

Chapter 15

Drug Resistance

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Abstract Drug resistance is a fundamental problem in the treatment of cancer since cancer that becomes resistant to the available drugs may leave the patient with no therapeutic alternatives. In this chapter, we consider the dynamics of drug resistance in blood cancer and the related issue of the dynamics of cancer stem cells. After describing the main types of chemotherapeutic agents available for cancer treatment, we review the different mechanisms of drug resistance development. Various mathematical models of drug resistance found in the literature are then reviewed. Given the well-known hierarchy of the hematopoietic system, it is critical to focus on those cells that have the ability to self-renew, since these will be the only cells able to induce long-term drug resistance. Thus, a recent mathematical model taking into account the complex dynamics of the leukemic stem-like cells is described. The chapter closes with a few applications of this model to chronic myeloid leukemia.

Keywords Drug resistance · Fluctuation analysis · Poisson process · Targeted therapy · Hematopoietic stem cells · Symmetric and asymmetric division · Leukemia · Hyperbolic PDE · Continuous-time branching processes · Probabilistic methods

Introduction

The development of drug resistance is a fundamental problem in the treatment of cancer. The beneficial effects induced by a drug at the beginning of cancer therapy are, more often than not, temporary and are typically lost due to the insurgence of drug resistance. In this chapter, we consider the dynamics of drug resistance in blood cancer and the related issue of the dynamics of cancer stem cells. We review the main biological mechanisms known to cause drug resistance as well as various mathematical models of drug resistance found in the literature. Subsequently, we focus on those leukemic cells that have the key ability to self-renew, that is, the

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leukemic stem cells. A recent mathematical model able to account for the complex dynamics of these cells is introduced and a few applications of this model to chronic myeloid leukemia are presented.

Chemotherapy

Aside for the possible surgical removal of a tumor, chemotherapy is the most common treatment against cancer (transplant, radiotherapy, and immunotherapy being the other major ones). While chemotherapeutic drugs are usually successful at reducing the initial tumor load, their effectiveness is often reduced or even completely lost after a few cycles of treatment. The main reason for their failure is the development of “drug resistance.” To better address the issue of cell resistance to anticancer drugs, we will briefly review what chemotherapy is, how it has evolved in time, and how it works.

A chemotherapeutic drug is, broadly speaking, a chemical compound with the ability to reduce the tumor load. The first modern chemotherapy drug used against cancer was discovered in 1942, when the US government asked two Yale assistant professors, L. S. Goodman and A. Gilman, to study mustard gas, which had been developed and used as a chemical warfare agent in World War I. The two researchers found that nitrogen mustard, an alkylating agent derived from mustard gas, caused a dramatic regression of lymphoma in the patient under study. This discovery led in the late 1940s and early 1950s to the investigation and subsequent use in clinical practice of various compounds: A. Haddow used urethane in chronic myeloid leukemia (CML) patients, J. Burchenal used methotrexate to treat leukemia in children, and S. Farber utilized aminopterin in acute childhood [1, 2]. Since then, many more compounds have been found that are able of producing a significant regression of a tumor load. We can broadly divide the chemotherapeutic agents in the following categories [3]:

- *Alkylating agents* (and variations): By attaching alkyl groups to the guanine base of DNA double-helix strands, they chemically modify a cell’s DNA, thus impairing its function. Indeed, by cross-linking guanine bases in DNA, they make the DNA strands unable to uncoil and separate. DNA replication is impaired and therefore the cell can no longer divide.
- *Antimetabolites*: Chemicals that are similar in structure to metabolites (molecules that are part of the normal cell metabolism) prevent these substances from being incorporated into the DNA during the S phase of the cell cycle (synthesis phase, when DNA replication occurs), consequently stopping normal cell development and division by damaging the DNA strand. In fact antimetabolites masquerade as purines or pyrimidines, molecules that are building blocks of DNA.
- *Plant alkaloids*: By inhibiting the assembly of microtubules they block cell division, due to the fundamental role played by microtubules in a cell.

