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Journal of Theoretical Biology 242 (2006) 220–236
Journal of Theoretical Biology
www.elsevier.com/locate/yjtbi

A reduced mathematical model of the acute inflammatory response: I. Derivation of model and analysis of anti-inflammation

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Received 24 October 2005; received in revised form 18 February 2006; accepted 22 February 2006
Available online 3 April 2006

Abstract

The acute inflammatory response, triggered by a variety of biological or physical stresses on an organism, is a delicate system of checks and balances that, although aimed at promoting healing and restoring homeostasis, can result in undesired and occasionally lethal physiological responses. In this work, we derive a reduced conceptual model for the acute inflammatory response to infection, built up from consideration of direct interactions of fundamental effectors. We harness this model to explore the importance of dynamic anti-inflammation in promoting resolution of infection and homeostasis. Further, we offer a clinical correlation between model predictions and potential therapeutic interventions based on modulation of immunity by anti-inflammatory agents.

Keywords: Immunology; Mathematical modeling; Anti-inflammatory cytokines; Sepsis; Bifurcation analysis

1. Introduction

Acute biological stress, such as severe infection or trauma, leads to the development of an acute inflammatory response. The goal of this response is to promote adaptation of the organism to stress, eliminate threats to survival such as pathogens, and promote tissue repair and healing. However, an excessive or inappropriate inflammatory response will lead to collateral tissue damage, organ dysfunction, a prolonged healing phase, or possibly death. This state of excessive inflammation is particularly common in association with extensive physiological organ support as provided in modern intensive care units (Goris et al., 1985; Takala et al., 1999). Organisms have developed regulatory mechanisms to contain the molecular and cellular cascades initiated by excessive inflammation. In general, pro-inflammatory elements that are key to ridding organisms of large numbers of pathogens also mobilize a negative feedback, or anti-inflammatory response, which downregulates the initial inflammatory wave (Fig. 1). Specific details of pro- and anti-inflammatory responses may be sculpted by the nature and magnitude of the initiating insults, as well as by genetic predispositions.

In prior work, we constructed a reduced mathematical model of the pro-inflammatory response (Kumar et al., 2004) consisting of a response instigator (pathogen) and early and late pro-inflammatory mediators. While that model captured a variety of clinically relevant scenarios associated with the inflammatory response to infection, the goal of the present work is to gain insight into the presumed advantage and robustness instilled by the presence of a time-dependent anti-inflammatory response. While anti-inflammation inhibits the subsequent build-up of pro-inflammation and the damage to tissue that may be caused by pro-inflammation, it also mitigates the subsequent production of anti-inflammatory mediators. Thus, the overall effects of anti-inflammation on the outcome following pathogenic infection, and how these

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doi:10.1016/j.jtbi.2006.02.016

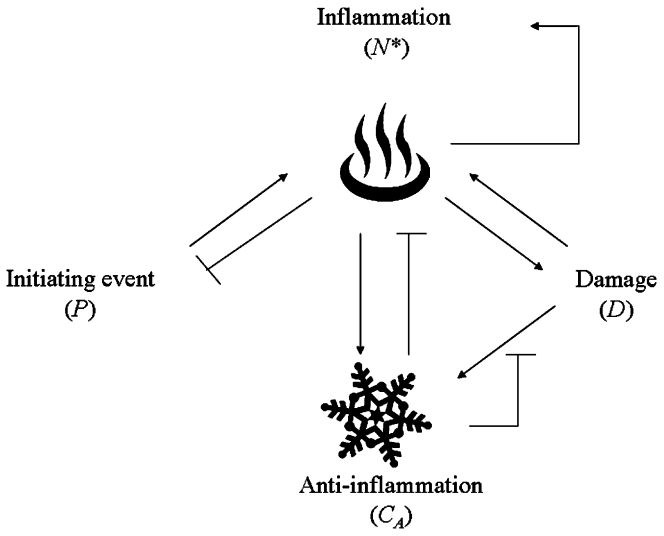

Fig. 1. Interactions included in our four-variable model of the acute immune response. Arrows and bars represent upregulation and inhibition, respectively. The bar between anti-inflammation and inflammation corresponds to the inhibition of both the production of inflammation and the ability of inflammation to interact with all other involved species.

effects depend on parameters such as pathogen growth rate and the anti-inflammatory response rate itself, may be difficult to predict by intuition alone but are well suited for dynamical systems analysis.

