Cell Adaptive Fitness and Cancer Evolutionary Dynamics

Youcef Derbal

Ted Rogers School of Information Technology Management, Toronto Metropolitan University, Toronto, ON, Canada.

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ABSTRACT: Genome instability of cancer cells translates into increased entropy and lower information processing capacity, leading to metabolic reprograming toward higher energy states, presumed to be aligned with a cancer growth imperative. Dubbed as the cell adaptive fitness, the proposition postulates that the coupling between cell signaling and metabolism constrains cancer evolutionary dynamics along trajectories privileged by the maintenance of metabolic sufficiency for survival. In particular, the conjecture postulates that clonal expansion becomes restricted when genetic alterations induce a sufficiently high level of disorder, that is, high entropy, in the regulatory signaling network, abrogating as a result the ability of cancer cells to successfully replicate, leading to a stage of clonal stagnation. The proposition is analyzed in the context of an in-silico model of tumor evolutionary dynamics to illustrate how cell-inherent adaptive fitness may predictably constrain clonal evolution of tumors, which would have significant implications for the design of adaptive cancer therapies.

KEYWORDS: Cell adaptive fitness, cancer evolutionary dynamics, entropy, signaling-metabolism coupling, oncogenic signaling, cancer, adaptive cancer therapy

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CORRESPONDING AUTHOR: Youcef Derbal, Ted Rogers School of Information Technology Management, Toronto Metropolitan University, 350 Victoria Street, Toronto, ON M5B 2K3, Canada. Email: yderbal@torontomu.ca

Introduction

The evolving genetic diversity and phenotypic plasticity of cancer cells make cancer a moving target for therapeutic interventions. Despite the increasing efficacy of available cancer therapies, resistant cancer cells persist after remission as a minimal residual disease which would ultimately lead to recurrence, therapeutic resistance and metastasis. Constraints on cancer evolutionary dynamics, such as the incidence order of genetic alteration events, may point to vulnerabilities that can be targeted to achieve effective management or cure.

Cancer is a nonlinear dynamical system driven by stochastic genetic events involving driver and passenger somatic mutations,[1] copy number alterations,[2] and structural variations, including translocations, chromosomal loss or gain and whole genome doubling.[3] A recent high accuracy DNA duplex sequencing of colorectal tumors shows that every DNA base is mutated in at least one cancer cell.[4] The assertion of such hyper genotypic diversity at diagnosis highlights the near boundless potential of tumor cells for phenotypic transformations and the vast space of possible trajectories of survival and proliferation they could explore under environmental and therapeutic selection pressures. Herein lies the limitations of therapeutic interventions that do not integrate the evolutionary perspective of cancer, first proposed by Nowell[5] and increasingly recognized as the most fitting viewpoint in the search for effective cancer treatments.[6] In particular, cancer evolutionary dynamics impose an intrinsic barrier to the cure or effective management of cancer using the common therapeutic paradigm of killing as many cancer cells as possible, argued to be evolutionary unsound.[7] Indeed, traditional therapeutic strategies, which are often based on genotoxic agents, eradicate therapy-sensitive cancer cells, leaving therapy-resistant cells to subsequently fuel resistance and disease recurrence,[8] as the most critical challenges in the fight against cancer. Treatment strategies that are designed to anticipate the evolutionary dynamics of tumor progression and accordingly preempt the adaptive survival of cancer cells are expected, in principle, to yield improved patient outcomes. However, this will hinge on the feasibility of predicting tumor progression trajectories. Genome wide studies have revealed genotypic patterns underlying cancer progression, whereby different cancer stages involve different sets of driver mutations and copy number alterations.[9-11] Although uncovering genotypic patterns in tumors' histories may inform the design of therapeutic strategies, predicting the course of tumor evolution would require delineating the dynamics of cancer progression as they relate to what evolution acts on, that is, the phenotype. Furthermore, while stochastic genetic events shape the emergence of distinct metabolic and cell proliferation phenotypes, the evolutionary dynamics of tumor progression are ultimately determined by selection pressures of the tumor microenvironment (TME) and therapeutic interventions acting on the phenotypic diversity of cancer cells. However, this does not preclude the existence of cell-intrinsic mechanisms that shape cancer cell fitness and modulate selection pressures. Indeed, whereas cancer evolutionary drivers are stochastic, the nonlinear tumor response to therapy is predictably adaptive to therapeutic challenges and fosters therapeutic resistance. The cell signaling and metabolic networks are the integrators of genetic alterations into observable phenotypes and hence constitute an appropriate level of abstraction to reason about potential mechanisms underlying any cell-intrinsic fitness adaptation modulating evolutionary selection. The adaptive fitness of cancer cells is ultimately manifested through the emergence of trajectories of confluence between metabolic reprograming and cell fate choices that support clonal proliferation.

