The reduced efficacy, as well as the lack of Ab-measured immunogenicity of a vaccine are reflected in alterations of the different circulating subsets of memory T cells.