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Dispersal evolution in neoplasms: The role of dysregulated metabolism in the evolution of cell motility

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Abstract

Here we apply the theoretical framework of dispersal evolution to understand the emergence of invasive and metastatic cells. We investigate whether the dysregulated metabolism characteristic of cancer cells may play a causal role in selection for cell motility, and thus to the tissue invasion and metastasis that define cancer. Using an agent-based computational model, we demonstrate that cells with higher metabolism evolve to have higher rates of movement and that ‘neoplastic’ cells with higher metabolism rates are able to persist in a population of ‘normal’ cells with low metabolic rates, but only if increased metabolism is accompanied by increased motility. This is true even when the cost of motility is high. These findings suggest that higher rates of cell metabolism lead to selection for motile cells in pre-malignant neoplasms, which may pre-adapt cells for subsequent invasion and metastasis. This has important implications for understanding the progression of cancer from less invasive to more invasive cell types.

Keywords

cell motility and migration; metastasis; dispersal; cell metabolism

Introduction

The evolutionary approach to cancer has been the dominant theory of cancer since it was proposed in the 1970s (1, 2) and has continued to be developed as a unifying theory for understanding the emergence and progression of cancers (2-5). Here we apply evolutionary and ecological theory to understand the transition from benign sedentary cells to invasive and metastatic cells. Dispersal, metabolism, niche modification and resource limitation play central roles in phenotypic change across species. These processes have clear parallels in cancer and neoplastic progression, including cell migration/motility (6), altered metabolism (7, 8), microenvironment modification (9) and resource limited conditions such as hypoxia (10, 11).

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Although it is well understood in the ecology literature that high rates of consumption and subsequent degradation of local environments leads to selection for mobile organisms, this idea has yet to be applied to understanding the relationships among cell metabolism, microenvironment quality and the evolution of motility in somatic cells. In this paper we describe the applicability of ecological dispersal theory to neoplastic progression and report the results of an agent based model designed to test the hypothesis that high rates of cell metabolism promote the evolution of cell motility.

The consumption of resources is a fundamental characteristic of living things, and a process that inevitably affects the local environment. Because resource limitation is an unavoidable consequence of exponential growth, it is a universal limitation on survival and reproduction across all ecological systems. High rates of resource use can generate a tragedy of the commons (12, 13), a type of social dilemma (14) that emerges from resource competition (15) and tends to favor individuals who can escape from resource limitation through dispersal (15, 16). In neoplastic progression, invasive and metastatic cells may be selected because their dispersal phenotype allows them to gain access to resources in spite of local scarcity. Cancer cells outstrip the local supply of resources, both because they outgrow existing vasculature and because they consume limiting resources at a higher rate than do normal cells (8, 17, 18). Here we explore whether increased motility of somatic cells is positively selected when cells have high rates of consuming resources in their microenvironments, i.e., high metabolic rates.

Disregulated metabolism, especially in the form of increased glucose metabolism, is a characteristic of neoplastic cells and an important factor in neoplastic progression (8). A variety of oncogenes have been implicated in the shift to higher glucose metabolism including mutations that affect *RAS*, *AKT*, and *MYC* (8). Mutations in the *TP53* (*p53*) tumor suppressor gene also affect tumor metabolism, in part through downstream effects on *SCO2* and *TIGAR* (8). Although it is clear that these mutations are associated with neoplastic cells, the causal role of disregulated metabolism in neoplastic progression is not well understood.

Because the nutrient conditions in neoplasms are not well characterized (19) and it is not yet known how many limiting resources there are to cancer growth (8), we have made our model general rather than basing it on a particular limiting resource. The applicability of this model depends only on the existence of some limiting resource for cell growth and proliferation.

In order to test the hypothesis that high rates of metabolism of limiting resources leads to the evolution of cell motility, we model populations of cells with varying metabolic rates and explore the evolution of motility rate. We report results from two related agent-based models, one in which the metabolic rate of cells is systematically varied, and one in which a population of normal cells can be invaded by a neoplastic cell type with a higher rate of resource metabolism. We predict that higher resource metabolism will lead to the evolution of higher cell motility. These results suggest that an evolutionary and ecological framework can provide insights into the transition from benign cells to invasive and metastatic cells.