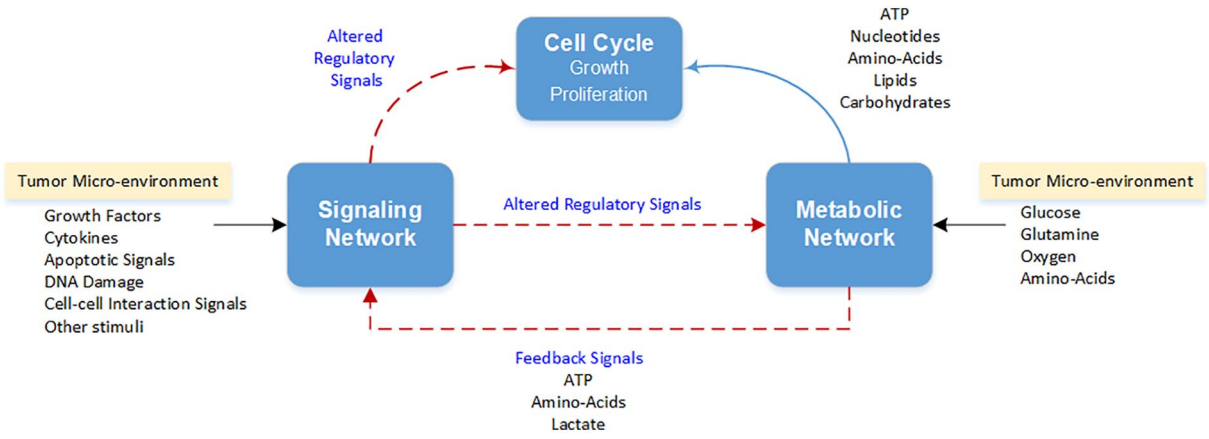

Figure 1. Cell cycle regulation. The cell cycle is under the regulatory control of the signaling network and is dependent for its progression on the output of the metabolic network. On the other hand, the signaling and metabolic networks are coupled through feedback signals, making the effect of genetic alterations reverberates through the entire signaling-metabolic system. The resulting perturbations of the coupling between signaling and bioenergetics would expectedly be a determinant of the growth and proliferation dynamics of cancer.

The proposed necessity of concordance between cell fate decision-making and altered metabolism to support cancer proliferative growth is rather intuitive given the feedback loops that couple the cell signaling and metabolic networks[12,13]. In other words, the set of potential cell fate choices of cancer cells may be limited by the integrated effects of genetic alterations on oncogenic signaling in closed loop with altered metabolism. The limitation on cancer cell fate choices, would ultimately translates into evolutionary constraints on tumor progression. That is, the signaling-metabolism feedback loop dampens the stochastic effect of genetic alterations, limiting as a result the set of possible cell fate trajectories that would be available to drive tumor proliferative growth. Characterizing the corresponding constraint as a function of genetic alterations may provide an avenue for one-step ahead predictions of evolutionary dynamics, which would be instrumental to the rational development of adaptive cancer therapies.

