Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Theoretical Biology 237 (2005) 390–400
Journal of Theoretical Biology
www.elsevier.com/locate/yjtbi

Computational modeling of the immune response to tumor antigens

Filippo Castiglione[a,*], Federico Toschi[a], Massimo Bernaschi[a], Sauro Succi[a], Roberta Benedetti[b], Brunangelo Falini[b], Arcangelo Liso[c]

[a]*Istituto Applicazioni del Calcolo (IAC) "M. Picone", Consiglio Nazionale delle Ricerche (CNR), Viale del Policlinico, 137–00161 Rome, Italy*
[b]*Sezione di Ematologia, Università degli Studi di Perugia, Policlinico Monteluce, Via Brunamonti 51–06122 Perugia, Italy*
[c]*Sezione di Ematologia, Università degli Studi di Foggia, Viale L. Pinto—71100 Foggia, Italy*

Received 17 January 2005; received in revised form 26 April 2005; accepted 26 April 2005
Available online 22 July 2005

Abstract

Vaccination protocols designed to elicit anti-cancer immune responses have, many times, failed in producing tumor eradication and in prolonging patient survival. Usually in cancer vaccination, epitopes from one organism are included in the genome or linked with some protein of another in the hope that the immunogenic properties of the latter will boost an immune response to the former. However, recent results have demonstrated that injections of two different vectors encoding the same recombinant antigen generate high levels of specific immunity.

Systematic comparison of the efficacy of different vaccination protocols has been hampered by technical limitations, and clear evidence that the use of multiple vectors has advantages over single carrier injections is lacking. We used a computational model to investigate the dynamics of the immune response to different anti-cancer vaccines based on randomly generated antigen/carrier compounds. The computer model was adapted for simulations to this new area in immunology research and carefully validated to the purpose. As a matter of fact, it reproduces a relevant number of experimental observations.

The model shows that when priming and boosting with the same construct, competition rather than cooperation develops amongst T cell clones of different specificities. Moreover, from the simulations, it appears that the sequential use of multiple carriers may generate more robust anti-tumor immune responses and may lead to effective tumor eradication in a higher percentage of cases. Our results provide a rational background for the design of novel strategies for the achievement of immune control of cancer.

Keywords: Tumor immunity; Vaccination; T lymphocytes; Antibodies

1. Introduction

Anti-cancer vaccination is based on the existence of antigens, selectively or preferentially expressed by tumors, called tumor-associated antigens (TAAs).

Cancer eradication using TAA vaccination has been demonstrated in numerous animal models. However, active immunotherapy of cancer in human beings has achieved very limited success to date (Finn, 2003). The compromised immune system of patients and the high tumor burden have been blamed as largely responsible for the clinical failures (Finn, 2003; Minev, 2002; Liso et al., 2001; Nouri-Shirazi et al., 2000; Ribas et al., 2003; Stevenson et al., 2004). Furthermore, in order to induce a stronger anti-tumor response, a number of challenges need to be faced such as what antigens to use, what schedule of vaccination to employ and what adjuvants to add to the inoculum. In fact, tumor antigens are known to be weak immunogens that hardly trigger an effective immune response.

Abbreviations: TAA, tumor-associated antigen; DC, dendritic cell; TH, CD4 T cell; TC, CD8T cell; CC, cancer cell; MA, macrophages; B, B lymphocyte; NR, no rotation; YR, yes rotation

*Corresponding author.
E-mail addresses: f.castiglione@iac.cnr.it (F. Castiglione), a.liso@medicina.unifg.it (A. Liso).

0022-5193/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2005.04.024

Most clinical trials contemplate multiple injections of one TAA (mainly in the form of protein, recombinant DNA or viruses modified to express TAA) inoculated along with one highly immunogenic molecule (named carrier). Carriers are typically derived from organisms that are phylogenetically very distant from the host (the genome of recombinant microorganisms engineered to express TAA can be regarded as a carrier itself).

However, recent results have demonstrated that injections of two different vectors encoding the same recombinant antigen (e.g. priming with plasmid DNA and boosting with recombinant modified vaccinia Ankara) generate high levels of specific immunity (Amara et al., 2001; Schneider et al., 1998).

