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Memory versus effector immune responses in oncolytic virotherapies

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AUTHOR-HIGHLIGHTS

- We model memory and effector immune responses on tumour–virus interactions.
- The model shows that cancer control is associated with high numbers of effector cells.
- Effector cell persistence requires high initial memory cell population.
- Cancer control from dormant state cannot be predicted by the initial memory size.

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ABSTRACT

The main priority when designing cancer immuno-therapies has been to seek viable biological mechanisms that lead to permanent cancer eradication or cancer control. Understanding the delicate balance between the role of effector and memory cells on eliminating cancer cells remains an elusive problem in immunology. Here we make an initial investigation into this problem with the help of a mathematical model for oncolytic virotherapy; although the model can in fact be made general enough to be applied also to other immunological problems. According to this model, we find that long-term cancer control is associated with a large number of persistent effector cells (irrespective of the initial peak in effector cell numbers). However, this large number of persistent effector cells is sustained by a relatively large number of memory cells. Moreover, the results of the mathematical model suggest that cancer control from a dormant state cannot be predicted by the size of the memory population.

1. Introduction

It is well known that after successful reaction to a pathogen, long-lasting immunity can be stimulated (Kumar et al., 2011). Harnessing this natural defence system, through the use of vaccines, has long been important in the fight against infections and diseases (Bachmann and Jennings, 2010; Dermime et al., 2002). More recently immune mechanisms have been employed to combat cancer through various immunotherapies such as virotherapies, adoptive transfer of immune cells, cytokine therapies or antibody therapies. The low success rates of these immunotherapies are mainly caused by the fact that the immune–cancer interactions are still not fully understood.

One of the emerging cancer therapies is oncolytic virotherapy, which involves both the direct action of tumour cell destruction by a virus (that usually carries tumour-associated antigens (TAAs)) and the indirect action of anti-tumour immunity (as the immune cells learn, through interaction with the virus, to recognise the TAAs) (Kelly and Russell, 2007; Pol et al., 2012; Russell et al., 2012). The interactions between the immune cells and the viruses lead to short term (or therapeutic) and long term (or prophylactic) immunity, which can be naively characterised by effector and memory immune cells, respectively (Bachmann and Jennings, 2010). In the short term effector cells act to eliminate a pathogen, while in the long-term memory cells act to prevent its reoccurrence. Memory cells are antigen-specific; they are stored after a pathogen has been eliminated (Crotty and Ahmed, 2004; Klebanoff et al., 2006; Wodarz, 2006) and are capable of generating new effector cells (Sallusto et al., 2004). Successful cancer treatment protocols seek persistent protection against the tumour whether through permanent elimination or control.

An important research question in immunology, still unanswered at this moment, refers to whether it is effector or memory cells which play the most important role in successful treatment protocols. It has been posited that multiple treatment protocols are likely to provide better success in immune therapies. In particular, for cancer therapies, multiple and subsequent treatments provide the

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possibility of activating the memory cells, which can then be used to generate a stronger more targeted response against the tumour (Klebanoff et al., 2005; van Duikeren et al., 2012; Wherry and Ahmed, 2004; Zhang, 2007). On the other hand, there is increasing evidence that long-term cancer control is accompanied by high numbers of effector cells (Baitsch et al., 2011; Berezhnoy et al., 2014; Paulis et al., 2013). Understanding the delicate balance between the anti-tumour role of effector and memory cells will improve the existent anti-cancer treatments.

Mathematical models (see, for example, Bozic et al., 2012; Eftimie et al., 2011b; Ferreira et al., 2005; Karev et al., 2006; Komarova and Wodarz, 2010; Paiva et al., 2009, 2011; Rommelfanger et al., 2012; Wein et al., 2003; Wodarz et al., 2012; Wodarz and Komarova, 2009 and the references therein) have shown that possible outcomes for anti-tumour therapies are as follows: tumour elimination, tumour dormancy, tumour escape or tumour control. A distinction between dormancy and control can be made: tumour control occurs when the tumour is held permanently at a constant but relatively low size, while tumour dormancy is described as a prolonged period in which the tumour remains small and as such is both asymptomatic and undetectable but will at some stage grow again (Quesnel, 2008). Although the nature of the biological mechanisms leading to tumour dormancy is not fully known (Almog, 2010; Uhr and Pantel, 2011), one possible means is through tumour–immune interactions, the so called immune-mediated dormancy (Farrar et al., 1999; Teng et al., 2008; Wilkie and Hahnfeldt, 2013a). It is thought that a constant interplay between the tumour and immune cells can lead to this temporary equilibrium, but eventually one population will overpower the other and either the tumour will "escape" and grow rapidly or it will be eliminated (Teng et al., 2008; Wilkie and Hahnfeldt, 2013b). Clearly, from a clinical outlook tumour escape is a negative outcome and cancer elimination is the goal of any treatment protocol. However, as we will discuss here (and as suggested before Gatenby, 2009), tumour control may be the only possible approach when tumour elimination is impossible. Tumour dormancy, although of short term therapeutic benefit, presents a clinical challenge in the long-term as predictions regarding its end stage (escape or elimination) may be unlikely.

