REGULATION OF TH1/TH2 CELLS IN ASTHMA DEVELOPMENT: A MATHEMATICAL MODEL

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ABSTRACT

Airway exposure levels of lipopolysaccharide (LPS) determine type I versus type II helper T cell induced experimental asthma. While high LPS levels induce Th1-dominant responses, low LPS levels derive Th2 cell induced asthma. The present paper develops a mathematical model of asthma development which focuses on the relative balance of Th1 and Th2 cell induced asthma. In the present work we represent the complex network of interactions between cells and molecules by a mathematical model. The model describes the behaviors of cells (Th0, Th1, Th2 and macrophages) and regulatory molecules (IFN-?, IL-4, IL-12, TNF-?) in response to high, intermediate, and low levels of LPS. The simulations show how variations in the levels of injected LPS affect the development of Th1 or Th2 cell responses through differential cytokine induction. The model also predicts the coexistence of these two types of response under certain biochemical and biomechanical conditions in the microenvironment.

INTRODUCTION

Asthma is a common chronic inflammatory disorder of the airways associated with reversible airway obstruction and airway hyperresponsiveness (AHR) [1]. There are approximately 300 million asthmatics worldwide [3]. The symptoms of asthma include wheezing, coughing, chest tightness and shortness of breath. The development of memory T cells to inhaled allergens is a critical event in initiation and orchestration of the inflammatory response in asthmatic airways [4]. Lipopolysaccharide (LPS) that is a cell wall component of gram-negative bacteria, present in the air including dust particles [5]. This LPS is known to control the differentiation of T cells into either Th1 or Th2 depending on its injection amount.

In this model, we propose a mathematical model that can explain the experimental results obtained by Kim et al [2].

GOVERNING EQUATION

The main variables are:

$$H_1(x,t) = \text{Th1 cell density}$$
$$H_2(x,t) = \text{Th2 cell density}$$
$$H_0(x,t) = \text{Th0 cell density}$$
$$M(x,t) = \text{Macrophage density}$$
$$F(x,t) = \text{IFN-}\gamma \text{ concentration}$$
$$I_1(x,t) = \text{IL-4 concentration}$$
$$I_2(x,t) = \text{IL-12 concentration}$$
$$T(x,t) = \text{TNF}\alpha \text{ concentration}$$

A system of governing equations of all variables ($H_1(x,t)$, $H_2(x,t)$, $H_0(x,t)$, $M(x,t)$, $F(x,t)$, $I_1(x,t)$, $I_2(x,t)$, $T(x,t)$) in the domain Ω is described by

$$\frac{\partial H_1}{\partial t} = D_{H_1}\Delta H_1 + \frac{\lambda_5 I_2}{\lambda_6^m + I_1^m} H_0 H_1 \left(1 - \frac{H_1}{K_1}\right) - \mu_{H_1} H_1,$$

$$\frac{\partial H_2}{\partial t} = D_{H_2}\Delta H_2 + \frac{\lambda_2 T I_1}{\lambda_7^k + F^k} H_0 H_2 \left(1 - \frac{H_2}{K_2}\right) - \mu_{H_2} H_2,$$

$$\frac{\partial H_0}{\partial t} = D_{H_0}\Delta H_0 + \beta - \left(\frac{\lambda_5 I_2}{\lambda_6^m + I_1^m} H_0 H_1 + \frac{\lambda_2 T I_1}{\lambda_7^k + F^k} H_0 H_2\right) - \mu_{H_0} H_0,$$

$$\frac{\partial M}{\partial t} = D_M \Delta M - \nabla \cdot \left(\chi \frac{M \nabla F}{\sqrt{1 + \lambda_F |\nabla F|^2}}\right) + \frac{\lambda_{13} F H_1}{\lambda_{14}^l + I_1^l} M \left(1 - \frac{M}{K_3}\right) - \mu_M M,$$

$$\frac{\partial F}{\partial t} = D_F \Delta F + \lambda_1 H_1 - \mu_F F,$$

$$\frac{\partial I_1}{\partial t} = D_{I_1}\Delta I_1 + \lambda_3 H_2 - \mu_{I_1} I_1,$$

$$\frac{\partial I_2}{\partial t} = D_{I_2}\Delta I_1 + \frac{\lambda_8 \alpha^n}{\lambda_9^n + \alpha^n} H_1 + \lambda_{10} M - \mu_{I_2} I_2,$$

$$\frac{\partial T}{\partial t} = D_T \Delta T + \lambda_4 H_1 + \lambda_{11} H_2 + \lambda_{12} M - \mu_T T.$$

Boundary conditions:

The boundary ($\partial\Omega$) of the computational domain (Ω) consists of two disjointed subsets, Γ_1, Γ_2, *i.e.* $\partial\Omega = \Gamma_1 \cup \Gamma_2, \Gamma_1 \cap \Gamma_2 = \emptyset$. Macrophages are provided from blood vessels and we prescribe the *Dirichlet* (fixed) boundary condition on a portion of boundary (Γ_1) near the blood vessel. We also assume that there is no flux on the other boundary Γ_2 (*Neumann* B.C.).

$$M = M_0, \qquad \text{on } \Gamma_1$$

$$\nu \cdot \left(D_M \nabla M - \chi \frac{M \nabla F}{\sqrt{1 + \lambda_F |\nabla F|^2}}\right) = 0, \text{ on } \Gamma_2,$$

where ν is the outer normal vector and M_0 is the fixed macrophage density on Γ_1. No flux boundary conditions (*Neumann*) were applied for all other variables on the whole boundary ($\partial\Omega = \Gamma_1 \cup \Gamma_2$):

$$\nu \cdot (D_{H_1} \nabla H_1) = 0, \;\; \nu \cdot (D_{H_2} \nabla H_2) = 0, \; \nu \cdot (D_{H_0} \nabla H_0) = 0,$$

$$\nu \cdot (D_F \nabla F) = 0, \quad \nu \cdot (D_{I_1} \nabla I_1) = 0, \;\; \nu \cdot (D_{I_2} \nabla I_2) = 0, \qquad \text{on } \partial\Omega$$

$$\nu \cdot (D_T \nabla T) = 0.$$

Initial conditions would be described for the local dynamics (ODE) and full dynamics (1D or 2D PDE) in the corresponding subsections below. In the next Section, we present the results of the model.

In this paper, we focused on identifying the basic 'flip-flop' dynamics of type I and type II asthma in response to various doses of LPS. We showed that (i) Th2 cells become dominant for low LPS levels ($\alpha \leq 1$) while Th1 cells become a major phenotype for high LPS levels ($\alpha \geq 10$). (ii) Steady states of two key phenotypes as a function of the injected LPS level (α) illustrate this switching behavior between Th1 and Th2 cells and also suggest coexistence of those two phenotypes in a narrow interval of intermediate levels of LPS ($2 < \alpha < 7$) (Figure **??**). (iii) High (low) levels of IL-12 were associated with high (low) LPS levels in both experiments and model simulations. (iv) Macraphage numbers increased according to LPS levels, which is consistent with the experimental observation. (v) The current model also predicts that the IL-4 level is significantly decreased when TNFα-deficient mice are used compared to the wild type. (vi) We also investigated the role of microenvironment in determining the dominant phenotype in asthma development. The model predicts that a perturbation of the microenvironment might lead to different types of asthma.

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