Of the many thousands of peptides encoded by a complex antigen potentially presented to CD8T cells, only a small fraction induces a non-negligible response in association with any given MHC class I allele, a phenomenon known as immunodominance (Yewdell and Bennink, 1999). This issue should be considered in order to design vaccination strategies able to induce an optimal cytototoxic T cell mediated immune response.

In order to evaluate the effects on both humoral and cellular immune response of repeated injections of TAA together with carriers, we used computer simulations based on a modified version of a well established computational model (Celada and Seiden, 1992). In particular, we compared protocols by using multiple different vectors/carriers and correlated the frequency of anti-tumor T cells and antibody titers with tumor control.

2. Modeling the immune response to cancer

The microscopic model we employ represents the most important entities of the immune system at cellular level and basic immunological processes including hematopoiesis, thymus selection of CD4 and CD8 T lymphocytes, antigen digestion and presentation (endogenous and exogenous pathways) by antigen processing cells (B lymphocytes, macrophages, dendritic cells), hypermutation of antibodies and cytotoxicity by CD8 T cytotoxic lymphocytes (Bernaschi and Castiglione, 2001; Bernaschi and Castiglione, 2002; Castiglione et al., 2003; Celada and Seiden, 1992; Celada and Seiden, 1998).

The model is *polyclonal*, meaning that different clones of lymphocytes are represented at the same time. In particular, each lymphocyte is equipped with a cell receptor drawn from a suitable mathematical space of representation. Here we use the space of binary strings. Hence, with a binary string of length l, we represent a repertoire of size 2^l. Although much smaller than the realistic estimated repertoire of B cells or T cells (about 2^{36} for B cell receptors and 2^{53} for T cell receptors (Perelson and Weisbuch, 1997), $l = 12$ gives a repertoire which is sufficient for our purpose. Therefore, cell receptors, but also antigens (hence the tumor peptide and the carrier) and immunoglobulins, are represented in the discrete space $\{0,1\}^{12}$. Actually we use two binary strings for the epitopes and two binary strings for the peptides; therefore an antigen is an object of the space $\{0,1\}^{48}$.

Immunogenicity of a molecule is defined as the Hamming distance (that is the number of complementary bits in the bit-wise comparison) from the subset representing the repertoire of the self-molecules. For the sake of simplicity, the self is defined by a single molecule and we set the TAA equal to the self-molecule. Therefore, any other molecule belongs to the non-self (i.e. the carriers are randomly chosen in $\{0,1\}^{12}$ but not equal to the TAA).

The interactions among entities are depicted in Fig. 1 where dashed lines indicate "non-specific" bindings whereas solid lines indicate "specific" bindings. Here the term "specific" means that the binding is modeled through a random boolean variable whose probability is an exponential function of the Hamming distance between the binary strings involved in the molecular recognition. In contrast, non-specific binding is equivalent to have a binding rate equal to a certain constant.

Interactions in Fig. 1 can be summarized as follows: antigens are captured and processed by antigen presenting cells (dendritic and B cells). Dendritic Cells (DCs) activate cytotoxic CD8T cells (TCs) upon recognition of the TCR with the MHCI-peptide molecule. Activated TCs are stimulated to proliferate. Moreover, activated TCs can kill MHCI-peptide bearing cells (i.e., DC as well as Cancer Cells, CCs). Stimulated TCs can enter the duplication phase but only in presence of IL-2 which is produced by CD4 T cells (Th cells). In turn, T helper cells produce IL-2 upon stimulation by APCs represented by macrophages (MA), B lymphocytes (B) and dendritic cells (DC).

A time step of the simulation corresponds to 8 h of real life. Cells and molecules interact in a simulated space that corresponds to multiples of one milliliter of blood. However, given the time resolution, cells are allowed to circulate to lymph nodes where the presentation of the antigen by APCs takes place. The concept of physical proximity is enforced so that cells reside on a two-dimensional lattice and interactions may happen only among cells and molecules living in the same lattice-site (Fig. 1 panel (b)).

The simulation is carried out by iterating the following steps:

Step 1: Generation of new cells from the bone marrow and thymus selection of immature CD4/CD8T lymphocytes.

Step 2: Interaction among entities executed in random order to avoid any bias toward a particular interaction.