Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Theoretical Biology 239 (2006) 351–366
Journal of Theoretical Biology
www.elsevier.com/locate/yjtbi

Stochastic modeling of drug resistance in cancer

Natalia Komarova[a,b,*]

[a]Department of Mathematics and Ecology and Evolution, University of California, Irvine, CA 92697, USA
[b]Department of Mathematics, Rutgers University, 110 Ferlinghuysen Road, Piscataway, NJ 08854, USA

Received 28 April 2005; received in revised form 21 July 2005; accepted 1 August 2005
Available online 27 September 2005

Abstract

One of the main causes of failure in the treatment of cancer is the development of drug resistance by the cancer cells. Employing multi-drug therapeutic strategies is a promising way to prevent resistance and improve the chances of treatment success. We formulate and analyse a stochastic model for multi-drug resistance and investigate the dependence of treatment outcomes on the initial tumor load, mutation rates and the turnover rate of cancerous cells. We elucidate the general principles of the emergence and evolution of resistant cells inside the tumor, before and after the start of treatment. We discover that for non-mutagenic drugs, pre-existence contributes more to resistance generation than the treatment phase; this result holds for the case where all drugs are applied simultaneously, and is not applicable for sequential therapy models. The application of mathematical modelling to aspects of adjuvant chemotherapy scheduling. J. Math. Biol. 48(4), 375–422]. Also, we find that treatment success is independent on the turnover rate for one drug, and it depends strongly on it for multi-drug therapies. For low-turnover rates, increasing the number of drugs will increase the probability of successful therapy. For very high-turnover rates, increasing the number of drugs used does not significantly increase the chances of treatment success.

Keywords: Multi-drug therapy; Mathematical model; Targeted drugs; Pre-existence; Treatment success

1. Introduction

One of the main causes of failure in the treatment of cancer is the development of drug resistance by the cancer cells. In general, several causes of drug resistance in cancers have been identified. These include (i) genetic changes/variability, (ii) increased expression of target proteins, (iii) failure of the drugs to enter the target cell and/or drug ejection, (iv) failure of the drugs to reach the target cells. The latter cause is of a geometric nature: depending on the size and location of the tumor, it is possible that the therapeutic agents may not be able to access the target cells, e.g. in large tumors, the central portions may be hard to reach due to limited blood supplies. The other types of resistance listed above are thought to be associated with genetic events that modify cellular phenotype inside the tumor. It is this type of resistance that we will consider in this paper.

There are different approaches to study resistance in cancer. One is of course to understand the molecular nature of resistance. What type of mutations lead to resistance? What are the mechanisms of resistance? Here, experimental research is making rapid advances. The other side of the problem concerns questions like: does resistance pre-exist treatment or is it mostly created during treatment? What is the role of selection in the generation of resistance? How does the likelihood of resistance generation change as we vary the dosage of the drug? How does treatment success depend on the tumor size? How does resistance generation depend on the number if drugs we use? Mathematical modeling can assist in providing answers to these questions.

The first stochastic model of drug resistance was created by Goldie and Coldman (1979), who developed a whole

Abbreviation: CML, Chronic myelogenous leukemia; ODE, Ordinary differential equation; PDE, Partial differential equation

*Corresponding author at: Department of Mathematics, University of California, Irvine, CA 92697, USA. Fax: +1 949 824 7993.
E-mail address: komarova@math.uci.edu.