Methods

This model was constructed in Netlogo 4.0.2, an agent-based modeling platform (20). The model description has been prepared following the standardized ODD protocol for describing individual and agent-based models (21, 22). The first three sections (purpose, state variables/scales, and processes/scheduling) provide an overview of the model. The fourth section describes central concepts underlying the design of the model. The last three

sections provide details regarding the initialization, input and submodels. Further details are given in the appendix.

Purpose

The emergence of cell motility is the critical step in the progression of cancer from a benign neoplasm to an invasive cancer. The goal of this model is to explore whether cell motility is selected when cells have a higher rate of metabolism. We conduct two main experiments, one in which we parametrically vary metabolic rate and measure the resulting motility rate that evolves, and another in which we model the introduction of a altered metabolism 'neoplastic' cell type into a population of 'normal' cells.

State variables and scales

In this simulation, space is modeled as a 2 dimensional 51×51 toroidal lattice (a grid with horizontal and vertical wrapping). Microenvironments are discrete entities with variables associated with them. However, cells occupy coordinates in continuous space. Time is represented as discrete steps.

There are two kinds of low-level entities in this model: cells and microenvironments. Microenvironments are associated with particular locations on the grid and represent the volume served by resource delivery (e.g., a single capillary). The spatial scale of the model resulted in 2601 microenvironments. More than one cell can occupy a single microenvironment. Cells and microenvironments each have several states variables associated with them, and there are also state variables associated with the entire model (globals). Table 1 provides a detailed description of the state variables associated with each entity.

Process overview and scheduling

This model proceeds in discrete time steps, and entities execute procedures according to the following ordering (a more detailed schedule is provided in Appendix):

For each CELL in random order:

1. **Move** according to movement rate
2. **Consume** resources according to metabolic rate
3. **Reproduce** and mutate motility rate of one daughter cell if energy is above reproduction threshold
4. **Die** if microenvironment resources or internal reserves are below death threshold

For each MICROENVIRONMENT **Renew** resource according to rate of renewal

For each MICROENVIRONMENT **Diffuse** resource according to diffusion rate

Ten repetitions were run for each metabolic rate. Every simulation was run for 200,000 time steps, with a 100,000 time step warm up period followed by a 100,000 time step data collection period. Average motility rate and the average number of agents of each type were calculated by tracking the running average of each over the data collection period and reporting the final values at the end of each run.

Design concepts

See Appendix.

Initialization

All runs were initialized according to default parameters in table 2 and a screen shot of the initial state of the model (for both experiments 1 and 2) is provided in figure 1. Metabolic rate was varied between runs. In experiment 1, all cells in a particular run were initialized with the same metabolic rate, but this initial value was different across runs. In experiment 2, we modeled two types of cells, ‘normal’ cells with a low metabolic rate and ‘neoplastic’ cells usually with an altered rate. The neoplastic metabolic rate was varied between runs, but kept constant within runs.

Input

We designed our model to be generally applicable to many types of cancer rather than modeling a specific type of cancer. We therefore based our model on two general empirical observations about cancer cells: 1) Many types of cancer cells exhibit dysregulated metabolism, often characterized by higher rates of resource consumption(8, 18). 2) Cancer cell survival and proliferation is often constrained by resource limitation, as demonstrated by the common occurrence of necrosis in areas of tumors that have a limited supply of oxygen (10, 11).

Submodels

See Appendix.

Results

Experiment 1: Parametric Variation of Metabolic Rate

Experiment Description—In experiment 1, the relative metabolic rate is varied systematically between runs and the evolution of motility rate is explored. Relative metabolic rate refers to the metabolic rate of the cell relative to the resource delivery in the microenvironment (and also the metabolic rate of ‘normal’ cells in experiment 2). Motility rate is initially set to .001 (*m_rate*) and then allowed to mutate. Motility rate and number of cells are reported from 10 runs for each of 6 cell metabolic rates (with cells consuming .5, 1, 1.5, 2, 2.5 or 3 units of resource per time step and each location received 1 unit of resource per time step).

