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Analysis of vaccine's schedules using models

F. Pappalardo [a,b,*], S. Motta [b], P.-L. Lollini [c], E. Mastriani [b]

[a] *Faculty of Pharmacy, University of Catania, Italy*
[b] *Deparment of Mathematics & Computer Science, University of Catania, Italy*
[c] *Sezione di Cancerologia, Dipartimento di Patologia Sperimentale, and Centro Interdipartimentale di Ricerche sul Cancro "Giorgio Prodi", University of Bologna, Italy*

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Abstract

We present a further, yet important, step in applying Catania Mouse Model & simulator (SimTriplex) of immune system response to vaccination. In particular we show that, as immune response can induce toxicity, one can calibrate the vaccine administrations in such a way to avoid toxicity effects, keeping immunoprevention from cancer. This result increases the model's potential applications.

Keywords: Cancer immunoprevention; Computational models; Mammary carcinoma

1. Introduction

Immunological prevention of tumors is a concept based on the ability of immunity to arrest tumor progression in healthy individuals with a high risk of cancer. Immunoprevention of mammary carcinoma in HER-2/neu transgenic mice was attempted using various immunological strategies, including cytokines, non-specific stimulators of the immune response, and HER-2/neu specific vaccines made of DNA, proteins, peptides, or whole cells.

We developed an accurate model of immune system responses to vaccination. We performed *in silico* experiments considering a large population of individual mice. Each individual mouse is characterized by a sequence of uniformly distributed random numbers which will determine the probabilistic events. Comparison with *in vivo* experiments shows excellent agreement.

In this paper we present a further, yet important, step in applying the model of immune system response to vaccination. In particular we show that, as immune response can induce toxicity, one can calibrate the vaccine administrations in such a way to avoid toxicity effects, keeping immunoprevention from cancer. This result increases the model's potential applications.

The plan of the paper is the following. Section 2 will introduce the biological problem along with a very short primer on tumor immunoprevention. Section 3 deals with the design of a model, referred as SimTriplex model, that describes the immune competition using an agent based method; moreover we present the use of SimTriplex for designing new vaccination protocols. In Section 4, we present analysis of vaccination schedules, while section 5 gives our conclusions and perspectives.

2. Tumor immunoprevention

To investigate cancer immunoprevention the Bologna group of tumor immunology opted for transgenic mouse model systems that recapitulate the entire natural history of tumors. Mice transgenic for the HER-2/neu oncogene (involved also in human breast cancer) are prone to mammary carcinomas that spontaneously develop over the course of several months. This is a very flexible system that was independently produced by various laboratories using

* Corresponding author. Address: University of Catania, Faculty of Pharmacy, Italy.
E-mail address: francesco@dmi.unict.it (F. Pappalardo).

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mice differing in their genetic background and different transgenes of human or rat origin, either in normal (prototoncogenic) form or harboring activating mutations. Here we will deal with a transgenic line named BALB-neuT that harbors a mutant rat HER-2/neu expressed in the mammary gland under transcriptional control of a mouse mammary tumor virus sequence.

Soon after birth in the mammary glands of BALB-neuT mice appear cells hyperexpressing HER-2/neu gene product, p185. Such cells start proliferating and give rise to multiple microscopic lesions identifiable as a typical hyperplasia (a preneoplastic condition), then progress to multiple carcinomas *in situ*, the first frank neoplastic lesion. Carcinomas *in situ* continue growing and coalesce into carcinomas that become macroscopically apparent around 4–5 months of age. Tumor formation proceeds independently in all ten mammary glands and, in later stages, gives rise to metastases detectable in the lungs.

To improve the efficacy of existing immunopreventive treatments we adopted a standard approach in oncology, i.e. we combined multiple immune signals in the same vaccine. The Triplex vaccine combines the target antigen with two ''adjuvant'' stimuli, IL-12 and allogeneic MHC molecules. The main purpose of IL-12 is to enhance antigen presentation and Th cell activation in response to the antigen. Allogeneic MHC molecules stimulate multiple T cell clones and cause a broad production of immunostimulatory cytokines that amplify immune responses.

The first formulation of the Triplex vaccine [3,1,9] consisted of MHC-allogeneic mammary carcinoma cells expressing HER-2/neu and of recombinant IL-12. Subsequently the need for IL-12 administration was bypassed through the transduction of vaccine cells with the transduction of IL-12 genes.

Repeated administrations of the Triplex vaccine (Chronic schedule) to young BALB-neuT mice resulted in a complete block of mammary carcinogenesis. More than 85–90% of vaccinated mice remained tumor-free at one year of age, whereas all untreated mice had multiple mammary carcinomas at six months of age. The major issue still unresolved with the Triplex vaccine is whether or not the Chronic schedule is the minimal set of vaccination yielding complete, long-term protection from mammary carcinoma. Shorter vaccination protocols failed to prevent cancer, but between shorter protocols and the Chronic one there still is an infinite set of schedules that might yield complete protection with significantly less vaccinations than the Chronic. From an experimental point of view this would require numerous sets of experiments each lasting one year, a feat that discouraged the biological part of our team from the pursuit of an experimental solution *in vivo*.

3. Modeling vaccine's effects

The immune system is characterized by a great complexity and it is very difficult to develop a detailed mathematical description of all phenomena related to the immune competition. However a significant effort has been devoted during the last three decades to mathematical approaches to describe the immune system-tumor competition. If one focuses the attention on specific types of interactions, one may attempt to develop *ad hoc* models for a specific phenomenon at the chosen observation and representation scale.

To satisfy the standard requirements for conceiving a good model we used an approach which reproduces *ab initio* the kinetic description of the interactions and diffusion of each relevant biological entity. Our model, referred as SimTriplex model, describes the immune competition using an agent based method. These methods are nowadays very popular as they find application in various fields. We used a Lattice Gas Automata (LGA) [12,2] technique which allows to describe, in a defined space, the immune system entities with their different biological states and the interactions between different entities. We restrict ourselves to a two-dimensional physical space as the organ which we need to represent is almost flat. The immune system evolution in space and in time is generated from the interactions and diffusion of the different entities.

The model is complete enough to describe the major aspect of the phenomenon and, after tuning the model parameters, it can predict the response to a vaccination schedule that prevented the formation of solid tumors in mice.

To describe the cancer-immune system competition one needs to include all the entities (cells, molecules, adjuvants, etc.) which biologists recognize as relevant in the competition. The choice of entities was driven by the experimental data on Triplex vaccine previously described.

These entities, which are either cells or molecules, have mechanical and biological states: position, lifetime, internal states and specificity. Position and lifetime are common to all of them; internal states apply only to cellular entities, while specificity can be found both in cellular and molecular entities.

The model, which has been extensively described in [5,10], includes the immune system and the tumor entities, described in Table 1.

All various classes of immune functional activity, phagocytosis, immune activation, opsonization, infection and cytotoxicity are described using probability functions and translated into computational rules. We also mimic the stochastic event ruling transition from normal to tumor cells, and biological diversity in mice samples [5]. An overall scheme of the interactions included in Simtriplex is shown in Fig. 1.

Catania Mouse Model & Simtriplex simulator [13] were designed to reproduce *in vivo* experiments. The key output from these experiments is the time associated to solid tumor formation in a set of mice treated with a given vaccine schedule.

As mentioned, the major issue still unresolved with the Triplex vaccine is whether or not the Chronic schedule is the minimal set of vaccination yielding complete, long-term