Agent Based Modeling of Lung Metastasis-Immune System Competition

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1 Extended Abstract

The Triplex vaccine is a cell vaccine developed as an immunopreventive approach to breast cancer. Recent studies showed that the same vaccine has a considerable therapeutic effect against lung metastases derived by mammary carcinoma[1].

Using three different signals (the target antigen, interleukin-12 (IL-12) and allogeneic MHC molecules) it stimulates immune system response in many ways. The IL-12 enhances antigen presentation, helper T cell (Th) activation and secretion of interfenron-γ (IFN-γ) by natural killer (NK) and Th cells. IFN-γ has a cytostatic activity on cancer cells (CC) and stimulates granulocytes and macrophages (MP) in infiltrating tumor cell nests in the lungs. Th cells have a major role at the systemic level releasing various cytokines such as interleukin-2 (IL-2) which enhances cytotoxic T cells (TC) activities and B cells antibodies (Ab) release. The allogeneic MHC favors the recognition by antigen presenting cells (macrophages, B and dentritic cells (DC)). A simplified scheme of the immune mechanisms induced by Triplex vaccine are shown in figure 1.

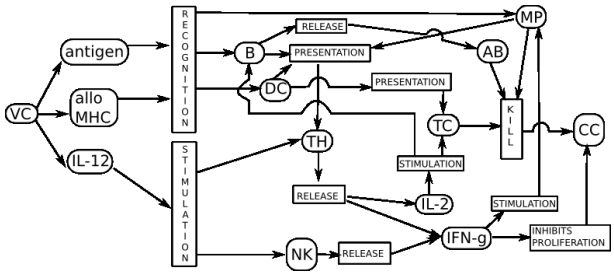

Fig. 1. Main immune responses induced by Triplex vaccine against lung metastases

The "in vivo" experiment lasts for 32 days. For the induction of lung micrometastasis, all mice received an intravenous injection of $2.5{\cdot}10^4$ metastatic cells at day 0. In standard "in vivo" experiments it is considered common practice to use multiple sets of mice, each treated with a different protocol. One of these sets (the control set) is usually treated with a placebo solution in order to study/represent

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the untreated mice case. This experiment counts three different mice sets: the untreated set (control), a set where mice are exposed to a "twice a week" vaccination cycle started at day 1 and repeated up to the end of the experiment (set 1) and a set where the same cycle is started at day 7 and repeated up to the end of the experiment (set 2). Mice from the control set developed ≈ 200 metastatic nodules, whereas mice from set 1and 2 showed, respectively, a reduction $> 99\%$ and $\approx 90\%$ of early lung metastasis formation. A major goal for biologists is to better understand biological behavior and to attempt to predict, for example, results from long-running experiments, in order to move faster towards clinical phase I trials (experiments in advanced cancer patients). A computational model to simulate "in vivo" experiments has then been requested.

We have created an agent based model (ABM) named MetastaSim, that is inspired by SimTriplex simulator [2]. In "in vivo" experiment, the number and dimensions of the metastatic nodules on the lungs surfaces are measured and taken as outcome of the experiment. The present release of MetastaSim uses a bi-dimensional 128x128 lattice with hexagonal geometry to represent the frontal ventral surface of the left lung of mice. The simulation of the complete left lung will be performed in the release of the model. At each time-step ($\Delta t = 8$ hours) every entity in a lattice-site has a chance (with probability p) to interact with all the other entities in the same site, according to the most immunologically relevant interaction rules deduced from the literature and "in vivo" experiment observations. In particular all the interactions previously showed in figure 1 (and others) are implemented. A more detailed description on how the interaction mechanism works can be found in [2]. After the interaction phase ends, entities are allowed to migrate to a lattice site in the neighborhood. Cell receptors are represented by binary strings and the probability of recognition and interaction of two entities is a function of the Hamming distance between their receptors [2]. This process models real receptor binding and it's able to reproduce relevant biological phenomena such as clonal selection. MetastaSim needs to correctly reproduce the three different biological scenarios given by the sample sets "in vivo" results. In particular, the untreated mice scenario has major importance for two reasons: firstly this scenario is the base on which the other scenarios have to be built; secondly it is the most computationally expensive. In fact, due to the lack of vaccination, the number of cancer cells grow enormously resulting in a computer memory intensive application. Here we present the main aspects of the untreated scenario. Biologists assumed that every metastatic nodule has originated from an individual "progenitor" cancer cell. This means that approximately only one cancer cell over 100 passes through lung capillary vessels and settles into the lungs. Since the positioning process is not relevant for the experiment, the simulation starts with cancer cells already settled in the lungs. At the beginning of the simulation n "progenitor" cancer cells are then randomly positioned on the lattice. Every nodule arises from the same progenitor. The cells of the nodule duplicate with a ratio which is proportional to the quantity of the provided nutrient. Since distribution of nutrient is not homogeneous, if we have n progenitors cells, we will observe n distinct families of cells growing

with different rates. Following results by Kendall [3], we reproduced the growth kinetics of the nodules using the Gompertz growth law. Future attempts will be focused on using more general approaches based on nutrients distribution [4]. To model "in vivo" nodules distributions, sizes and number of nodules data from 8 different real mice are used with the inverse transform sampling method to generate n random nodule measures. These values are converted in n sets of parameters for the Gompertz growth law and used at any time-step to compute the duplication rates that cancer cells belonging to the specific nodule should have. Interactions of the immune system entities with cancer cells are present and observed in simulations as well, but they are not so relevant to influence nodules growth. The two samples Kolmogorov-Smirnov statistical test told us that "in silico" obtained nodule sizes distributions are in close agreement with the "in vivo" ones. In figure 2 we show an example of the nodules spatial distributions obtained "in vivo" and "in silico".

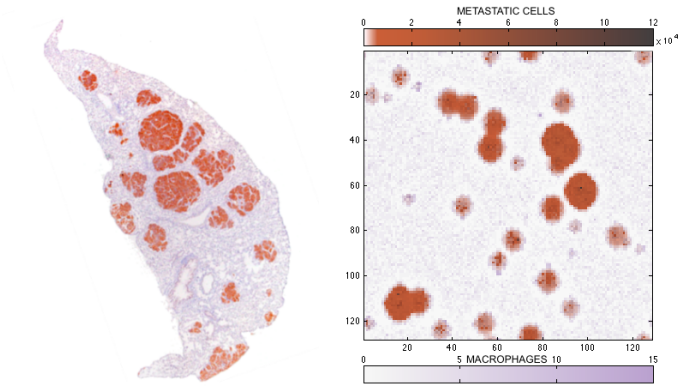

Fig. 2. Examples of nodules distributions obtained "in vivo" (l.s.) and "in silico" (r.s.)

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