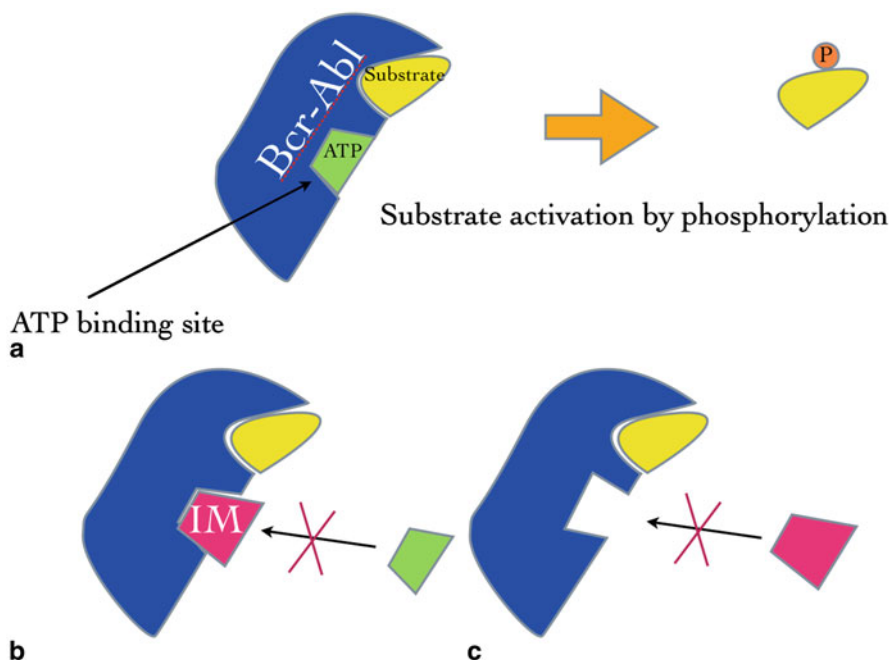


Fig. 15.1 A point mutation causing drug resistance. **a** The bcr-abl enzyme (blue) activates the substrate (yellow) via phosphorylation causing unregulated proliferation among the leukemic cells. **b** Imatinib (red) binds competitively to the ATP binding site inhibiting the enzyme's activity. **c** A point mutation induces a conformational change in the ATP binding site that does not allow imatinib to bind anymore, thus allowing ATP (green) to reach its binding site and therefore resulting in bcr-abl's activity. *ATP* adenosine triphosphate

- *Topoisomerase inhibitors*: By inhibiting topoisomerases, which are essential enzymes that maintain the topology of DNA, they cause damages to the transcription and replication of DNA (interfering with proper DNA supercoiling).
- All these types of drugs do not differentiate between cancer and normal cells, with the resulting well-known toxic effects. However, the inhibition of cell division or the interference against DNA replication is expected to harm cancer cells more than healthy cells, given that cancer cells should divide more often than normal.
- *Targeted therapies*: In the past decade, new and less toxic drugs have been designed to target only a particular molecular attribute that characterizes a given type of cancer cell and not its healthy counterpart. Imatinib mesylate, for example, works by inhibiting the bcr-abl enzyme activity (see Fig. 15.1), which characterizes CML cells [4, 5]. Because of the potential of these new therapies, we are witnessing the rise of a new discipline, molecular oncology, whose focus is to understand the genetic and biochemical mechanisms involved in cancer [6].

The Biology of Drug Resistance

A general phenomenon for all standard chemotherapeutic agents is that successive applications of the treatment will yield decreasing therapeutic benefits due to the development, in the cancer cells, of resistance to the drug. Thus, while standard chemotherapy has proven to be effective in the treatment of a few types of cancer—such as lymphomas, germ cell, and some pediatric malignancies—in the majority of cases the results are modest [6]. Even for the new and promising targeted therapies, the development of drug resistance constitutes a fundamental problem. For example, in CML patients, the occurrence of specific mutations in the bcr-abl domain of the leukemic cells will result almost invariably in the relapse of the disease due to the lost effectiveness of imatinib [7]. We briefly summarized here some of the various classifications of drug resistance. For a more comprehensive overview, we refer to the book by Teicher [8] and to the references therein. For a comprehensive treatment of drug resistance to targeted therapies, we refer to the book by Daniel [9].

Resistance may be *relative* or *absolute*. Relative resistance refers to cases where the level of resistance of a cancer cell depends on the drug's dosage: the higher the dosage the less probable for the cell to be resistant. With absolute resistance instead, no matter what the dose is, the drug will not affect the resistant cell. In general, resistance to standard chemotherapy appears to be relative [1, 10, 11]. Drug resistance can be both a *spontaneous* phenomenon (e.g., caused by random genetic mutations which occur independently and even before the drug is administered, as we will see) as well as an *induced* one, which means that drug resistance may originate as a consequence of taking a drug [12–14]. Drug resistance depends on many factors. We may divide them broadly into two categories [8, 15]:

- *Physiological resistance*, which depends on host factors, like, for example, the size, location, and growth rate of the cancer, the blood supply, the immune system status, the tumor microenvironment, the tumor pH, or the patient's intolerance to the effects of a drug. Location resistance is also known as diffusion resistance.
- *Biological resistance*, given by kinetic resistance or genetic and epigenetic alterations in the cancer cells.