Results—Figure 2a reports the average number of cells. As metabolic rate increases, the number of surviving cells decreases in a logistical fashion ($R^2 = .9589$). When relative metabolic rate is 2.5 or 3, a large number of runs (8 and 7, respectively) result in all cells becoming extinct. These runs ending in extinction of all cells were excluded from the analysis of the evolution of motility rate in Figure 2b. There was a positive linear relationship between motility rate and metabolic rate (Figure 2b, linear regression $R^2 = .9836$, $p < 0.001$). Changes in resource availability and cell density over time can be seen in Figure 3.

Experiment 2: Competition Between Normal and Neoplastic Cells

Experiment Description—In experiment 2, we modeled cells with normal and neoplastic metabolic rates. In these runs, normal cells always had a metabolic/consumption rate of 1 unit of energy per time period. We varied the metabolic rate used by neoplastic cells, with 10 runs using the same values as in experiment 1 (.5, 1, 1.5, 2, 2.5 or 3 units per time periods). Cells could mutate from being normal to neoplastic (and vice versa), at a rate of .01 per cell division (with only 1 daughter cell mutating). Neoplastic cells have a fixed metabolic rate within runs, reported here as the ‘relative neoplastic metabolic rate.’ This number describes the relative rate of metabolism of neoplastic cells compared to normal

cells (and also compared to the sustainable rate of resource metabolism for a single sedentary cell on a microenvironment). We measured the resultant motility rate and number of cells for both neoplastic and normal cells.

Results

Selection and invasion: First we explored the viability of normal and neoplastic cells when the metabolic rate for neoplastic cells was varied and selection could act on cell motility. Somewhat surprisingly, neoplastic cells (with higher metabolic rates than their normal counterparts) did not take over the population of cells. In fact, the proportion of neoplastic cells was highest in the control condition where the neoplastic metabolic rate was 1, representing no difference from normal cells ($F(5, 54) = 15, p < .0001$; see Figure 4a). This indicates that, on average, selection disfavored neoplastic cells with higher metabolic rates. However, a subset of cells with high metabolic rates persist in the population: those that had evolved high rates of motility (see discussion).

Effects on motility: Cells with higher metabolic rates consistently evolved to have higher motility rates. In all the simulations in which neoplastic metabolic rate was higher than that of normal cells, the motility rate of neoplastic cells evolved to be consistently higher (One tailed t-test, $t(9) = 4.55, p < 0.001$) at each of the metabolic rates. Further, neoplastic cells with lower metabolic rates (.5) than normal cells evolved lower motility rates, (one-tailed t-test, $t(9) = 22.25, p < 0.0001$), and, as predicted, there was no difference when neoplastic cells had a metabolic rate equivalent to normals (two-tailed t-test, $t(9) = 0.68, p = 0.51$). Figure 4b shows the mean motility rates of neoplastic and normal cells after equilibration of the model for 10 runs each. Figure 5 shows the changes in resource availability and cell density over time in the model.

Experiment 3: Motility cost

Experiment Description—In order to determine whether the addition of a motility cost substantially affects the results, we varied the cost of cell motility (0, .01, .02, .03, .04, .05). These runs were identical to experiment 2 (with the metabolic rate of neoplastic cells kept constant at 1.5).

Results

Selection and invasion: At low motility cost, normal cells made up a larger proportion of the population than neoplastic cells. However, as motility cost increased (to .05), the advantage of normal cells disappeared and neoplastic cells made up approximately half the population (Figure 6a). This indicates normal cells become less fit relative to neoplastic cells as the cost of cell motility increases (all else being equal).

Effects on motility: When motility cost was higher, the motility rate that evolved was lower than was the case with no motility cost. However, the motility rate of neoplastic cells was still consistently higher than the motility rate of normal cells (Figure 6b).

Discussion

We tested and found support for the hypothesis that high metabolism characteristic of neoplastic somatic cells leads to selection for cell motility. This suggests that the somatic evolution of high metabolic rates and high motility rates might be causally linked, with important implications for prevention of invasion and metastasis. These results are also consistent with other theory from evolutionary ecology including the work on public goods (13) and dispersal ecology (15, 16), as well as models of the evolution of multicellularity (23).

