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A nonlinear competitive model of the prostate tumor growth under intermittent androgen suppression

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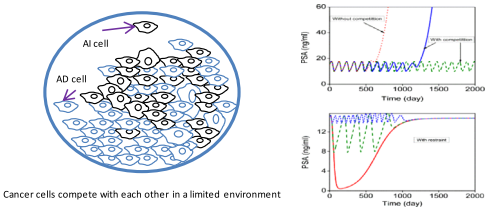
HIGHLIGHTS

- A new tumor growth model under intermittent androgen suppression is proposed.
- The relapse is postponed even avoided with the positive growth rate of cancer cells.
- The tumor growth eventually reaches a stable state in a finite carrying capacity.
- The competition and the restraint can enhance the possibility of relapse prevention.

GRAPHICAL ABSTRACT



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ABSTRACT

Hormone suppression has been the primary modality of treatment for prostate cancer. However long-term androgen deprivation may induce androgen-independent (AI) recurrence. Intermittent androgen suppression (IAS) is a potential way to delay or avoid the AI relapse. Mathematical models of tumor growth and treatment are simple while they are capable of capturing the essence of complicated interactions. Game theory models have analyzed that tumor cells can enhance their fitness by adopting genetically determined survival strategies. In this paper, we consider the survival strategies as the competitive advantage of tumor cells and propose a new model to mimic the prostate tumor growth in IAS therapy. Then we investigate the competition effect in tumor development by numerical simulations. The results indicate that successfully IAS-controlled states can be achieved even though the net growth rate of AI cells is positive for any androgen level. There is crucial difference between the previous models and the new one in the phase diagram of successful and unsuccessful tumor control by IAS administration, which means that the suggestions from the models for medication can be different. Furthermore we introduce quadratic logistic terms to the competition model to simulate the tumor growth in the environment with a finite carrying capacity considering the nutrients or inhibitors. The simulations show that the tumor growth can reach an equilibrium state or an oscillatory state with the net growth rate of AI cells being androgen independent. Our results suggest that the competition and the restraint of a limited environment can enhance the possibility of relapse prevention.

1. Introduction

Hormone therapy has been the mainstay in the treatment for advanced prostate cancer. It has been the basis for two Nobel prizes, the first to Charles Huggins for the initial observation and the second to Andrew Schally for the discovery of the luteinizing hormone-releasing hormone agonists (Klotz, 2013). Androgen deprivation is initially effective because prostate cancer cells are dependent on androgens (Huggins and Hodges, 1941). However, many patients eventually suffer from the recurrent AI prostate cancer in continuous androgen suppression (CAS) therapy, as the

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cancer cells can develop alternative signaling pathways to escape from androgen deprivation (Feldman and Feldman, 2001). It is possible to stop and restart androgen suppression by medical castration, which is achieved by using of pharmacological agents such as luteinizing hormone-releasing hormone analogs (Goldenberg et al., 1995). Therefore the strategy of IAS with off-treatment periods was proposed to improve the quality of patients' life and attempt to delay or prevent the AI relapse (Klotz et al., 1986; Akakura et al., 1993). Bruchovsky et al. initially compared IAS with CAS to demonstrate the efficiency of IAS in addition to reduction in adverse effects and improvement in quality of life during off-treatment periods (Bruchovsky et al., 2006, 2007, 2008). Recent studies establish that, in men with biochemical failure, IAS offers non-inferior survival, with fewer side effects of therapy and better quality of life (Klotz and Toren, 2012).

Mathematical models of tumor growth are simple but indeed still indicate the complicated interactions involved (Sachs et al., 2001). As far as we know, Jackson first proposed a mathematical model describing prostate tumor growth in the CAS therapy under the assumption that the tumor is a mixed assembly of androgen-dependent (AD) and AI cells (Jackson, 2004). Since then, models of prostate tumor growth under the IAS therapy have been developed to assist in understanding the progression to hormone-refractory prostate cancer, predicting this progression and studying the effects of hormone therapies (Ideta et al., 2008; Shimada and Aihara, 2008; Suzuki et al., 2010; Tanaka et al., 2008, 2010; Tao et al., 2009). Ideta et al., to our knowledge, initially developed a mathematical model of the IAS therapy for prostate cancer based on the CAS model (Ideta et al., 2008). The Ideta model can be described as a hybrid dynamical system incorporating continuous and discrete variables (Ideta et al., 2008; Aihara and Suzuki, 2010). The discrete variables are the upper threshold value of serum prostate-specific antigen (PSA) level to start medication and the lower one to interrupt medication which can switch the two different continuous systems for tumor growth in on-treatment and off-treatment periods (Ideta et al., 2008). By modifying the Ideta model, Shimada and Aihara proposed a model with competitive interactions between AD and AI cells and considered the competition as a candidate mechanism to prevent the AI relapse (Shimada and Aihara, 2008).