In the following, we will focus only on the second kind. *Kinetic resistance* refers to the reduction in effectiveness of a drug caused by the cell division cycle. Such resistance is generally only temporary. As we have seen, many standard chemotherapeutic drugs (such as methotrexate, vincristine, and cytosine arabinoside, to name a few) are effective during only one specific phase of the cell cycle, e.g., during the S phase when the DNA is synthesized. Thus, in the case of a short exposure to the drug, the cancer cell will not be affected if it is found in a different phase. Even more importantly, the cell will be substantially invulnerable if it is out of the cell division cycle, i.e., in a “resting state” or G_0 state. This implies that the number of cells that are affected by the drug is lower for cell populations that have low proliferation rates.

Resistance to drugs may instead develop as a consequence of genetic events such as mutations, rather than developing due to kinetic reasons. This category includes both point mutations and chromosomal mutations, also known as gene amplifications.

Point mutations are genetic changes causing the replacement of a single base nucleotide or pair with another nucleotide or pair in the DNA or RNA. These mutations may occur, for example, during DNA replication. If the mutation is nonsynonymous, it will change the cellular phenotype possibly making the cancer cell resistant to the drug. A major reason for the development of resistance to imatinib in CML patients is due to point mutations that alter the adenosine triphosphate (ATP) binding site of bcr-abl, which is the specific binding target of imatinib, thus inhibiting the activity of the drug [4, 5, 7]. This mechanism is depicted in Fig. 15.1.

Gene amplification is either the consequence of an abnormally large number of copies of a particular gene or the result of an overproduction of transcripts of particular gene. This means that a limited portion of the genome is reproduced to a much greater extent than the replication of DNA composing the remainder of the genome. Such a defect amplifies the phenotype that the gene confers on the cell, which, in turn, induces resistance by essentially providing the cells with more copies of a particular gene than the drug is able to cope with. The classical example is given by the amplification in the number of efflux transporters a cell is endowed with, thus increasing the ability of the cell to eliminate, expel the drug. While gene amplification (and consequently the resistance induced by it) may be a temporary phenomenon, point mutations appear to be permanent.

The cause for genetic mutations is not completely clear. Is it a random phenomenon, possibly occurring even before the therapy is started, or rather a drug-induced, directed one, perhaps both? Such a fundamental question has been the focus of the Nobel Prize winning work of Luria and Delbrück [16]. Using fluctuation analysis, Luria and Delbrück showed that drug resistance in *in vitro* bacterial cultures is primarily a random phenomenon rather than a drug-induced, directed one. Many further *in vitro* experiments with tumor cell lines confirmed this result. *In vivo* experiments have instead provided somewhat contradictory results, with some results supporting and others opposing the idea of drug resistance being a random phenomenon, see references [2, 17].

Mathematical Models of Drug Resistance

Drug resistance has been extensively studied in the mathematical literature. Originally, the modeling of resistance due to random point mutations was motivated by the experimental findings of Luria and Delbrück in 1943 on the development of resistance to antibiotics in bacteria due to mutations [16]. The mathematical model the authors formulated in order to answer that fundamental question was then used for estimating the rate at which mutations causing resistance occurred. In that model, Luria and Delbrück assumed that the process starts with one normal cell and no mutants. A random process, specifically a Poisson process with an intensity function,

modeled the occurrence of mutations. Importantly, both normal and mutant cells were assumed to grow deterministically in an exponential fashion. The probability of no mutations was then calculated as well as the mean and the variance of the distribution of the number of mutants [16]. Given these estimates, it was possible to implement methods for the estimation of mutation rates from the data. This Nobel Prize winning work has been followed by a large literature on the study of the distribution of the number of mutants in a population which grows exponentially, known as the Luria and Delbrück distribution [18].

The first model of resistance to chemotherapy due to point mutations in cancer is the celebrated model by Goldie and Coldman and its extensions [2, 19–24].