Analysis of results and model limitations

Our model represents somatic evolution within a spatially encapsulated and resource-constrained environment, similar to the conditions in pre-malignant neoplasm. Interestingly, high-metabolism neoplastic cells do not have an overall advantage compared to normal cells in these conditions. Rather, a minority of motile neoplastic cells persist within a population primarily made up of cells with low metabolic rates and low motility. This may be a reasonable model for changes in population composition that may occur as a result of dysregulated metabolism in an encapsulated premalignant lesion. Our findings suggest that cells with dysregulated metabolism will evolve to become more motile and invasive, though they may not be able to take over within a resource-restricted and encapsulated region.

However, these neoplastic cells do transiently out-compete normal cells in this model. However, they degrade their microenvironment and therefore are able to survive only if they are able to move to a new environment that can sustain their high metabolic needs (Figure 2b). Therefore, the neoplastic cells that do survive have significantly higher rates of motility than normal cells. We also found that normal cells became less fit relative to neoplastic cells as motility cost increased. This is most likely because the costs of motility were more easily borne by neoplastic cells (since they had a rate of resource uptake that was 1.5 times that of normal cells). Nevertheless, the evolved motility rate of neoplastic cells was consistently higher than that of normal cells, even when the cost of motility was high.

Although we did not explicitly model the ability of cells to escape from a spatially encapsulated and resource restricted region (as our model was an encapsulated torroid with 51×51 microenvironments with fixed resource delivery), the evolution of traits that enable cells to escape from resource restriction would give an advantage to cells that have previously evolved high motility rates. Further, neoplastic cells with increased metabolic needs would be under strong selective pressure to evolve invasion into new microenvironments and angiogenesis so as to increase the supply of nutrients. In these ways, progression to invasion and metastasis could be facilitated by prior selection for motility in the pre-malignant neoplasm.

There are additional traits that would be likely to give neoplastic cells a competitive advantage over normal cells that we have not included in the model, such as insensitivity to anti-growth signals, suppression of apoptosis, and the other hallmarks of cancer (24). We hope to explore the relationship between motility evolution and these traits in future work. However, as these phenotypes were not necessary to test our hypothesis, they were left out of the model. This allowed us to avoid unnecessary complexity and isolate the relationship between metabolic rate and selection for motility in the current model.

Resource limitation and cancer

In general, researchers have recognized the key role of the tumor's local resource environment in influencing cancer progression (9, 25, 26) but have less often considered the implications of neoplastic cells' modification and often degradation of their own local resource environments. Based on mathematical and computational models of cancer cells, Anderson et al. (25) concluded that harsh local environments lead to the somatic evolution of invasive cells, but did not address the origin of harsh local environments. Similarly, Basanta et al. (27) conclude that resource-rich environments disfavor cell motility. In contrast, our model explicitly implements different metabolic phenotypes and explores the subsequent effects on motility evolution. Our general approach is similar to that taken by Pfeiffer and Bonhoeffer (23), who modeled the evolution of cell clustering in the transition to multicellularity. They found that cells using more efficient aerobic metabolism are selected to cluster, while cells using less efficient fermentative metabolism are selected to

disperse. They conclude that more efficient metabolism (as well as cooperation in the use of external energy) may have played a role in the first stages of the evolution of multicellularity. We suggest that the shift to more suggested that a shift to shorter metabolic pathways which improve short-term competition may be a consequence of the shift in levels of selection (from organism to cell) that occurs in cancer initiation (28). The present model shows that a shift to more rapacious metabolism could facilitate selection on the fundamental phenotype of cancer: the cell motility underlying invasion and metastasis.

It has been suggested that the altered tumor microenvironment exerts selection pressures on the metabolic characteristics of neoplastic cells (8). However, the disregulated metabolism of cancer cells also affects their microenvironment, leading to greater scarcity of limiting resources. Ecological dispersal theory predicts that such resource scarcity and subsequent habitat instability will lead to the evolution of dispersal (16, 29). At the cellular level, tissue invasion and metastasis require cell motility and migration (6), the cellular version of dispersal. Because of the centrality of these processes in neoplastic progression, it is important to understand the process by which previously sedentary neoplastic cells acquire the cancer phenotype of cell motility.

