An integrative physiologically-based model of T lymphocyte homeostasis and exogenously administered T cell kinetics

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MODELING & SIMULATION DECISIONS

Abstract

In this work, we developed a physiologically-based pharmacokinetic (PBPK) model that describes endogenous T cell homeostasis and the kinetics of exogenously administered T cells in mouse. The model adequately described experimental data on both types of T cells and could be applied to numerical simulations of T cell therapies and features of T cell homeostasis.

Introduction

- Processes related to the migration and circulation of lymphocytes are critical for the functioning of the immune system and have been extensively studied over the past 60 years. Nonclinical studies have been mostly conducted in experimental murine models, starting from the administration of lymphocytes to the thoracic duct, to studies of CAR-T and other T cell products engineered ex vivo.
- A detailed quantitative understanding of T cell trafficking processes and resultant tissue distributions is therefore essential, from both a fundamental immunological perspective and a practical standpoint, specifically to support strategies and decision-making in the development of novel engineered T cell therapies.

Methods

- Modeling was performed in Monolix 2020 software (Monolix documentation - LIXOFT, www.monolix.lixoft.com) and R Statistics software, version 4.0.2.
- Experimental data relevant for model development and validation were digitized and curated.
- Parameter calibration was performed using a nonlinear fixed-effects modeling approach based on published data on T cell kinetics and steady-state levels in different tissues of mice.
- A Partial Rank Correlation Coefficient (PRCC) method was used to perform a global sensitivity analysis of the model.
- To estimate the impact of kinetic parameters on exogenously administered T cell dynamics, a local sensitivity analysis was conducted.

Results

Model structure

The model was formulated as a system of ordinary differential equations describing multi-compartmental processes of T cell trafficking in the organism; exclusive trafficking of CCR7+ T cells to lymph nodes (LNs) was explicitly included.

The model included 6 compartments: blood, lung, spleen, liver, ‘regional LNs’ and ‘generalized LNs’ (the latter representing secondary lymphoid structures).

For modeling purposes, endogenous T cells were produced in the thymus and migrated to blood (parameter *Vinf_thymus*) and various organs. The rate of homeostatic T cell proliferation in the spleen was described using a Michaelis-Menten like equation.

For the lung and liver compartments, the model considered T cell trafficking to lymph nodes through afferent lymphatic vessels.

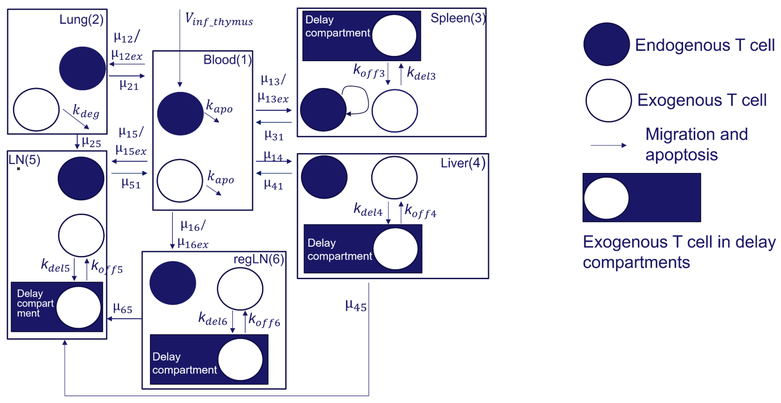

FIGURE 1. Scheme of mathematical model: T cell migration and homeostasis.

Parameter estimation procedures

The model consistently described the experimental data [1-3], including the accumulation of endogenous T cells in lymphoid organs, at concentrations of ~1.57*10^8 cells/ml in the spleen and ~3.36*10^8 cells/ml in LNs, and steady-state levels of T cells in blood, lungs and liver (respectively, ~1.70*10^6 cells/ml, ~4.22*10^6 cells/ml, and ~4.20*10^5 cells/ml) (Figure 2).