As the first step in performing this mathematical analysis, we derive a reduced model of the acute immune response that incorporates pro- and anti-inflammation. This model does not include components of the adaptive immune response, such as T-cells and specific antibodies. Therefore, this model describes the generic response to pathogenic insult (Janeway and Medzhitov, 2002). Our derivation proceeds through several stages, based on calibration of subsystems to generally accepted features of the interactions of particular immune system components, as observed in previous experimental studies. We construct a reduced model of inflammation from these subsystems, where the impact of dynamic anti-inflammation is evaluated through simulations and bifurcation studies. Our results illustrate the health advantage conferred by a dynamic anti-inflammatory response and suggest that the rates of this response may be well tuned to yield optimal outcomes following pathogenic infection. Our findings also point to risks associated with manipulation of the levels of the anti-inflammatory mediator present, either before an initial infection or following an initial infection that is on its way to, but has not yet reached, a healthy resolution. We conclude with a discussion in which we elaborate on these and other possible therapeutic implications of our results.

2. Methods

Our reduced model of the acute inflammatory response consists of a system of four differential equations in which the dependent variables represent the levels of pathogen (P), activated phagocytes (N^*) such as activated neutrophils, tissue damage (D), and anti-inflammatory mediators (C_A) such as cortisol and interleukin-10. This model describes the interactions depicted in Fig. 1. We develop this model by first considering the two-variable subsystems N^*/P and N^*/D, treating C_A as a parameter, then combining these subsystems to form a three-variable subsystem, and finally incorporating the dynamics of the anti-inflammatory mediator to create the reduced model. We adopted a subsystem approach to ensure that the interactions of the model variables are consistent with biological observations.

Baseline parameter values for both the subsystems and the reduced model are provided in Table 1 and are selected to remain within the given ranges and constraints found in the experimental literature. This baseline parameter set is used for all simulations except where noted in the text. Parameters that could not be documented from existing data were estimated such that the subsystems behave in a biologically appropriate manner for plausible levels of the anti-inflammatory mediators. Furthermore, when the pathogenic insult is replaced by endotoxin as an initiating event, as presented in Day et al. (2006), the resulting model qualitatively reproduces the responses of immune mediators measured experimentally during repeated endotoxin administrations. Further details on the derivation of parameter ranges, constraints and estimated values, are presented in the Supplementary Materials. Units for the model variables and many of the associated parameters cannot be determined, since the variables represent various types of cells, signaling proteins such as cytokines, and/or other mediators concurrently. More precisely, these variables quantify the response of the immune function they represent rather than, for example, an exact cell count. Therefore, units of most parameters related to these variables are not in conventional form, but rather in terms of the associated variable.

Throughout the analysis of the reduced model and its subsystems, we will be tracking the existence and values of fixed points, determining the parameter regimes in which particular fixed points are stable, and locating bifurcations. A fixed point is a point where the derivatives of all variables in the system are zero, also known as a critical point or equilibrium point. This occurs where the nullclines[1] of the system intersect. We will refer to a fixed point as stable if the real part of each eigenvalue associated with the linearized system at that fixed point is negative. In the systems that we consider, it is exactly the stable fixed points that represent possible asymptotic steady states attained by open sets of initial conditions. A bifurcation

[1]For a system of the form $dx/dt = f(x,y)$; $dy/dt = g(x,y)$, the x-nullcline (y-nullcline) is the set of points in the (x,y) plane that satisfy $f = 0$ ($g = 0$). Intersections of nullclines are fixed points, since at an intersection both dx/dt and dy/dt are zero. These ideas generalize directly to systems with more than two equations.