Cell Dynamics in the Wound Healing Process in Tumor Environment After Treatments

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Abstract

Although the failure of cancers treatments has been mostly linked with the existence of resistant cells or cancer stem cells, new findings show a significant correlation between circulating inflammatory biomarkers and treatment failures. Most cancer treatments cause necrotic cell deaths in the tumor environment. Necrotic cells send signals to the immune cells to start the wound healing process in the tissue. Therefore, we assume after stopping treatments there is a wound that needs to be healed. The stochastic simulations of epithelial cell dynamics after a treatment, which only kills cells without changing the tumor's inflammatory environment, show that higher fitness of cancer cells causes earlier relapses. Moreover, the tumor returns even if a single cancer cell with high fitness remains in the wound's boundary after such treatments. Although the involvement of cancer cells in the wound healing after treatments leads to the fast relapse, the cancer cells outside of the wound can also cause a slow recurrence of the tumor. Therefore, the absence of relapse after such treatments implies a slow-developing tumor that might not reach an observable size in the patient's lifetime. Conversely, a large solid tumor in a young patient suggests the presence of high fitness cancer cells and therefore a high likelihood of relapse after conventional therapies. Additionally, the location of remaining cancer cells after treatments is a very important factor in the recurrence time. The fastest recurrence happens when a high fitness cancer cell is located in the middle of the wound. However, the longest time to recurrence corresponds to cancer cells located outside of the wound's boundary.

Highlights

- The tumor's recurrence time depends on the location of remained cancer cells after treatments as well as their fitness.
- The fastest recurrence happens when a high fitness cancer cell is located in the middle of the wound.
- The tumor returns even if a single cancer cell with high fitness participates in the wound healing process after treatments.
- The absence of relapse after cancer treatments implies a slow-developing tumor that might not reach an observable size in the patient's lifetime.
- A large solid tumor in a young patient suggests the presence of high fitness cancer cells and therefore a high likelihood of relapse after conventional therapies.

Introduction

Failure of traditional cancer therapies has been observed in almost all inflammatory cancers, and the high level of circulating inflammatory biomarkers is highly associated with the failure of treatments [1]. Some scientists argue that the reason behind the treatments' failures might be the existence of resistant cells or cancer stem cells [2]. Here, we suggest another possible reason, which is based on the wound healing process in the tumor micro-environment after the treatments. Unnaturally dying cells send signals to the immune system to replace them and cure the wound. One of these damage-associated molecular pattern (DAMP) molecules, which triggers inflammation and immunity, is extracellular high mobility group box 1 (HMGB1) [3]. HMGB1 is passively released from necrotic cells, or actively secreted from stressed cancer cells and immune cells [4]. It has been observed that the release of HMGB1 in response to chemotherapy in leukemia increases resistance to the therapies [5]. Moreover, binding of HMGB1 to toll-like receptor 4 (TLR4) on dendritic cells (DCs) causes early relapse after chemotherapy in breast cancer patients [6]. High levels of HMGB1 have also been observed in patients with non-small cell lung cancer (NSCLC) after tumors removed by surgery. In addition, significantly high levels of both HMGB1 and transition factor p65 were seen in NSCLC tumors with node metastasis [7]. Nasopharyngeal carcinoma (NPC) patients with high levels of HMGB1 expression had poor overall, disease-free survival [8]. These insights imply that most common cancer therapies such as surgery, radiation, and chemotherapy cause necrotic cell death [9], which activates the immune system in the same way as the wound-healing process [10].

In addition, in one experiment, human ovarian cancer cells were added to bone marrow cells recovered from irradiated mice with 1000 cGy. The irradiated bone marrow cells significantly increases proliferation of human ovarian cancer cells compared to non-irradiated ones [11]. Furthermore, micro-metastases in bone marrow are frequently observed after chemotherapy, and their existence significantly reduces the survival rate [12].