Much of the research and discourse on the role of cell metabolism in neoplastic progression centers on the Warburg effect (30), the increased glucose metabolism characteristic of cancer cells. Normal cells metabolize oxygen (via oxidative phosphorylation), while cancerous cells can switch from aerobic to anaerobic (fermentative) metabolism. Fermentative metabolism is characterized by a dramatic increase in glucose consumption, with cells relying solely on glycolysis of glucose to pyruvate for production of ATP (8, 30). This change in cell metabolism increases the rate of ATP production, reduces oxygen dependence and creates a more acidic environment (7, 31, 32).

Though increased glucose metabolism is currently the best-studied example of disregulated metabolism in cancer cells, the nutrient conditions of the tumor microenvironment have not yet been examined carefully (8) and it is not known which other resources limit cell growth and proliferation. It is clear, however, that cancer cells differ from normal cells with regard to elemental and biochemical composition (19) making it probable that cancer cells rely on a variety of fuel sources to maintain ATP levels (8). The limiting resources may even differ importantly across organs. Recent work applying biological stoichiometry to cancer suggests that phosphorous is a limiting resource in high turnover epithelial cells of the colon and lung, but not in the liver and kidney (19).

Further, mitogens such as hormones and growth factors limit cell proliferation, and cells may escape from this limitation through autocrine production of the mitogen or the upregulation of receptors (33, 34). Growth limitation due to hormone availability is particularly important in reproductive cancers such as breast cancer, where estrogen and progesterone availability and sensitivity are key factors in neoplastic progression (35) and cancer treatment (36, 37).

The connection between metabolism and cancer is a growing area of interest, and recent work suggests that there may be important links between cell-level metabolism and organism-level metabolism (38). The relationship between cellular level metabolism and cancer is likely to involve dynamics beyond just the increased consumption of resources that we have focused on here. Increased cell metabolism produces more reactive oxygen species, (39-41) potentially leading to an increase in genetic lesions (i.e., a higher rate of somatic mutations). Altered metabolism can also produce lactic acid, which may facilitate invasion and metastasis (7) and reduce the fitness of competing normal cells.

Applications and predictions

Not only can models such as these facilitate thinking about the large-scale processes underlying cancer progression, but they can also make empirical predictions and stimulate research in new directions. For example, the results of this model suggest that motility rates are likely to be highest in cells that have high metabolic rates, a prediction that can be tested *in vitro*. If one were to separate cancer cells based on their migration rates, rapidly migrating cells should be found to have the highest metabolic rates.

In addition to extending existing theory and generating testable hypotheses, the present work can be applied to developing strategies for treating and preventing cancer. Most existing therapies focus on killing cancer cells, but the somatic evolutionary perspective has challenged that approach (5, 42, 43) noting that simply killing cancer cells can generate drug-resistant relapse. It has also been proposed that better cancer cure rates may result from alternative interventions that are less prone to acquired resistance through somatic evolution (5, 42, 43).

The basic findings of this model suggest potential links to diabetes-related cancer risk. It is possible that some portion of the increased cancer risk and cancer mortality associated with diabetes (44) is due to the changes in glucose metabolism among cells (45), which may lead to increased somatic selection for cell motility, invasion and metastasis.

Another potential target for prevention and treatment would be drugs that alter the tumor environment in ways that decrease selection for motile cells in favor of less invasive cell lineages, as suggested by Maley et al (46). It may be possible to reduce selection for motility by actually *increasing* the availability of limiting resources within the local environment of the neoplasm. There is some evidence that this counterintuitive approach of ‘feeding’ the tumor may reduce cell motility: recent experiments showed that improved tumor perfusion and oxygenation inhibit tumor cell invasion and metastasis (47).