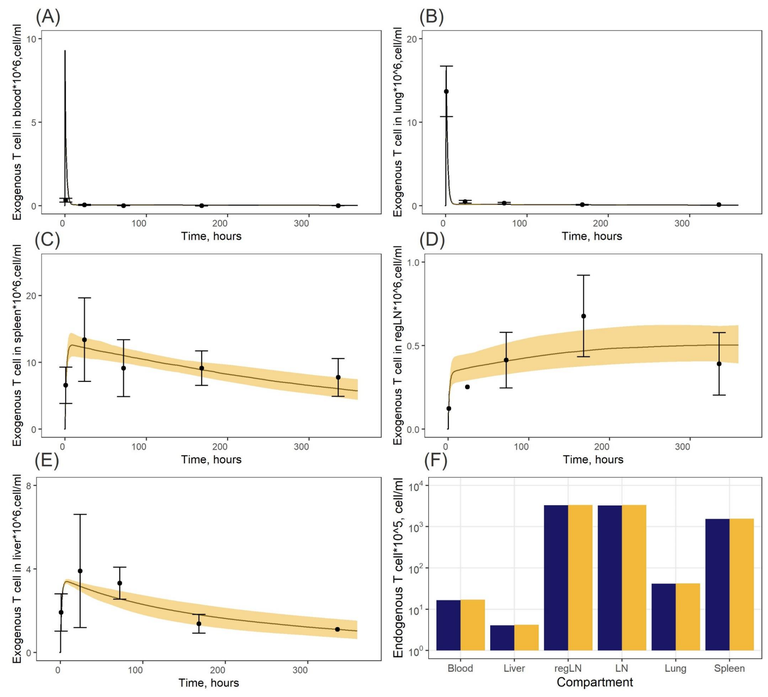

FIGURE 2. (A–E) Model calibration against data on exogenously administered T cells in: (A) blood, (B) lungs, (C) spleen, (D) regional LN compartment, and (E) liver. Points: Experimental data (mean ± error), calculated from [4]. Curves: Model predictions; yellow uncertainty prediction bands: 95% confidence intervals (CI). (F) Model calibration against data on endogenous T cells. Dark blue columns: Model predictions; yellow columns: Experimental data, calculated from [1-3].

The model adequately reproduced data on exogenously administered T cell kinetics [3], including the rapid T cell elimination process from blood and infiltration into the lungs, as well as the slower cell kinetics in the spleen (Cmax of ~12.6*10^6 cells/ml at 9 hrs) and the liver (Cmax of ~3.4*10^6 cells/ml at 8.0 hrs) (Cmax: maximal T cell count per ml). It also satisfactorily described the cellular kinetics in the regional LN compartment, with a Cmax of ~0.5*10^6 cells/ml at 45.5 hrs post IV administration.

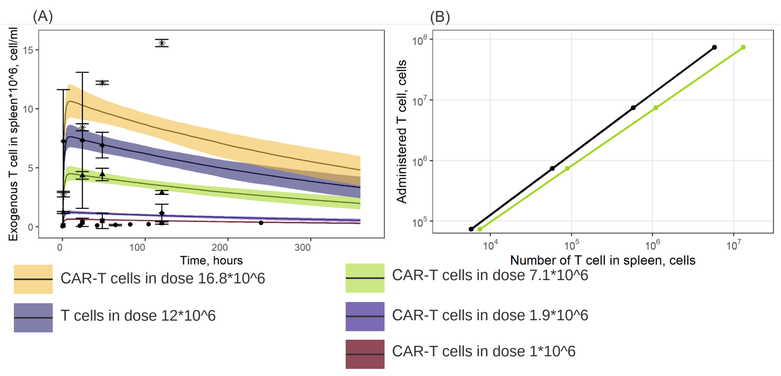

FIGURE 3. Model validation results. Exogenous T-cell kinetics after intravenous administration. Curves represent model simulations, yellow areas represent 95% confidence intervals, points represent experimental data with confidence intervals. Numerical experiments were also conducted to describe the kinetics of T-cells during the infusion of various doses of exogenous cells.