In summary, the most common cancer therapies generate a wound in the tumor by producing necrotic cell death. Necrotic cells in the tumor microenvironment activate the immune system to initiate the wound healing process. In many tumors, epithelial cells are adapted to divide in a much higher rate than normal cells; for example, tumor suppressor genes are inactivated. Moreover, in some cancers, like colitis associated cancer, there are some immune deficiencies, and immune cells are adapted to send a high level of proliferation or angiogenesis signals [13,14]. If the tumor includes adapted tissue or/and adapted immune cells, these adapted cells start the wound healing process in the tumor microenvironment. Adapted activated immune cells send more signals of proliferation and/or angiogenesis than normal cells [15]. Furthermore, if there were adapted tissue cells, they would divide at a much higher rate in response to these signals than normal cells. Thus, not only would the tumor come back after the treatment, but it would also grow more aggressively.

Recently, several mathematical models have been designed to study cell dynamics in normal tissue as well as tumors. Some stochastic models were also developed to investigate the cell dynamics in the process of tumor formation [16–21] . Although there are mathematical models studying the wound healing process [22–24], there are not many computational studies about the wound healing process after stopping treatments. In this paper, we develop two stochastic models (spatial and non-spatial) for cell dynamics

after a treatment, which kills epithelial cells. We apply a stochastic model, because cell dynamics are stochastic, but we also obtain a deterministic model which approximately predicts the results of the non-spatial stochastic algorithm. We assume after the treatment there is a wound that needs to be healed. We denote the fitness of cancer cells over the normal cells by r. Briefly, assuming two cells: one cancerous and one normal, receive proliferation signals to fill out an empty location, then the probability that the cancer cell divides is r times the normal one. Vermeulen et al. [25] obtained the probability P_R that a mutant stem cell replaces its neighbor for various mutants; $P_R(Kras^{G12D}\ v.s.\ WT) = 0.78$, $P_R(Apc^{+/-}\ v.s.\ WT) = 0.62$, $P_R(Apc^{-/-}\ v.s.\ WT) = 0.79$, under the normal condition $P53^{R172H}$ did not confer a benefit $P_R^{norm}(P53^{R172H}\ v.s.\ WT) = 0.48$, however in colitis $P_R^{colits}(P53^{R172H}\ v.s\ WT) = 0.58$. The fitness r in our model is given by $\frac{P_R}{1-P_R}$, thus $r(Kras^{G12D}) = 3.5$, $r(Apc^{+/-}) = 1.6$, $r(Apc^{-/-}) = 3.8$, $r^{norm}(P53^{R172H}) = 0.9$, and $r^{colits}(P53^{R172H}) = 1.4$. Therefore, in this work the fitness of cancer cells are assumed to be $r = 3.8$ (advantageous), $r = 1$ (neutral), and $r = 0.9$ (disadvantageous). The simulations show that if $r > 1$, then a single cancer cell would outcompete 100 normal cells and take over the entire tissue.

Materials and Methods

Two stochastic models (non-spatial and spatial) are developed to simulate the recovery of cells after a treatment, which kills most of the cancer cells. The number of cancer cells and non-cancer cells at a given time t are respectively denoted by $C(t)$ and $N(t)$. The initial time at this simulation is right after stopping the treatment. The model's assumption is that after treatments there is a wound, and cells start to divide to heal the wound, and reach approximately their normal number D. In other words, there are empty spaces that need to be filled via cells divisions, i.e. around $D - N(0) - C(0)$ cells need to be produced. At each updating time step, with probability $p_{div} = \frac{D^{10}}{D^{10}+(C(t)+N(t))^{10}}$ a cell divides, and with probability $1 - p_{div}$ a cell dies. The probability division function p_{div} is designed in such a way that if the total number of cells is less than D, then the division rate is much higher than death rate. However, when the total number of cells is approximately D, then the probability that a division happens is the same as the probability that a death occurs. Moreover, when a cell dies, with probability $p_d = \frac{rN(t)}{rN(t)+C(t)}$, a non-cancer cell dies, or a cancer cell dies with probability $\frac{C(t)}{rN(t)+C(t)}$. That means, higher fitness (i.e. higher probability of division) of cancer cells leads to the lower probability of their death. In this simulation, each updating step is the time that a change happens in the whole system, i.e. a cell divides or a cell dies. If a cell cycle is approximately 2 days, then the updating time t corresponds to approximately $\frac{2t}{n}$ days, where n is the total number of cells.