Essentially, there are two theories about the AI recurrence of prostate cancer (Isaacs and Coffey, 1981). One is mutation and adaptation: AD cells may mutate into AI cells under the androgen deprived condition. The other is selection and competition: AI cells are minor but exist before the start of the treatment and will win the competition between AD and AI cells to become the dominant cell population under the androgen suppression condition. Natural selection prefers competitors who enhance their fitness at the expense of other competitors' fitness in the game theory (Cleveland et al., 2012). Game theory models have analyzed the hypothesis that tumor cells can adopt genetically determined survival strategies to harm other tumor cells and gain a benefit for themselves (Tomlinson, 1997). In this paper, we assume the survival strategies as the competition advantage of tumor cells and propose a model with competitive interactions between AD and AI cells to mimic the prostate tumor growth in IAS therapy. Our goal is to propose a competition model to investigate the possibility to enhance the relapse prevention by numerical simulations. Further, in consideration of nutrients or inhibitors, we simulate the tumor growth in a finite carrying capacity environment with the competition model including quadratic logistic terms. We will show that the new model can exhibit a successfully IAS-controlled state with the androgen independent net growth rate of AI cells and the eventual stable state of tumor development in a finite environment.

2. Competition model

2.1. Model construction

Here we search a competition model for prostate tumor growth under IAS based on the construction of the Ideta model. The concept of IAS is based on the hypothesis that the maintenance of apoptotic potential by successive rounds of androgen withdrawal and replacement might forestall tumor progression (Hurtado-coll et al., 2002). In the Ideta model, prostate tumor is considered to consist of AD and AI cells. The level of PSA is assumed to be as a biomarker for the prostate tumor growth (Swanson et al., 2001). Thus, the switching on or off the androgen deprivation is based on the level of the serum PSA. We extend the Ideta model to a competition model in consideration of the selection and competition about the AI recurrence of prostate cancer. We assume that AD and AI cells may use different genetically determined survival strategies to enhance their fitness and compete with each other during on-treatment and off-treatment periods, as the tumor cells should have different susceptibilities against the environment (Chandawarkar and Guyton, 2002). Thus, the competition terms presented here are asymmetric and vary with the changing of the environment, which are different from those of the Shimada competitive model. The competition model takes the form:

$$da/dt=-\gamma(a-a_0)-\gamma a_0 u, \tag{1}$$

$$dx_1/dt=\left[\alpha_1 p_1(a)-\beta_1 q_1(a)-\mathrm{m}(a)-f_1(a)x_2\right]x_1, \tag{2}$$

$$dx_2/dt=\mathrm{m}(a)x_1+\left[\alpha_2 p_2(a)-\beta_2 q_2(a)-f_2(a)x_1\right]x_2, \tag{3}$$

$$y=c_1x_1+c_2x_2, \tag{4}$$

$$u=\begin{cases}0\rightarrow 1, \text{when } y=r_1 \text{ and } dy/dt>0,\\ 1\rightarrow 0, \text{when } y=r_0 \text{ and } dy/dt<0.\end{cases} \tag{5}$$

where a, a_0, x_1 and x_2 represent the androgen concentration, the normal androgen level, the population of AD cells and the population of AI cells, respectively. The tumor growth dynamics is described with the changes in the populations of AD and AI cells. The parameter γ dominates the speed of the recovery and decay of the androgen level. In (2), $\alpha_1 p_1$ and $\beta_1 q_1$ represent the proliferation and the apoptosis rates of the AD cells respectively. The mutation rate m means that AD cells mutate into AI cells. The net growth rate of AI cells is determined by the proliferation rate $\alpha_2 p_2$, the apoptosis rate $\beta_2 q_2$ and the mutation rate m. The coefficients α_1, β_1, α_2 and β_2 are the parameters that depend on the metastatic sites, the values of which are obtained from the experimental data (Berges et al., 1995). Herein $f_1(a)x_1x_2$ is the competitive term from AI to AD cells, whereas $f_2(a)x_1x_2$ is the competitive term from AD to AI cells. As a large amount of PSA is secreted by cancer cells, the serum PSA concentration y is defined as $y=c_1x_1+c_2x_2$, where $c_1=c_2=1$ for simplicity. It is assumed that the administration is alternatively either present ($u=1$) or absent ($u=0$). The treatment is suspend (u is changed from 1 to 0) when the serum PSA concentration falls below the lower threshold value r_0 (ng/ml) during on-treatment periods, and it is restarted (u is changed from 0 to 1) when the PSA concentration exceeds the upper one r_1 (ng/ml) ($r_1>r_0>0$) during off-treatment periods.

The net growth rates of AD and AI cells and the mutation rate are dependent on the androgen level, which are defined as the