In Goldie and Coldman [21], the growth of the drug-sensitive cancer cell population was approximated by using a deterministic exponential curve. At each division, it was assumed that there is a small positive probability that a cancer drug-sensitive cell may give rise to one drug-resistant cancer cell daughter because of a random point mutation. Such a mutant generated a clone growing according to a birth process. A Poisson distribution approximated the number of mutations occurring in the drug-sensitive population at any given time. It was also assumed that back mutations could not occur. Then, by using a filtered Poisson process, it was possible to calculate the number of mutants present in the cancer cell population. The probability of having no resistant cells present in a tumor was then calculated, where the nonexistence of resistant cells was assumed to be the condition for being cured. We note that in the model by Goldie and Coldman, the drug-sensitive population is modeled deterministically as in Luria and Delbrück [16], but the drug-resistant population is modeled stochastically rather than deterministically. The main results of Goldie and Coldman are that the probability of having no drug resistance present in a tumor is inversely related to the tumor size and that more frequent dosage repetitions are more successful in minimizing the risk of drug resistance development than less frequent doses administered for a longer period of time [21]. In Coldman et al., the authors extended the model to multi-drug resistance. It was assumed that multiple drug resistance occurred in single step where now a cancer cell may be sensitive to all drugs, resistant to only one of the drugs, to two given drugs, and so forth [23, 24]. The main conclusion of their study was that the best strategy was to use all available drugs simultaneously. Furthermore, it was shown that, if the simultaneous administration of all drugs is not possible, the sequential alternation of all drugs is optimal when these drugs are equally effective. Goldie and Coldman extended their mathematical model to consider also the development of drug resistance when the cancer stem cell hypothesis is considered [2, 22]. Unfortunately, they assumed that a stem cell could either renew symmetrically, producing two daughter stem cells, or differentiate symmetrically, producing two differentiated (not stem cells) daughters. In this way, the two division modes are simply equivalent to either a stem cell birth or death, leaving out from the stem cell dynamics the fundamental case of an asymmetric division, where a stem cell and a differentiated daughter cell are produced. Their model then reduces to the usual birth and death process of a growing population. Notwithstanding this limitation, their model was the first model on drug resistance that somehow considered the cancer stem cell dynamics.

A more recent study on random point mutations is by Komarova et al. [25–28]. For example, a model based on stochastic birth and death processes on a combinatorial mutation network was used to describe the development of resistance to multi-drug treatments [25, 27]. Thus, probabilistic methods and a hyperbolic partial differential equation were used to show how the pretreatment phase is more significant in the development of drug resistance than the treatment phase. This is a very natural, intuitive result given that the treatment will, in general, drastically reduce the cancer cell population and consequently also reduce the number of cell divisions from which random point mutations may arise. The main result obtained by the author is the following: In the case of a single-drug treatment, the probability to have resistant mutants generated before the beginning of the treatment and present, including their progeny, at some given time afterward, does not depend on the cancer turnover rate contrary to the multidrug scenario [25]. A consequence of such result would also be that the probability of single-drug treatment success would not depend on such a rate. In Tomasetti et al., however, it has been shown that this result does not hold for finite times (those of biological interest), especially if the difference between the death and the birth rate of the cancer cells is small [29]. Komarova et al. used the same methodology to analyze the development of resistance in CML [26, 27]. The authors suggested that a combination of three drugs with different specificities might overcome the problem of resistance [27]. At the same time, they observed that combining more than two current drugs may not provide any further therapeutic advantage, due to the problem of cross-resistance [26].

Another recent work on point mutations is by Iwasa et al. [29]. Continuous-time branching processes were used to calculate the probability of resistance at the time of detection of the cancer, as well as the expected number of mutants found at detection if resistance developed. These estimates were found both for the case where drug-sensitive and drug-resistant cells have the same birth and death rates as well as for the cases where the drug-resistant cells have a fitness advantage or disadvantage with respect to the wild-type cancer cells. Similarly to the results [21], the authors showed that the probability of resistance is an increasing function of the detection size and the mutation rate [29].

Finally, Durrett et al. used multi-type branching processes to study multi-drug resistance, obtaining estimates for the distribution of the first time when k mutations have accumulated in some cell, as well as for the growth of the various subpopulations of mutant cells [30].