In this paper, we will introduce and investigate a mathematical model for oncolytic virotherapy, which allows us to study the balance between the memory and effector immune responses that can control tumour growth or lead to tumour dormancy. Although there are many mathematical models for cancer virotherapies (see, for example, Bajzer et al., 2008; Biesecker et al., 2010; Friedman et al., 2006; Komarova and Wodarz, 2010; Wein et al., 2003; Wodarz, 2001; Wu et al., 2004 and the references therein), the model investigated in this study is based on a more complex ODE model described in Eftimie et al. (2011b), which incorporated effector and memory immune responses and replicated a treatment protocol derived in Bridle et al. (2010). In that protocol, two viruses that carried the same tumour-associated antigen (human dopachrome tautomerase, or hDCT) were administered 14 days apart. The first virus, Adenovirus (Ad), acted as a vaccine virus by provoking an immune response against the tumour antigens. As this immune response receded, memory cells were created. The second virus, Vesicular Stomatitis Virus (VSV), was an oncolytic virus. This virus not only destroyed the cancer cells directly, but provoked a much stronger immune response to the tumour antigens due to the memory cells created in the first phase. The protocol, tested on mice, did not eradicate tumours in the majority of cases but did lead to improved survival times (compared with survival times for mice treated with just one virus). The mathematical model introduced in this study focuses on the second part of this treatment protocol, i.e., on the oncolytic virus (injected after the formation of memory cells). Using this model, we will investigate how differences in the magnitude of the initial memory cell population lead to control, dormancy or escape of tumour cells. We will also determine the role of parameters governing the behaviour of effector cells on the outcome of the treatment.

The paper is structured as follows. In Section 2 we describe the mathematical model. In Section 3 we begin our investigation of the long-term dynamics of this model by focusing on the steady states and their stability. To get a better understanding of the balance between effector and memory immune responses, in Section 4 we discuss the steady-state behaviour of a simplified virus-free model. In fact, this simplified model is general enough to be applied to any immunotherapy and so may permit us to make stronger conclusions about the relative importance of different immune cell types in targeting cancer. In Section 5 we investigate numerically the long-term dynamics of both the full model and the simplified model paying particular attention to the effects of varying the initial memory cell population size. Finally, in Section 6 we return to the simplified model and investigate the parameters that govern the effector cells. We conclude in Section 7 with a summary and discussion of the results.

2. Model description

To model the tumour–immune–virus interactions, we focus on the following populations: the uninfected (x_u) and infected (x_i) tumour cells, the memory (x_m) and effector (x_e) immune cells, and the virus particles (x_v). We assume that the virus particles are VSV particles, and that the effector/memory cells are $CD8^+$ T cells. The equations below, which are adapted from Eftimie et al. (2011b), take into account the fact that effector cell proliferation is stimulated by both the presence of the free virus particles (as considered in Eftimie et al., 2011b) and the uninfected tumour cells (an aspect not considered in Eftimie et al., 2011b). Since the data in Bridle et al. (2010) ignored the spatial aspect of solid tumours, we decided to use an ODE model, with saturated interaction terms accounting for some of the tumour spatial structure:

$$\frac{dx_u}{dt} = rx_u\left(1-\frac{x_u+x_i}{k}\right) - d_v\frac{x_u}{h_u+x_u}x_v - d_u x_u\frac{x_e}{h_e+x_e}, \tag{1a}$$

$$\frac{dx_i}{dt} = d_v\frac{x_u}{h_u+x_u}x_v - \delta x_i - d_u x_i\frac{x_e}{h_e+x_e}, \tag{1b}$$

$$\frac{dx_m}{dt} = p_m\frac{x_v}{h_v+x_v}x_m\left(1-\frac{x_m}{M}\right), \tag{1c}$$

$$\frac{dx_e}{dt} = p_e\frac{x_v+x_u}{h_v+x_v+x_u}x_m - d_e x_e - d_t x_u x_e, \tag{1d}$$

$$\frac{dx_v}{dt} = \delta b x_i - \omega x_v. \tag{1e}$$

These equations incorporate the following biological assumptions:

- The uninfected tumour cells grow logistically at a rate r, up to their carrying capacity k. We use logistic growth because some experimental studies show evidence of a reduced rate of tumour growth at larger sizes (see, for example, the *in vivo* and *in vitro* growth of various human and rodent solid tumours shown in Guiot et al., 2003; Laird, 1964; Looney et al., 1980). An alternative would be to assume straight exponential growth (or other growth laws Bonate, 2011), which might lead to different results but are not investigated here. The large carrying capacity k (see Table A2 for its value) – chosen to correspond to the humane endpoint for experimental protocols with mice (Bridle et al., 2010; N.I.H., O.A.C.U., 1996) – allows us to