The effective development of interventions to target motility will rely on both theoretical advances in understanding cancer malignancy and a thorough understanding of the underlying genotypes and physiological mechanisms, including the biophysical, genetic, and epigenetic basis of cell motility (see {Wells, 2006 #680} for a review). The present paper represents a step towards a more comprehensive theory of cancer based on somatic evolution, extending the scope of the theory to explain the evolution of cellular motility. It was formerly unclear how somatic selection leads to invasion and metastasis, and in particular, what the driving selective pressures are (48). Our results suggest that there is selection for cell migration in pre-malignant neoplasms which may pre-adapt cells for subsequent invasion and metastasis.

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Appendix

Model Schedule

Here we provide additional details regarding the subprocesses and schedule underlying the model. The pseudocode schedule provided earlier in the model description is expanded upon

to provide more detailed information regarding the subroutines within each of the main processes.

For each CELL in random order:

1. **Move** according to movement rate
 - a. Move forward 1 microenvironment width in the direction of heading
 - b. Set heading randomly (0-359 degrees)
2. **Consume** resources according to metabolic rate
 - a. Cells augment their energy level by metabolic rate
 - b. Resource of level of microenvironment declines by metabolic rate
3. **Reproduce** and mutate motility rate of one daughter cell if energy is above reproduction threshold
 - a. Cells split their energy between two daughter cells upon reproduction
 - b. Motility rate mutates in one daughter cell every time a cell reproduces
 - c. The size of the mutation is a random number drawn from a distribution with a mean 0 and a standard deviation of .01.
 - d. Daughter cells are placed in the same microenvironment as parent
4. **Die** if microenvironment resources or internal reserves are below death threshold
 - a. If a cell is occupying a microenvironment with resources below the death threshold it dies
 - b. If the internal stores of a cell are below 0, the cell dies

For each MICROENVIRONMENT **Renew** resource according to rate of renewal

For each MICROENVIRONMENT **Diffuse** resource according to diffusion rate

- a. A proportion (.01) of total resource diffuses to each of 8 neighboring microenvironments

Design concepts

Adaptation

In experiment 1, cells have only one adaptive trait: their motility rate. However, this motility rate changes over evolutionary time through mutation and differential survival, not over the course of a single cell's lifetime. In experiment 2, cells have the additional adaptive trait of either being normal (i.e., having a low metabolic rate) or neoplastic (with an altered metabolic rate).

Fitness

Fitness is modeled implicitly through differential survival and reproduction of cells.

Prediction

Cells do not have the ability to predict resource levels in neighboring microenvironments or move towards regions with more resources.

Sensing

Cells do not sense any features of the environment or other cells.

Interaction

Cells interact with other cells indirectly through resource consumption (generating resource competition). Microenvironments interact through diffusion of resources.

Stochasticity

This model includes stochastic movement of cells. Also, mutation is modeled as a stochastic process.

Observation

Ten repetitions were run for each metabolic rate. Every simulation was run for 200,000 time steps, with a 100,000 time step warm up period followed by a 100,000 time step data collection period. Average motility rate and the average number of agents of each type were calculated by tracking the running average of each over the data collection period and reporting the final values at the end of each run.

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Figure 1. Screen shot of initial state of the model (for both experiments 1 and 2) Yellow circles represent cells and concentration of resources in each lattice location is indicated by lighter shades of red/pink. Each lattice location produces enough resources in each time period to support a single cell with normal metabolism. Initially cells are arranged systematically (as in organized tissues), with one cell per lattice location.

Figure 2.

a) As the relative metabolic rate increases, the number of cells at the end of each run is lower. **b)** Cells evolve to have higher motility rates (means with error bars) when metabolic rate is higher.

Figure 3.

Screen shots from experiment 1. Cells have a relative metabolic rate of 1.5 (consuming 1.5 times as many resources per time period as normal cells). **a)** At time 5,000, the population size has decreased substantially and high resource patchiness is apparent (with lighter shades of red signifying more resources). Cells with higher motility are favored because they can gain access to new resource rich regions. **b)** At time 10,000, the population size increased and cells have begun moving into the resource rich areas. **c)** By time 20,000, most resource rich areas have been colonized by cells. **d)** Some resource patchiness remains even after 100,000, contributing to continued selection for cell motility.