While we will not consider the modeling of drug resistance due to gene amplification, kinetic resistance, drug-induced or physiological resistance, we would like to briefly comment on some of the works on these types of resistance and refer interested readers to the references therein. Modeling of resistance due to gene amplification can be found, e.g., in [31–33]. Drug resistance in these works is studied using stochastic branching models. Kinetic resistance has been mathematically studied in [34, 35]. The models in these papers are based on ordinary differential equations. An alternative approach on kinetic resistance, using age-structured models, can be found in [36–40]. Instead, for mathematical models and experimental findings on drug-induced resistance, we refer to [14, 41, 42].

A Model of Drug Resistance for Leukemias: Including the Dynamics of Leukemic Stem Cells

In the previously mentioned mathematical models of drug resistance, cancer cells are considered as a homogeneous population (aside from being or not drug resistant). In fact, cancer cells will typically differ in size, morphology, division rate, death rate, and resistance to a given drug [43, 44]. This diversity is caused by genetic differences, as well as by epigenetic plasticity [45].

Blood constitutes possibly the best example of a tissue with a large variety of cell types, and where homeostasis is maintained by a small subset of slowly replicating cells, known as the hematopoietic stem cells. These cells have the capacity of both self-renewal and differentiation into more mature—and much shorter lived—differentiated blood cells. From the point of view of drug resistance, this hematopoietic hierarchy implies that only the cancer cells that have the capacity for self-renewal can propagate long-term drug resistance. Therefore, these cancer cells should be taken into account in any model of drug resistance. In fact, only these cells should be taken into account. Note that this is true even if cancer stem cells were to be always drug resistant due to some intrinsic property related to their stemness.

Tomasetti et al. modeled drug resistance by focusing on the dynamics of a growing leukemic stem cell population where all their possible modes of division are included: symmetric self-renewal, asymmetric division, and symmetric differentiation [46]. We will review this model in some detail.

Consider the following question: What is the probability that by the time a patient is diagnosed with, e.g., CML some of the leukemic stem cells (LSCs) have been already hit by specific point mutations causing these cells and all their progeny to be resistant to a given targeted therapy? Since point mutations seem to represent the main cause of resistance to targeted therapies and since it appears that the main effect of these therapies on leukemic stem cells is cytostatic, it follows that an answer to the above question is the key in order to understand what is the probability, for a newly diagnosed CML patient, to incur in a later relapse of the disease due to the development of resistance to the treatment.

If we assume for simplicity that point mutations occur randomly during DNA replication, and letting u be the probability that when a leukemic stem cell divides one of its daughter cells will carry a point mutation, we can think about this problem as depicted in Fig. 15.2.

Denote by $S(t)$, the total number of wild-type LSCs present in a patient at time t . Denote by l and d , the rates at which LSCs divisions and deaths occur, respectively. Also, denote by a , b , and c the probabilities that a cell division will be asymmetric, symmetric differentiation, or symmetric self-renewal, respectively (thus $a + b + c = 1$).

The average dynamics of the wild-type LSC population can then be described by the following equation:

$$\frac{dS(t)}{dt} = \left[l(1-u)(1-a-b) - \left(d + bl + \frac{ual}{2} \right) \right] S(t) \quad (15.1)$$

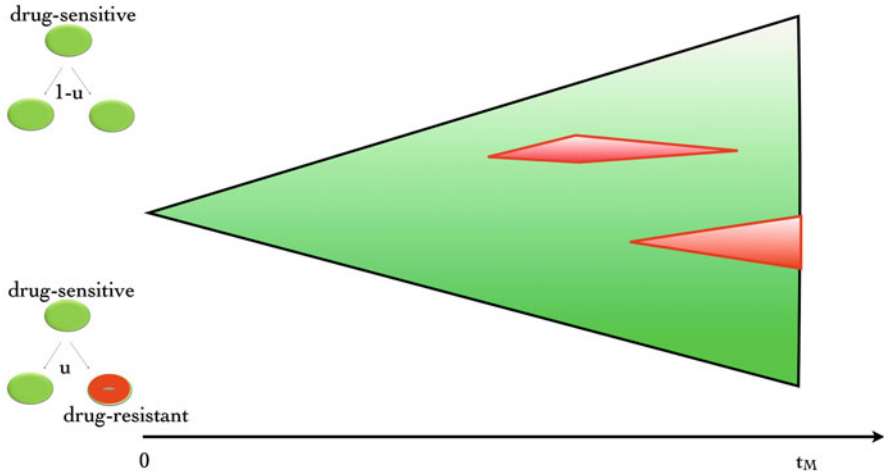


Fig. 15.2 Clonal expansions. The wild-type leukemic stem cells expansion (*in green*) from the first LSC, at time 0, up to the time of diagnosis t_M . Mutated LSCs subclones (*in red*) may appear and go subsequently extinct or grow and be present at the time of diagnosis. The model estimates the probability of having mutated LSCs (*red*) at time t_M . LSC leukemic stem cell