Non-spatial model

The ratio of fitness of cancer cells to the normal cells is denoted by r. That means if a division happens at updating time t, with probability $p_c = \frac{rC(t)}{rC(t)+N(t)}$, a cancer cell divides and with probability $\frac{N(t)}{rC(t)+N(t)}$, a non-cancer cell divides. At each updating time step, we run the following algorithm:

- With probability $p_{div} = \frac{D^{10}}{D^{10}+(C+N)^{10}}$ a cell divides:

  - With probability $p_c = \frac{rC}{rC+N}$, this division is the division of a cancer cell.
  - Or, with probability $1 - p_c$, this division is the division of a non-cancer cell.

- Or, with probability $1 - p_{div}$ a cell dies:
  - With probability $p_d = \frac{rN}{rN+C}$, this death is the death of a non-caner cell.
  - Or, with probability $1 - p_d$, it is the death of a cancer cell.

After repeating the above algorithm for T updating time steps, we calculate the ratio of number of mutants over the total number of cells. Since this simulation is a stochastic model, we run the whole algorithm $10,000$ times and we obtain the mean and standard deviations.

At each updating time step t, the number of cancer cells $C(t)$ and non-cancer cells $N(t)$ can be approximately obtained by the following deterministic system of equations.

$$\begin{aligned}\frac{dC}{dt} &= p_{div}p_c - (1-p_{div})(1-p_d)\\ &= \frac{D^{10}}{D^{10}+(C+N)^{10}}\frac{rC}{rC+N} - \frac{(C+N)^{10}}{D^{10}+(C+N)^{10}}\frac{C}{rN+C}, \qquad (1)\\ \frac{dN}{dt} &= p_{div}(1-p_c) - (1-p_{div})p_d\\ &= \frac{D^{10}}{D^{10}+(C+N)^{10}}\frac{N}{rC+N} - \frac{(C+N)^{10}}{D^{10}+(C+N)^{10}}\frac{rN}{rN+C}. \qquad (2)\end{aligned}$$

At the steady state of this system of equations, all cells are cancer cells (i.e. $N = 0$ and $C = D$), if $r > 1$, and if $r < 1$, then all cells become normal cells, (i.e. $N = D$ and $C = 0$).

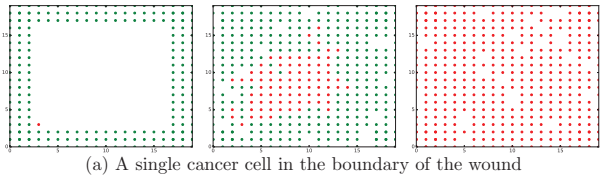
Spatial model

A two dimensional lattice for the tissue is designed. The assumption is cells at the middle of the lattice are missing because of treatments. Note, necrotic cells send signals to the immune cells to start the wound healing process. Moreover, necrotic cells directly send signals of proliferations to the nearby cells. For this reason, in this algorithm, only cells in the boundary of the empty spaces are dividing to replace missing cells. In other words, if the cell at the location (i, j) is missing, then any available cell at the locations $\{(i-1, j-1), (i-1, j), (i-1, j+1), (i, j-1), (i, j+1), (i+1, j-1), (i+1, j), (i+1, j+1)\}$ has a chance to divide to fill out the location (i, j). For example in Figure 1 (a), only cells located at $\{(3, 3)\} \cup \{(i, 2) \ : \ 3 \leq i \leq 17\} \cup \{(i, 17) \ : \ 2 \leq i \leq 17\} \cup \{(2, j) \ : \ 2 \leq j \leq 17\} \cup \{(17, j) \ : \ 2 \leq j \leq 17\}$ have a chance to divide in the first updating time step.

