

Healthy aging and Immunology: A Quantitative Model-Based Meta-Analysis (MBMA) of Age-Dependent Human T-Lymphocyte Homeostasis

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Objective

This study aims to quantify age-related changes in the homeostasis of T-lymphocytes in healthy individuals by integrating the available quantitative data covering a wide range of T-cell subpopulations, subject ages and organs.

Introduction

- T-lymphocytes development throughout human life is characterized by a coordinated staging of maturation processes and age-related changes in cell counts and functionality. After egress from the thymus, T-lymphocytes experience sequential differentiation from recent thymic emigrants (RTE) and naïve cells into different types of effector- and memory cells (**Figure 1**).
- Aging processes, which comprise several mechanisms such as thymic involution and memory cells accumulation, lead to a decrease in the body's ability to resist infections and tumors [1].
- Relationships between various phenotypically distinct T-lymphocyte subpopulations, as well as their age-dependent homeostasis, warrant a comprehensive quantitative evaluation for developing new anti-infectious and T-cell based treatments.

Methods

- Data processing, visualization and meta-analyses were performed using the R Statistics (version 4.2.3).
- A schematic representation of the analysis workflow, the methods used, and the results obtained is shown in **Figure 2**.

Results

- The proposed quantitative analysis resulted in obtaining reference values (in absolute terms and percentages) of various T-lymphocyte subpopulations in blood and other organs (**Figure 2.1**) within narrow age intervals.
- No differences in age-dependent homeostasis were found among relative values of lymphocytes in blood vs. lymphoid organs (**Figure 2.2**).
- A substantial decrease in T-lymphocyte counts was observed in the first 10 years of life for total lymphocyte populations as well as RTE, naïve and effector CD4+ and CD8+ T-lymphocytes (**Figure 2.3. A,B**).
- Conversely, blood concentration of memory T-lymphocytes (central-memory and effector-memory cells) tended to increase in older age groups, particularly after ~50 years of age (**Figure 2.3. C,D**).
- Notably, the extensive dataset compiled enabled to explore the differences in times-to-maximal cell counts among cell subpopulations. The more differentiated T-lymphocytes reached their maximal cell number later (1–5 years of age) (**Figure 2.3. A,B**) than their less differentiated counterparts (0–1 year of age) (**Figure 2.3. C,D**).

FIGURE 2. Schematic representation of analysis workflow, utilized methods and main results

Workflow

Systematic review

- Databases: PubMed, Google Scholar
- Keywords: “CD4”, “CD62L”, “CD45RO”, “CD45RA”, “naïve”, “central-memory”, “effector-memory”, “effector”, “human”, “healthy”, “flow cytometry”
- Inclusion criteria: clinical data on T-lymphocyte numbers from control (healthy) groups

Data standardization

Data was standardized by:

- Cell phenotype
- Organ

Individual-level data handling

Modified 2-stage approach was used to handle individual-level patient data (IPD) [3]

Stage 1. Mean and SD values (•) were computed for individual subject observations (•) in the pre-specified age intervals.

Stage 2. Computed estimates based on such individual subject-level data were then treated as aggregated (•) for further analysis

Piece-wise meta-analysis

Piece-wise equal-effect meta-analysis methodology was used to evaluate the age-dependent homeostasis of each T-lymphocyte subpopulation with weighted average calculation within each pre-specified age interval.

$\hat{\theta}$ is the weighted average of the true outcomes in the k studies

n is the number of subjects in the i^{th} study

Weighting by subject numbers rather than via the conventional inverse variance weighing method was implemented due to the observed nonproportional decrease in variance with an increase in subject numbers.

$\hat{\theta} = \frac{\sum_{i=1}^k \omega_i y_i}{\sum_{i=1}^k \omega_i}$

$\omega_i = \frac{n_i}{\sum_{i=1}^k n_i}$

Methods

Figure 2.1: Percentage distributions of unique observations of lymphocytes by organ in the database

Figure 2.2: Age-dependent homeostasis of naïve CD4+ T-lymphocyte subpopulation in blood and lymphoid organs (% from total CD4+ T-cells)

Figure 2.3: Meta-analysis of age-dependent homeostasis of T-lymphocyte subpopulations in blood (A – total CD4+; B – CD4+ naïve; C – CD4+ central memory; D – CD4+ effector-memory)

Results

The final database includes:

- 124 unique studies with 11722 observations
- 21 T-lymphocyte subpopulations
- Age range: 0 – 111 years of age
- Organs: Blood, Lymphoid organs, GI tract, Lungs, and others

Total subpopulations:

- Lymphocytes (CD45+)
- T-lymphocytes (CD3+)
- CD4+ T-lymphocytes
- CD8+ T-lymphocytes
- CD4+ memory T-lymphocytes (CD45RA+)
- CD8+ memory T-lymphocytes (CD45RA+)

Specific subpopulations (CD4+ and CD8+):

- Recent-thymic emigrants (CD31+; CD45RA+)
- Naïve (CD45RA+; CD45RO-; CD62L-; CCR7+)
- Activated (CD38+; HLADR+)
- Central-memory (CD45RA-; CD45RO+; CD62L+; CCR7+)
- Effector-memory (CD45RA-; CD45RO+; CD62L-; CCR7-)
- Effector (CD45RA+; CD45RO-; CD62L-; CCR7-)
- Resident-memory (CD45RO+; CD69+; CD103+)

Immunological markers

- CD4/CD8 ratio

References

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[3] Burke DL, et al. Stat Med. 2017;36(5):855-875.
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