Indeed, the wild-type population grows only when a symmetric self-renewal without mutations occurs, an event of probability $(1 - u)(1 - a - b)$, while it decreases due to cell death, symmetric differentiation, or when the stem cell daughter of an asymmetric division is hit by a mutation. Since u is very small ($< 10^{-6}$ in CML), we can approximate the above equation by

$$\frac{dS(t)}{dt} = [l(1 - a - 2b) - d] \cdot S(t) \tag{15.2}$$

By solving Eq. (15.2), we find that the average time for which the wild-type LSC population will consist of x cells is

$$t_{x+1} - t_x = \frac{\ln(1 + 1/x)}{l(1 - a - 2b) - d}, \tag{15.3}$$

where t_x is the time at which the population reaches size x . Thus, the average number of mutations occurring while $S = x$, which we defined as m_x , is given by multiplying the number of cells present at that time by the mutation rate and by the average time for which $S = x$,

$$m_x = xul(1 - a/2 - b) \frac{\ln(1 + 1/x)}{l(1 - a - 2b) - d} \approx \frac{ul(1 - a/2 - b)}{l(1 - a - 2b) - d} \tag{15.4}$$

since $x \ln(1 + 1/x) \rightarrow 1$. It is important to note that m_x is not a function of x .

Now, we will use branching processes [47] to model the mutant LSCs. Let M and T be the total number of wild-type and mutated LSCs present in a patient at the time of diagnosis, respectively, and let G_T be the probability generating function of T .

Then

$$G_T(\xi) = E[\xi^T] = E[\xi^{K_1+\dots+K_{M-1}}] = E[E[\xi^{K_1}|r_1]] \cdots E[E[\xi^{K_{M-1}}|r_{M-1}]]], \quad (15.5)$$

where K_x is the number of mutated LSCs that are present at the time of diagnosis, t_M , and whose originating mutations (r_x being their total number) occurred when $S=x$. Letting r_x be Poisson with mean m_x we obtain

$$G_T(\xi) = \prod_{x=1}^{M-1} \sum_{r_x=0}^{\infty} \left(\frac{m_x^{r_x}}{r_x!} e^{-m_x} g_x(\xi)^{r_x} \right) = \exp \left(- \sum_{x=1}^{M-1} m_x [1 - g_x(\xi)] \right), \quad (15.6)$$

where $g_x(\xi)$ is the probability generating function, at time t_M , of a mutant clone originated when $S=x$.

To find $g_x(\xi)$, we let $g_x(\xi, t)$ be the probability generating function, at time t , of a mutant clone originated when $S=x$. Here, time is measured from the time of occurrence of the originating mutation. Then, this generating function satisfies the Kolmogorov backward equation

$$\frac{\partial g}{\partial t} = l(1-a-b)g^2 + (d+bl) - (l(1-a-b) + d+bl)g. \quad (15.7)$$

Solving the above partial differential equation and noting that

$$M \approx x e^{l(1-a-2b)-d]t_{M-x}}, \quad (15.8)$$

where, t_{M-x} is the average time it takes for the wild-type LSCs to go from x to M , we find that

$$g_x(\xi) = g_x(\xi, t_{M-x}) \approx \frac{(\xi - 1) \left(\frac{d+bl}{l(1-a-b)} \right) \frac{M}{x} - \left(\xi - \frac{d+bl}{l(1-a-b)} \right)}{(\xi - 1) \frac{M}{x} - \left(\xi - \frac{d+bl}{l(1-a-b)} \right)}, \quad (15.9)$$

Plugging Eq. (15.9) in Eq. (15.6), we find that the probability, P_R , that at the time of detection, t_M , there are already present some mutated, drug resistance LSCs given by

$$P_R = 1 - G_T(0) \approx 1 - \exp \left(-uM \left(\frac{1-a/2-b}{1-a-b} \right) \frac{1}{C} \ln \frac{1}{1-C} \right), \quad (15.10)$$

where

$$C = \frac{d+bl}{l(1-a-b)}. \quad (15.11)$$

Moreover, it is now possible to calculate, from the probability generating function G_T , the various moments of the distribution of resistant LSCs. For example, the expected value at the time of diagnosis is given by

$$E[T] = G'_T(1) \approx uM \ln(M) \left(\frac{1-a/2-b}{1-a-2b-d/l} \right). \quad (15.12)$$