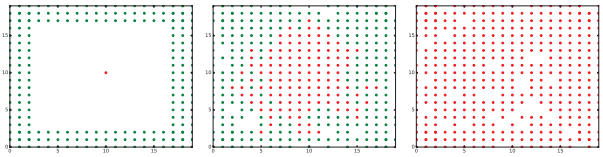
The best case scenario that can happen after the treatments is modeled in both non-spatial and spatial simulation. In the best case scenario, after the wound has been healed cells follow the normal homeostasis, i.e. the death rate is approximately the same as the division rate.

Results

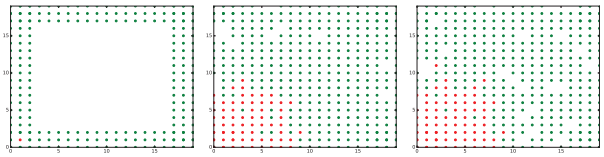
In this work, we model the cell dynamics in the tumor microenvironment after stoping treatments, which cause a wound in the tissue. Right after stopping treatments, the division rate is high because the tissue wants to reach its normal concentration. We assume the best case scenario happens and cells go toward the normal homeostasis during the wound healing process. In other words, the tissue follows the normal cell division and death rates after the wound has been healed. Thus, the total number of cells stays approximately constant after the wound has been healed. However, the progeny of cancer cells left after treatments are able to take over the entire tissue, and cause the recurrence of the tumor. Therefore, we denote the time that more than 99% of the tissue cells are cancer cells as the relapse time. In the spatial model, the wound is placed in the center of a grid and cells are located at the boundary of the wound. In order to obtain the effect off the location of cancer cells, at each simulation a single cancer cell is located in a specific location; center, border, or outside of the wound (See Figure 1). In this model, only cells located near an empty space are able to divide, and any cell can go toward the normal cell death. However, in the non-spatial model, all cells are able to divide and die. In both models, the number of empty spaces and the number of desired cells, i.e. the normal tissue's size, is respectively denoted by E and D.



(a) A single cancer cell in the boundary of the wound



(b) A single cancer cell in the middle of the wound

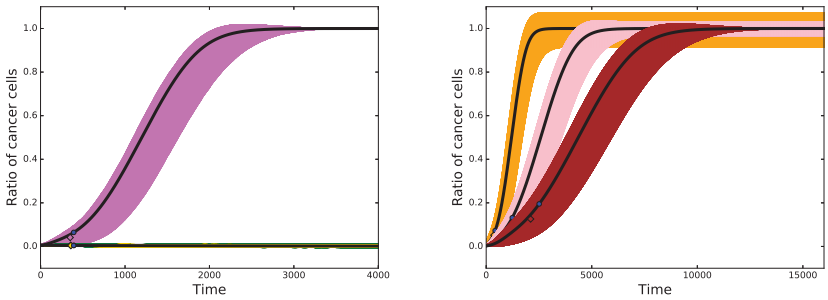


(c) A single cancer cell outside of the wound's boundary

Figure 1. Spatial model. This figure shows the cell dynamics in the wound healing process after treatments. At the initial time of these simulations, a single cancer cell is located in the boundary of the wound (sub-figure (a)), in the center of the wound (sub-figure (b)), or outside of the wound's border (sub-figure (c)). The left plots show the initial time of simulations. The middle plots indicate the healing time, and the plots in the right show the final time of simulations, which corresponds to $T = 2000$ number of updating time steps. In this figure, red circles are cancer cells, and green circles are normal cells. The fitness of cancer cells in these simulations is $r = 3.8$.

