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Energy cost of infection burden: An approach to understanding the dynamics of host–pathogen interactions

Alexei A. Romanyukha[a], Sergey G. Rudnev[a], Igor A. Sidorov[b,*]

[a]*Institute of Numerical Mathematics, Russian Academy of Sciences, Gubkin Str. 8, 119991 Moscow, Russian Federation*
[b]*Center for Cancer Research Nanobiology Program, CCR, NCI-Frederick, NIH, Bldg. 469/110, P.O. Box B, Frederick, MD 21702-1201, USA*

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Abstract

A mathematical model of long-term immune defense against infection was used to estimate the energy involved in the principal processes of immune resistance during periods of health and infection. From these values, an optimal level of energy was determined for immune response depending on infection burden. The present findings suggest that weak but prevalent pathogens lead to latent or chronic infection, whereas more virulent but less prevalent pathogens result in acute infection. This energy-based approach offers insight into the mechanisms of immune system adaptation leading to the development of chronic infectious diseases and immune deficiencies. Published by Elsevier Ltd.

Keywords: Infection burden; Immune defense; Energy cost; Adaptation; Trade-off

1. Introduction

Epidemiological, clinical and experimental data suggest that the immune system interacts with pathogens in the body in various but predictable ways. Non-specific arms (phagocytes, complement, interferon) and specific arms of immune defense (lymphocytes, antibodies) involve about 10^{12} cells and 10^{20} molecules in humans and cannot provide absolute protection against frequent infections caused by various microorganisms. Though the immune system adjusts its defense parameters to decrease substantially the rate and severity of infectious disease, why, nevertheless, does it maintain a level of defense which permits considerable morbidity? Usually, this question is treated as a problem of choice between defense as a resistance to infection and disease as a compromise (Gemmill and Read, 1998). It can be assumed that a strong immune response, resulting in prolonged periods of good health, and weak immune response, leading to frequent illness, are both too costly to an organism and lead to a decrease in fitness.

In this paper, energy is used as a cost measure of host–pathogen interactions. The relationship between the cost of immune resistance and disease-persistence may be considered as an example of a physiological trade-off (Stearns, 1992) and the problem of searching for immune defense strategies which are optimal for given environmental conditions can be formulated (Schmalhausen, 1949; Rashevsky, 1961).

The main processes of infectious pathology are: inflammation, immune response and damage to the target organ. Although we have a considerable understanding of inflammatory reaction, the role of inflammation in immune response is not completely understood (Fedoseev, 1998; Ley, 2000; MacDonald and Monteleone, 2005). Most mathematical models of infectious diseases describe the dynamics of specific immune responses (Marchuk, 1997; Nowak and May, 2000). Following from an analysis of mechanisms of common infections caused by opportunistic pathogens, the role of specific immune response during early stages of infection is not as crucial as immune response during final stages (Korol', 1983; Jakab, 1985; Karpov and Romanyukha, 1992). For opportunistic infections of the lungs, non-specific immune protection such as phagocytosis plays the principal role (Mayanski

*Corresponding author. Tel.: +301 846 1449; fax: +301 846 6189.
E-mail addresses: eburg@inm.ras.ru (A.A. Romanyukha), rudnev@inm.ras.ru (S.G. Rudnev), sidorovi@ncifcrf.gov (I.A. Sidorov).

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Table 1
Morphometric data characterizing size, structure and cellular composition of lungs in healthy human adults