As shown in Figure 3, the model adequately described experimental data for doses of 1.9*10^6 and 7.1*10^6 CAR-T cells. The model slightly over-predicted peak levels following doses of 1.0*10^6 and 1.9*10^6 . At the same time, T cell levels at later timepoints, following a dose of 16.8*10^6 cells were under-estimated, with a predicted value Cmax of 1.02*10^7 cells/ml vs. a higher Cmax of 1.50*10^7 cells/ml observed in the experimental data.

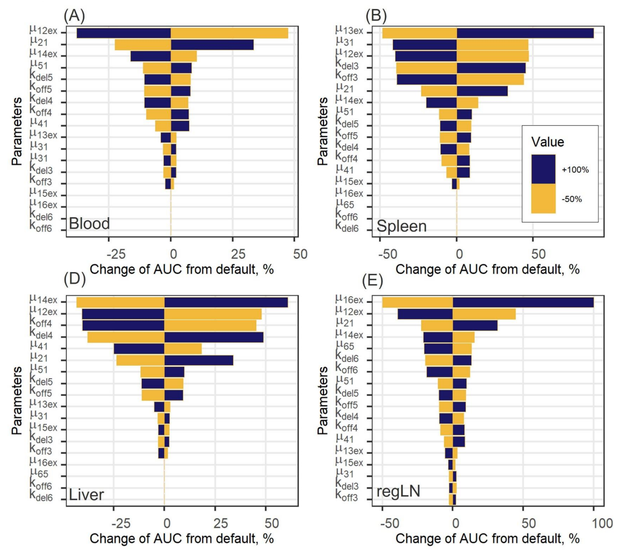

FIGURE 4. Local sensitivity analysis for exogenous T cell steady-state concentrations in: (A) blood; (B) spleen; (C) liver; and (D) regional LN compartment.

For all compartments excluding blood, the most important parameters were the rate constants of T cell inflow from blood to organ.

Modeling simulations

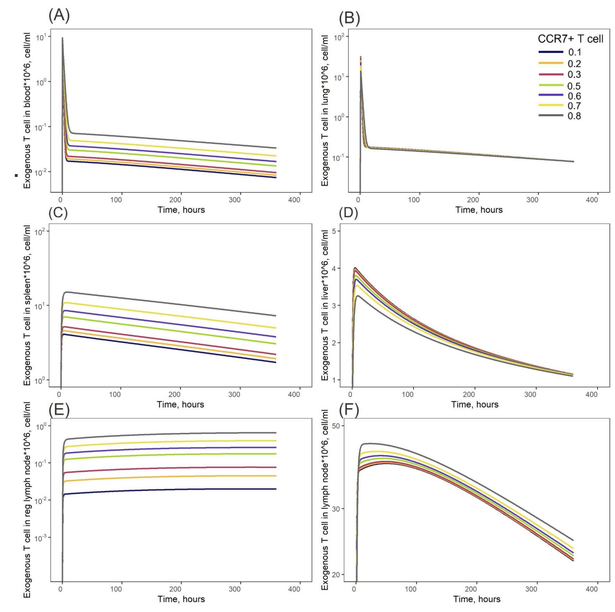

FIGURE 5. Model simulations of exogenous T cell recirculation kinetics following an administration of T cells in doses of 20 million cells with different CCR7+ T cell proportions (0.1 - 0.9), (A) blood; (B) lungs; (C) spleen; (D) liver; (E) generalized LN compartment; and regional LN compartment (F).

The model showed a linear dependence between the dose of exogenously administered T cells and the kinetics of lymphocytes in various compartments. Simulations using various CCR7+ T cell proportions in the exogenously administered product significantly impacted CCR7-expressing T cell numbers in the lymphoid organs and the spleen (Figure 5C,E).

Conclusions

- The proposed physiologically-based model adequately described the homeostatic recirculation patterns of endogenous T cells and the kinetics of exogenously administered T cells upon an IV infusion.
- The model was used to perform predictive simulations of distribution patterns of genetically-modified T lymphocyte levels in various organs, following the adoptive administration of T cells.

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