High fitness of cancer cells leads to fast relapse

Our stochastic models show that the time to recurrence is a decreasing function of the fitness of cancer cells. In other words, if cancer cells have high fitness then the tumor would reappear after stopping the treatments in a very short time. Figure 2(a) shows the effect of the fitness of cancer cells left after treatments in the time to relapse for non-spatial model. Although the disadvantageous cancer cells, i.e. the cancer cells with fitness less than one, will be removed from the tissue, the advantageous cancer cells will always take over the wound and then the entire tissue. High fitness cells that are involved in the wound healing process will rapidly divide, and fill out the empty spaces. Moreover, in the spatial model if a cancer cell is located close to an empty space generated from a normal cell death, then the progeny of the cancer cell will fill out the empty space with a high probability (See Figure 1(c)). Note, necrotic cells send proliferation signals to the nearby cells, and high fitness cells are more likely to respond to these signals and divide.



(a) (b)

Figure 2. Non-spatial model. This figure presents the ratio of cancer cells over the total number of cells as a function of time, i.e. the $x-$axis is the number of updating steps. In this plot, the blue circles (the result of the formula) and diamonds (the result of simulations) indicate the healing time, i.e. the first time t that total number of cells reaches the desired number, $N(t) + C(t) = D$. The black lines show the solutions of the system of equations. In sub-figure (a), at the initial time there are 195 normal cells and a single cancer cell, and the desired number of cells is approximately $D = 400$. The gold, green, and orchid colors show the average and standard deviation of 100 independent runs for $r = 0.9$, $r = 1.0$, and $r = 3.8$, respectively. The ratio of cancer cells is around zero for $r = 0.9$ and $r = 1.0$. In sub-figure (b), the fitness of cancer cells is $r = 3.8$. The orange, pink, and brown colors respectively show the mean plus/minus standard deviation of 1000 independent runs for $(N(0), D) = (80, 400)$, $(575, 900)$, and $(1155, 1600)$. Where $N(0)$ is the initial number of normal cells, and D is the desired number of cells.

Figure 3 shows the results of 100 independent individual runs for the advantageous ($r > 1$), neutral ($r = 1$), and disadvantageous ($r < 1$) cancer cells. Figure 3(a) indicates that the wound heals faster if the cancer cells are advantageous and they are involved in the wound healing process. Moreover, if advantageous cancer cells are involved in the healing process, then their progeny will rapidly take over the entire tissue. However, the disadvantageous cancer cells located in the border of the wound or outside of the wound's boundary are not able to colonize, and will be eventually washed out from the tissue.

Small wounds and fast recurrence

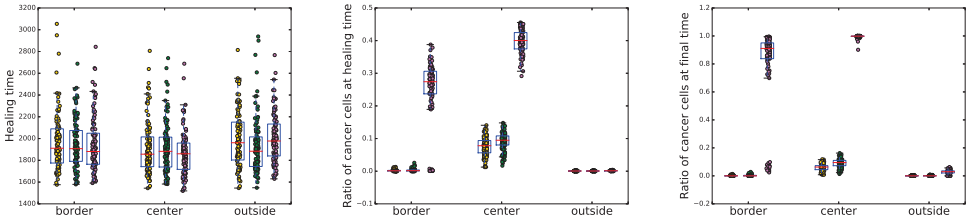
In order to simulate the effect of the wound's size in the recurrence time, we change the grid's size in the spatial model. In other words, we create a large grid for a large wound. For all grids, we consider three layers of cells around the wound (See Figure 1). To compare the spatial and non-spatial model, in Figure 4 we consider the same number of cells and empty spaces for the non-spatial model at the initial time of simulations as the spatial model. Expectedly, simulations show that small wounds heal fast (See Figure 5). However, the ratio of cancer cells over the total number of cells after healing depends on the location and the fitness of cancer cells as well as the wound's size. The non-spatial model shows that time to recurrence is an increasing function of the wound size (See Figure 2(b)). However, the spatial model indicates that if cancer cells are located at the wound's boundary or outside the wound, then the smaller wounds relapse faster than larger ones (See Figure 4). In other words, a smaller desired number of cells, i.e. a smaller wound, corresponds to an earlier relapse when cancer cells are not located in the center of the wound. This means that when we see earlier relapses after removing large tumors more often than small ones, it is because cancer cells in larger tumors have higher fitness than smaller ones or there is a higher chance that cancer cells remain in the middle of the wounds after treating larger tumors.

