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On the dynamics of radially symmetric granulomas

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ABSTRACT

A granuloma is a collection of macrophages that contains bacteria or other foreign substances that the body's immune response is unable to eliminate. In this paper we present a simple mathematical model of radially symmetric granuloma dynamics. The model consists of a coupled system of two semi-linear parabolic equations for the macrophage density, and the bacterial density. The boundary of the granuloma is free. This simple framework makes it possible to conduct a mathematical analysis of the system dynamics. In particular, we show that the model system has a unique solution, and that, depending on the biological parameters; the bacterial load either disappears over time or persists. We use numerical methods to establish the existence of stationary solutions and examine how a stationary solution changes with the reproductive rate of the bacteria. These simulations show that the structure of the granuloma breaks down as the reproductive rate of the bacteria increases.

1. Introduction

A granuloma is a collection of macrophages that contains bacteria or other foreign substances. Granulomas occur in a wide variety of diseases including, for example, rheumatoid arthritis, schistosomiasis and Crohn's disease. A typical example is the granuloma of tuberculosis which prevents residual bacteria from re-infecting the body.

In order to create a detailed, disease-specific granuloma model, one needs to consider, in addition to macrophages and bacteria, pathogen-specific cytokines, the activation state of various immune cells, and the dynamics of both extracellular and intracellular bacteria. This was done in the case of tuberculosis by D. Gammack et al. [1] using a PDE model, by J.L. Segoria-Juarez et al. [4] using an agent-based approach, and by S. Marino et al. [3] using a hybrid multi-compartment model. In the present paper we introduce a simple model of a generic granuloma. The model explicitly describes the interactions between bacteria and macrophages. Implicit in the model is the assumption that the cytokines and T cells are present in abundance, i.e. we assume that all of the macrophages have been activated by IFN-γ secreted by the T cells. Similarly, the model does not consider intracellular bacteria, although several types of granulomas, including those of tuberculosis, are caused by intracellular pathogens. We assume that the granuloma occurs in a region $\Omega(t)$ which varies in time. Inside $\Omega(t)$ the macrophage cell density, M, and the bacteria cell density, B, satisfy a system of PDEs. We also assume that the cellular density of macrophage and bacteria is fixed, thus our model does not account for necrotic cells and debris that may be present in several types of granulomas. Under the assumption that the cellular density is fixed, the free boundary of $\Omega(t)$ moves with a velocity that is determined by the proliferation of the bacteria, the immigration of macrophages, and the death of both cell types.

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The aim of this paper is to initiate rigorous mathematical analysis of the dynamics of granulomas as free boundary problems. Accordingly, in the present paper, we consider a very simple model of a generic radially symmetric granuloma, deferring the study of more inclusive models to future work. We prove the existence and uniqueness, and exhibit steady state solutions numerically.

2. Theory

The variable x varies in a bounded domain $\Omega(t)$ in $\mathbb{R}^3$ with boundary $\Gamma(t)$. We introduce the variables $M(x,t)$ and $B(x,t)$ to represent the density of macrophages and bacteria respectively. Due to cellular proliferation and death there is a velocity field $\vec{v}(x,t)$ which is assumed to be common to both macrophages and bacteria. By conservation of mass, for $x\in\Omega(t)$ and $t>0$ we have

$$\frac{\partial M}{\partial t}-\Delta M+\nabla\cdot(M\vec{v})=-\mu_1 MB-\alpha M, \tag{1}$$

$$\frac{\partial B}{\partial t}-(1+\delta)\Delta B+\nabla\cdot(B\vec{v})=-\mu_2 MB+\lambda B, \tag{2}$$

where μ_1 is the rate at which macrophages are killed by bacteria, μ_2 is the rate at which bacteria are killed by macrophages, λ is the bacterial growth rate, and α is the rate at which macrophages undergo apoptosis. Intracellular bacteria do not disperse on their own but are dispersed through the dispersal of the cells that contain them, while extracellular bacteria, being smaller than macrophages, have a larger diffusion coefficient than macrophages. Hence, we consider the case where $\delta\geqslant 0$; our results can be extended, with minor changes, to the case where $\delta<0$. In addition, we assume that the cells are evenly distributed in $\Omega(t)$ so that, after normalization,

$$M+B=1 \quad \text{for } x\in\Omega(t),\ t>0. \tag{3}$$

Adding Eqs. (1) and (2) and using (3), we derive the following equation for $\vec{v}$:

$$\nabla\cdot\vec{v}=-\delta\Delta M+\lambda-(\lambda+\mu+\alpha)M+\mu M^2, \tag{4}$$

where $\mu=\mu_1+\mu_2$. In addition, replacing B with $1-M$ in (1) yields the following equation for M:

$$\frac{\partial M}{\partial t}-\Delta M+\nabla\cdot(M\vec{v})=-\mu_1 M(1-M)-\alpha M. \tag{5}$$

In this paper we consider only the case of radially symmetric granulomas. In this case $\vec{v}$ is determined by (4) together with $\vec{v}(0)=0$. In the non-radially symmetric case one would need to impose a constitutive condition on the tissue where the granuloma develops. Such a condition could be the porous medium assumption characterized by Darcy's Law: $\vec{v}=\nabla p$, where p is the internal pressure, and p satisfies an appropriate boundary condition on the boundary $\Gamma(t)$. This more general granuloma model could be considered in future work.

It is easily seen that if M satisfies (5) with $\vec{v}$ defined by (4), then the pair (B,M) satisfies the system (1)–(2). In the sequel we shall primarily use the version (4)–(5) of the system (1)–(3).

We impose the boundary conditions

$$\frac{\partial M}{\partial \nu}=\beta(1-M) \quad \text{on } \Gamma(t), \tag{6}$$

$$v_{\Gamma(t)}=\vec{v}\cdot\nu \quad \text{on } \Gamma(t), \tag{7}$$

where ν is the outward normal direction, $v_{\Gamma(t)}$ is the velocity of the free boundary, $\Gamma(t)$, in the direction ν, and $\beta>0$. Finally, we prescribe initial conditions:

$$\Omega(t)|_{t=0}=\Omega_0, \qquad M(x,0)=M_0, \quad 0\leqslant M_0\leqslant 1. \tag{8}$$

Note that (6) implies (by (3)) that

$$\frac{\partial B}{\partial \nu}+\beta B=0 \quad \text{on } \Gamma(t). \tag{9}$$

In addition, (8) implies that

$$0\leqslant B(x,0)\leqslant 1. \tag{10}$$

By the maximum principle for (1) and (2) we then have that

$$M(x,t)\geqslant 0 \quad \text{and} \quad B(x,t)\geqslant 0.$$

Thus by, (3), the solution of (4)–(5) satisfies

$$0\leqslant M(x,t)\leqslant 1. \tag{11}$$