Figure 4.

a) The number of neoplastic and normal cells (means with error bars) at the end of each run is shown for various neoplastic metabolic rates. **b)** Higher rates of metabolism of neoplastic cells led to higher rates of mobility for neoplastic cells (means with error bars).

Figure 5.

Screen shots from experiment 2. Yellow cells represent normal cells with a consumption rate of 1 and blue cells represent neoplastic cells (relative metabolic rate of 1.5). **a)** At time 5,000, some neoplastic cells have emerged due to background mutation. **b)** By time 10,000, the number of neoplastic cells has increased. **c)** Neoplastic cells continue to increase in the population at time 20,000. **d)** Neoplastic cells do not take over the population, but instead coexist with normal cells (time 100,000). Throughout, neoplastic cells (i.e., cells with a higher metabolic rate) evolve higher rates of motility while normal cells motility rate remains low (see Figure 6).

Figure 6.

a) The number of neoplastic and normal cells (means with error bars) at the end of each run is shown for various motility costs. **b)** Higher mobility costs led to lower rates of mobility for both normal and neoplastic cells (means with error bars). However, selection still leads to higher mobility in the neoplastic cells compared to the normal cells in all cases.

Table 1

Overview of state variables associated with each type of entity, including initial and default values for all variables. Bold indicates the independent variable and arrows indicate dependent variables.

Entity	State variable	Description	Initial / default value	Units
<i>Global</i>	• Motility mutation	The standard deviation of change in motility rate upon reproduction	.01	Standard deviation
	• Neoplastic mutation	Rate of mutation from normal to neoplastic cell and vice versa upon reproduction (Exp. 2 only)	.01	Rate per cell division
	• Rate of renewal	Amount of energy added to each patch per time step	.1	Resource per time step
	• Diffusion rate	Proportion of patch resource that diffuses per time step; split evenly between all 8 neighbors	.001	Proportion of resource per time step
	• Death threshold	Amount of resource necessary on a patch for cell to survive	1	Resource level in a patch
	• Reproduction threshold	Amount of energy cell needs to divide	50	Energy in a cell
	➤ Number cells	Total number of cells	2601	Count
	➤ Number normal	Number of normal cells (Exp. 2 only)	2601	Count
	➤ Number neoplastic	Number of neoplastic cells (Exp. 2 only)	0	Count
<i>Microenvironments</i>	• Location	Coordinates of the patch	(-25 - 25, -25 - 25)	Coordinates
	• Resource	Amount of resources available on patch	Random from uniform distribution 0-50	Resource
<i>Cells</i>	• Metabolic rate	Amount of resource cell can consume (transform into energy) in one time setp	.5, 1, 1.5, 2, 2.5, 3	Energy per time step
	• Energy	Amount of energy accumulated by cell through consumption/metaboism of resources	5	Energy in a cell
	➤ Motility rate	Likelihood that a cell will move per time step	.001	Probability
	• Heading	Direction of cell movement	Random from uniform distribution 0-359	Degrees
	• Location	Coordinates of cell	One cell was placed in the middle of each patch	Continuous coordinates

Table 2

Initial and default values for all variables. Bold indicates the independent variable and arrows indicate dependent variables.

Entity	State variable	Initial / default value	Units
<i>Global</i>	• Motility mutation	.01	Standard deviation
	• Neoplastic mutation	.01	Rate per cell division
	• Rate of renewal	.1	Resource per time step
	• Diffusion rate	.001	Proportion of resource per time step
	• Death threshold	1	Resource level in a patch
	• Reproduction threshold	50	Energy in a cell
	➤ Number cells	2601	Count
	➤ Number normal	2601	Count
	➤ Number neoplastic	0	Count
<i>Microenvironemnts</i>	• Location	(−25 - 25, −25 - 25)	Coordinates
	• Resource	Random from uniform distribution 0-50	Resource
<i>Cells</i>	• Metabolic rate	.5, 1, 1.5, 2, 2.5, 3	Energy per time step
	• Energy	5	Energy in a cell
	➤ Motility rate	.001	Probability
	• Heading	Random from uniform distribution 0-359	Degrees
	• Location	One cell was placed in the middle of each patch	Continuous coordinates

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