Location of cancer cells is important

In the spatial simulations, a single cancer cell is placed in different locations. If an advantageous cancer cell is involved in the wound healing process, i.e. it is located in the middle of the wound or at the wound's border, then it would outcompete normal cells in the wound healing process. Therefore, the tumor reoccurs very quickly, because after the wound has been healed there are many cancer cells that are involved in the tissue's normal homeostasis. However, if the advantageous cancer cell is located outside of the wound, then the wound is healed by normal cells. In this case, the tumor would slowly re-generate because of the cancer cell's involvement in the normal homeostasis of the tissue.

The tissue's size is as important as the wound's size

After healing, the percent of cancer cells involved in the normal homeostasis is a very important factor in the recurrence time. If the wound is large and cancer cells are involved in the wound's healing process, then cancer cells will cover a high percent of the tissue. However, if cancer cells are involved in the healing of a very small wound, then cancer cells only cover a small portion of the tissue after healing. Moreover, if the cancer cells are not involved in the wound healing process, i.e. are located outside of the wound's boundary, then they are only involved in the normal homeostasis. A high percent of the cancer cells involved in the normal homeostasis leads to a fast recurrence. For this reason, if a single cancer cell is located outside of the wound's border, then the tumor reoccurs faster when the tissue's size is smaller. Furthermore, when the tissue's size is fixed and advantageous cancer cells are not involved in the wound healing, then smaller wound leads to faster recurrence. Note, smaller wounds heal faster and as soon as the wound is healed, then tissue goes toward the normal homeostasis.



(a) (b) (c)

Figure 3. Cell dynamics in the spatial model. The sub-figure (a) shows the healing time, while the sub-figures (b) and (c) indicate the ratio of cancer cells over the total number of cells at the healing time and final time, respectively. In each of these sub-figures, the result of 100 individual runs is shown by circles when a single cancer cell is located in the border, center, and outside of the wound at the initial time of simulations. The orchid, green, and gold colors correspond to the fitness of cancer cells $r = 3.8$, $r = 1.0$, and $r = 0.9$, respectively.

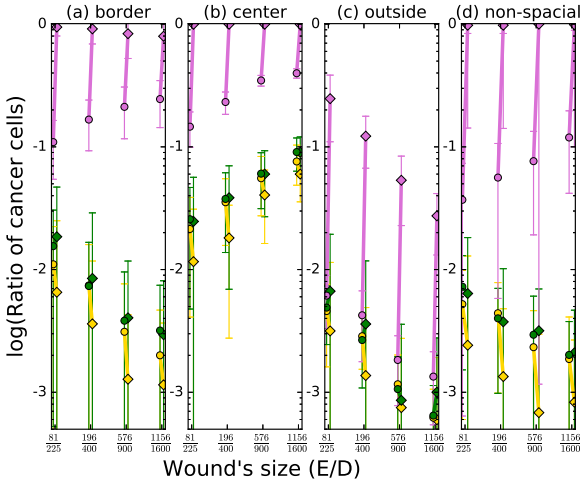


Figure 4. Ratio of cancer cells. This figure shows the ratio of the number of cancer cells over the total number of cells. The circles and diamonds indicate the ratio of cancer cells at the healing time and the final time of simulations, respectively. At the initial time of these simulations, a single cancer cell is located in the boundary of the wound (sub-figure (a)), in the center of the wound (sub-figure (b)), or outside of the boundary of the wound (sub-figure (c)). The final time of simulations, which corresponds to $T = 10D$ number of updating time steps, where D is the tissue's size, i.e. the desired number of cells. In this figure, the x-axis is the ratio of E/D, where E is the number of empty locations. The orchid, green, and gold colors correspond to the fitness of cancer cells $r = 3.8$, $r = 1.0$, and $r = 0.9$, respectively.