Characteristics, dimension	Value	Reference
Total volume of lung airways (ml)	4500–5000	Weibel (1963)
Volume of lungs between the 1st and 8th airway generations (ml)	30–35	Weibel (1963)
Perimeter of trachea (mm)	50	Fedoseev (1998
Perimeter of terminal bronchioli (m)	30	Weibel (1963)
Surface area of conducting airways between trachea and bronchioli (m^2)	0.25	Mercer et al. (1994)
Diameter of respiratory bronchioli (μm)	600–700	Weibel (1963)
Diameter of alveoli (μm)	250–300	Weibel (1963)
Volume of lung respiratory compartment (ml)	3150	Weibel (1963)
Total volume of alveoli (ml)	2300–2900	Weibel (1963)
Total volume of lung capillaries (ml)	140	Weibel (1963)
Diameter of lung capillary (μm)	8	Weibel (1963)
Total number of alveoli	3×10^8	Weibel (1963)
Surface area of gas exchange in lungs (m^2)	81	Weibel (1963)
Surface area of alveoli (m^2)	70−80	Weibel (1963)
Surface area of lung capillaries (m^2)	70	Weibel (1963)
Minimal thickness of alveolar-capillary membrane (μm)	0.4	Weibel (1963)
Volume of alveolus (ml)	1.05×10^{-5}	Weibel (1963)
Number of epithelial cells in conducting airways	10.5×10^9	Mercer et al. (1994)
Number of cells in lower respiratory tract:		
Total number of cells in alveoli	1.9×10^{11}	Mercer et al. (1994)
Alveolar macrophages	2.2×10^{10}	Crapo et al. (1982)
Lymphocytes	$(2-5) \times 10^8$	Holt et al. (1986), Saltini et al. (1991)
Number of alveolar parenchyma cells:		
Epithelial cells type I	1.9×10^{10}	Crapo et al. (1982)
Epithelial cells type II	3.7×10^{10}	Crapo et al. (1982)
Endothelial cells	6.9×10^{10}	Crapo et al. (1982)
Interstitial cells	8.3×10^{10}	Crapo et al. (1982)
Interstitial lymphocytes	$(0.4-1.0) \times 10^{10}$	Holt et al. (1986)

and Mayanski, 1983). In many bacterial infections, phagocytes represent the only type of host cells capable of eliminating the pathogens. Few mathematical models exist which describe the dynamics of inflammatory reaction (Lauffenburger and Kennedy, 1981; Lauffenburger, 1985). Examples of specific and non-specific defense reactions can be found in Rudnev and Romanyukha (1995) and Marino and Kirschner (2004).

Pulmonary inflammation caused by a bacterial infection leads to a significant increase in the volume of alveolar fluid (a medical condition known as alveolar edema), but the influence of this phenomenon on the course of infection has yet to be studied. In this work, we describe a mathematical model of bacterial pneumonia which accounts for phagocytosis, edema, cellular infiltration and immune response, as well as damage to and the regeneration of target tissue. We identified model parameters using clinical data, estimated the values of energy cost for immune and pathological processes associated with pneumonia, and examined the minimum energy cost of immune defense regimens and their dependence on the parameters of infection burden.

2. Mathematical model of pneumonia

The lungs represent a principal site of invasion for many pathogens. In particular, respiratory infections cause about 30% of infection-related deaths each year (WHO, 2004). At present, there are much data available which characterize the anatomical structure, morphological organization and cellular composition of the human lungs; some of them are summarized in Table 1.

The lungs consist of two major compartments: conducting airways and bronchoalveolar respiratory tract. Conducting airways are protected against inhaled pathogens by various immune system agents. Among them: secretory antibodies (sIgA), lysozyme, lactoferrin, lactoperoxidase, and interferons. Microorganisms deposited on mucous membranes of the trachea, bronchi and terminal bronchioli are usually removed from the lungs within 1 day or less by mucociliary transport (Mims et al., 2001).

In contrast to the conducting airways, the lung respiratory compartment (target tissue in pneumonia) is protected mainly by alveolar macrophages (AMs). When these AMs become impaired, the lungs are more susceptible to bacterial infections (Reese and Betts, 1991; Caretzky et al., 1993).

An important difference between inflammatory reaction and immune response to pneumonia is found in their spatio-temporal organization (Fig. 1). An interaction between phagocytes and bacteria occurs in the lower respiratory tract, primarily in the alveoli (Fig. 1A, E). In the case of AM dysfunction, bacteria can grow more easily in number and cause a significant inflammatory reaction.