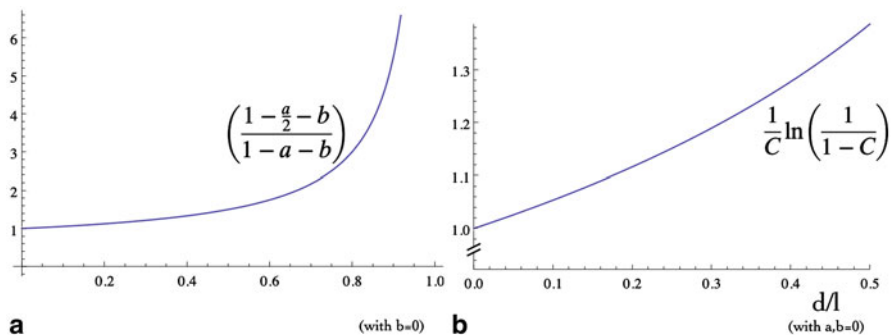


Fig. 15.3 Modes of division versus turnover rate. Plots of the given mathematical expressions, as functions of the parameter a (left), and of the turnover rate d/l (right)

In Fig. 15.3, where two key parts of the formula given in Eq. (15.10) are depicted, we can observe the important role played by the mode of division chosen by the LSCs in determining the amount of drug resistance generated before the start of the therapy. In fact, the first expression changes considerably, going from 1 to values above 6 (for realistic values of the parameter a), while the range for the second expression (accounting for the influence of the turnover rate d/l) is much smaller. Thus, it is fundamental to account for the mode of division chosen by the stem cells in any model of drug resistance development.

Applications of the Model

We will briefly consider two applications of the above model, both to CML.

A first straightforward application considers the effects that a targeted therapy, like imatinib, has on the LSCs. Assume that, when the therapy starts, the drug does not affect the LSC population dynamics at all, i.e., assume that the LSCs are insensitive to the drug. This has been the established point of view in the medical literature, and a mathematical model has been often used to support this hypothesis [48]. Interestingly, the mathematical model had that hypothesis included among its assumptions.

If this hypothesis were to be correct, then the LSC population will continue to grow also after the start of the therapy, beyond the number present at the time of detection given by M in Eq. (15.10). Therefore, the probability of developing LSCs resistant to the drug would continue growing, according to the formula found in Eq. (15.10). But this clearly contradicts the evidence observed in the data coming from long clinical trials [49]. Thus, it must be that imatinib also affects the LSC population [50].

A second nontrivial application considers the preferred mode of division of leukemic stem cells in CML. We have already seen that the mode of division chosen

by the cancer stem cells will dramatically affect the dynamics of the tumor's growth as well as the generation of drug resistance due to random point mutations. Interestingly, there appears to be a link between symmetric self-renewal and an inherent risk of cancer [51], while it has been observed that the preferred mode of division of healthy hematopoietic stem cells is given by asymmetric division: Their probability to divide asymmetrically, given by the parameter a in Eq. (15.10), has been estimated to be close to one, and generally $a > 0.9$ [52, 53]. By using again the data coming from the International Randomized Study of Interferon and STI571 (IRIS) clinical trial [49], it is possible to show that the amount of resistance found among patients is too small for the parameter a in the formula of Eq. (15.10) to be close to one. We must rather have $a < 0.5$ (see [46] for further details). Thus, the model allows us to infer that the LSCs should have a much lower than normal tendency to divide asymmetrically hence indicating a substantial shift toward an increased symmetric self-renewal among leukemic stem cells.

Conclusions

We have reviewed a few elements of the basic biology behind the development of drug resistance in cancer and some of the mathematical models found in the literature. Given the key role played by cancer stem cells in carrying long-term drug resistance, we have analyzed in some detail a recent stochastic model that includes the dynamics of stem cells among its elements, and a few applications of this model to CML have been considered. Interestingly, the formulas obtained with this model have also been recently used in predicting drug resistance to targeted therapy in colorectal cancer [54]. In conclusion, mathematical modeling has proven to be a useful tool for analyzing the dynamics of drug resistance.

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