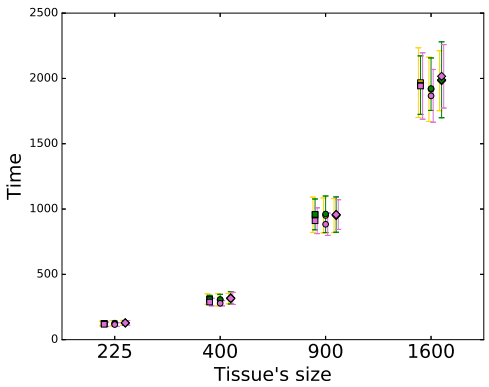


Figure 5. Healing time. This figure indicates the first time that the wound is healed, i.e. the total number of cells is approximately the same as the desired number of cells. The squares, circles and diamonds indicate the healing time when a single cancer cells is located at the border, center, and outside of the wound, respectively, in the initial time of simulations. In this figure, the orchid, green, and gold colors correspond to the fitness of cancer cells $r = 3.8$, $r = 1.0$, and $r = 0.9$, respectively.

The non-spatial model has some advantages

The wound healing process is a complex phenomena and different cell types such as immune cells and epithelial cells are involved in this process. These cells send inflammatory signals such as epithelial?mesenchymal transition (EMT) signals, causing cells' migration from different parts of the tissue into the wound. In other words, many tissue cells located in a margin of the wound may be involved in the wound healing process. The non-spatial method is able to capture this phenomena, i.e. modeling the involvement of all cells in the healing process regardless of their position. However, after the wound is healed the tissue goes toward the normal cell division and death rate, and the spatial methods are more suitable for modeling the normal homeostasis. Both spatial and non-spatial models show that the percent of the cancer cells involved in the healing and then involved in the normal homeostasis is a very important factor in the tumor's relapse time.

Discussion

Since the disadvantageous cancer cells are not able to colonize, the development of the tumor before the treatment indicates that the fitness of cancer cells must be more than one. The stochastic simulations of cell dynamics show that if any cancer cells with fitness more than one remain after the treatments that only kill epithelial cells, then the tumor will relapse. However, no relapses have been detected after the treatment for some non-inflammatory cancers. It is very unlikely for any treatment to kill every single cancer cell. Therefore, if the cancer does not come back, then the fitness of cancer cells after the treatment should be slightly more than one. Since the growth rate of tumors is an increasing function of the fitness of cancer cells, the treated tumor has been created over a very long time. This implies, if a treatment is working, then most likely the tumor is old. We can also conclude that if a young patient

has a large solid tumor, i.e. the tumor developed in a short time, then tumor cells must have high fitness. Simulations also reveal that high fitness cancer cells correspond to the poor outcome, which is consistent with clinical observations [26]. For these patients, common treatments, which kill all cells, can not increase the survival time significantly, because as soon as the treatment stops, tumor cells begin the healing process, get to the normal concentration, and grow.

There are many reports about the occurrence of the metastasis to the surgical wounds [27, 28]. The incidence of wound metastasis provides evidence for the importance of the location of the tumor cells after the treatments. In agreement with the clinical observations, the stochastic simulations show that the involvement of cancer cells in the wound healing process after the treatments is a very important factor in the recurrence time. The simulations indicate that if the advantageous tumor cells are located in the middle of the wound, then the tumor will rapidly relapse. According to Vermeulen et al. [25], the fitness of mutant $P53^{R172H}$ stem cells in normal conditions is not more than one, but it is more than one in inflammatory environments. Note, proliferation signals from immune cells and necrotic cells are a very important factor in the tumor growth. In this work, it is assumed that cells follow the normal homeostasis after the wound has been healed. However, if there is still an inflammation after filling out empty spaces in the tissue, then the level of inflammatory signals like proliferation signals can be very high in the tissue. That can lead to a high number of divisions of epithelial cells, causing re-growth of the tumor. Based on these insights, one can conclude that inflammation plays a more important role in the progression of tumors than mutations in epithelial cells. The inflammation not only can cause mutation in epithelial cells [14], but can also change their fitness. Thus, the effective treatment for inflammatory carcinomas must change the inflammatory environment of the tumor.

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Competing interests

I have no competing interests.

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