0022-5193/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2005.08.003

new approach to mathematical treatment of resistance in their subsequent work, see e.g. Goldie and Coldman (1983a, b), Coldman and Goldie (1985), Goldie and Coldman (1985), Coldman and Goldie (1986) and Goldie and Coldman (1998). A number of important theoretical and numerical results have been obtained by the authors for the case of one and more drugs. Since this groundbreaking work, a lot of mathematical models of drug resistance in cancer have been proposed. Several models, including stochastic branching models for stable and unstable gene amplification and its relevance to drug resistance, were explored by Kimmel and Axelrod (1990), Harnevo and Agur (1991, 1993), Axelrod et al. (1994) and Kimmel and Stivers (1994). Methods of optimal control theory were used to analyse drug dosing and treatment strategies (Cojocaru and Agur, 1992; Kimmel et al., 1998; Coldman and Murray, 2000; Swierniak and Smieja, 2001; Murray and Coldman, 2003; Smieja and Swierniak, 2003) (for a review of the optimal control theory in chemotherapy see Swan, 1990). Models for tumor growth incorporating age-structured cell cycle dynamics, in application to chemotherapy scheduling, have been developed by Gaffney (2004, 2005). Mechanistic mathematical models developed to improve the design of chemotherapy regimes are reviewed in Gardner and Fernandes (2003). Jackson and Byrne (2000) extended an earlier PDE model of Byrne and Chaplain (1995) to study the role of drug resistance and vasculature in tumors' response to chemotherapy; in this class of spatial models, the tumor is treated as a continuum of different types of cells which include susceptible and resistant cells. Another class of models is based on the Luria–Delbruck mutation analysis (Kendal and Frost, 1988; Jaffrezou et al., 1994; Chen et al., 2000).

In this paper, we will formulate a stochastic model for multi-drug resistance and investigate the dependence of treatment outcomes on the initial tumor load, mutation rates and the turnover rate of cancerous cells. The main goal of this paper is to elucidate the general principles of the emergence and evolution of resistant cells inside the tumor, before and after the start of treatment. The stochastic model follows the tradition of Goldie and Coldman (1983a) and Coldman and Goldie (1986), and takes this classical work a step further. In particular, it has been possible to include a non-zero death rate for cancer cells and still obtain analytical results. Another difference between the present model and those by Goldie and Coldman (1998) is that instead of a *sequencing therapy*, where no two drugs can be applied simultaneously, we consider a combination therapy where several drugs are applied at the same time. This means that the therapy strategy we consider is different, and it also shifts the focus of the mathematical modeling. In studies by Goldie and Coldman (1998), Gaffney (2004) and other authors, the main objective was to find the optimal sequencing strategy (in terms of dosage and timing) which would maximize the likelihood of treatment success. In the present paper, we are mostly concerned with the question: how does treatment success depend on the tumor size, the turnover rate and the number of drugs used in combination?

The main results of this paper can be formulated as follows:

- For one-drug treatments, the probability of resistance generation before treatment is independent of the turnover rate (we define the turnover rate as the ratio of the natural death rate and the replication rate of cancer cells in the absence of treatment).
- In the case of two or more drugs, the generation of fully resistant mutants in the pre-treatment phase strongly depends on the turnover rate. For larger turnover rates, the probability of pre-existence is larger.
- Pre-existence of resistant mutants plays a more important role than the generation of resistant mutants during therapy. This effect becomes stronger for larger numbers of drugs used. Note that this result holds for the case where all drugs are applied simultaneously, and is not applicable, for instance, for adjuvant therapy models of Gaffney (2004).
- Treatment success is independent on the turnover rate for one drug, and it depends on it for two or more drugs. The dependence is especially strong for high-turnover cancers. For low-turnover rates, increasing the number of drugs will increase the probability of successful therapy. For very high-turnover rates, increasing the number of drugs used does not significantly increase the chances of treatment success.

This paper is organized as follows. In Section 2, we formulate the general stochastic model. In Section 3, we discuss the applicability of our method to different in vitro and in vivo situations. In Section 4, we calculate the rate of generation of resistant mutants before and after the start of therapy; analytical results are obtained in the cases of one and two drugs. In Section 5, we calculate the probability of treatment success depending on various parameters of the system; both analytical and numerical results are presented and parameter values are discussed. Section 6 is reserved for discussion.

2. Cancer growth and generation of mutations

2.1. The basic concept

Let us describe the dynamics of birth, death and mutations in a colony of cells. Because of mutations, there may be cells of different types in a colony. The states of the system are characterized by vectors, where different entries stand for the numbers of cells of each type. We will model the dynamics as a stochastic process which is a sequence of transitions between different states. For each cell in a colony, we assume that there is a certain probability to undergo death, faithful division, division with a mutation, or a transformation (which can be caused by environmental factors or can be a direct consequence of treatment