Phenotypic Measure of Genetic Alterations

Recent studies of cancer evolutionary history have shed light on the sequence of genetic events implicated in different cancer types.[9,11] Although trends and patterns of cancer evolution may be used to stratify patients for treatments, the semblance of order represented by such patterns is still wrapped in a stochastically driven evolution whose prediction would require the definition of measures that go beyond the stochasticity of the genotypic drivers and focus rather on the phenotypic diversity on which evolution acts. The generation of such phenotypic diversity is necessarily bound to the pathway-integrated effects of genetic alterations and to the dynamics of the closed loop system that couples the signaling and metabolic networks of cancer cells (see Figure 1) and lead to the reprograming of metabolism, cell death evasion, and sustained proliferation.[14]

The intertwined metabolic and cell fate decision-making pathways (eg, cell division, differentiation, senescence and apoptosis) constitute clearly delineable dimensions along which the effects of genetic alterations are integrated to yield the survival and proliferation potentials of cancer cells, which ultimately determine their evolutionary fitness. This highlights the need to quantify the dysregulation of signaling and metabolic pathways in order to characterize the phenotypic trends of cancer evolution. Network entropy, defined based on Kolmogorov–Sinai entropy,[15] has been applied to the study of various aspects of protein-protein interaction networks, including their robustness and the evolution of their structures.[16] Network entropy was also used to discriminate between cancer and normal cells[17] and predict sensitivity to cancer drugs.[18] Given the dominance of various set of oncogenic pathways in the oncogenesis and progression stages of different cancers, the notion of pathway entropy is introduced with the explicit consideration of oncogenic pathways that are relevant to the cancer at hand. It is used as a measure of the rewiring of oncogenic signaling pathways which drives clonal exploration of proliferation trajectories that feed tumor growth. The cell signaling network is modeled as a directed graph where nodes represent signaling proteins, while directed edges represent protein-protein interactions. Pathway entropy Q is defined for a system of m directed graph paths channeling signals from cell receptors to end-effector proteins such as RB (retinoblastoma) and AMPK (AMP-activated protein kinase) as follows[19] :

$$Q = -\frac{1}{1+\log(m)} \sum_{j=0}^{m-1} \pi_j \log \pi_j \qquad (1)$$

Given L_j as the set of edges in path j, $\pi_j = \prod_{k \in L_j} p_k$ is the probability that path j is an oncogenic driver path where p_k is the probability that the protein-protein interaction represented by edge k is altered. This latter probability is defined based on the perturbation of the product of the mRNA expressions of the interacting proteins, as follows[19,20]:

$$p_k = \frac{R_x(R_y - \overline{R_{0y}}) + R_y(R_x - \overline{R_{0x}})}{R_x(R_y + \overline{R_{0y}}) + R_y(R_x + \overline{R_{0x}})} \qquad (2)$$

R_x and R_y are the mRNA expression levels of genes x and y for a given tumor sample, while $\overline{R_{0x}}$ and $\overline{R_{0y}}$ are the respective averages of mRNA expressions of these genes in a normal tissue.

Pathway entropy was shown to discriminate between cancer and normal cells for lung squamous cell carcinoma (LUSC) and colorectal adenocarcinoma (COADREAD).[19] It can be computed for any set of signaling pathways as a measure of the effect of genetic alterations on the proliferative potential and therapeutic resistance of cancer cells. Depending on the cancer type under consideration, pathway entropy may be used as a resistance biomarker by focusing on the most relevant oncogenic pathways, such as the consideration of the MET, ALK, and EGFR pathways in the treatment for NSCLC (Non-Small Cell Carcinoma) using tyrosine kinase inhibitors. Ultimately, pathway entropy is a phenotypic measure of genetic alterations, formulated at the pathway level of abstraction considered for reasoning about the hallmarks and treatments of cancer and is hence plausible as a source of insight into cancer evolutionary dynamics.

Cell Adaptive Fitness

The entropy of cell signaling pathways provides a quantification of the genetically-induced perturbations to cell fate decision-making and bioenergetics in cancer cells. The regulation of the cell life-cycle, cell fate decision-making, and metabolic activities depend on the processing of signals and cues from the environment. The underlying cell information processing capacity is represented by the cell information state, denoted $H(t)$, and is defined as an instantaneous quantity that is inversely varying with respect to the entropy of signaling pathways. This definition is built on the classical interpretation of entropy as a measure of uncertainty created, in this case, by the increase in the number of possible wiring configurations of oncogenic pathways that result from genetic alterations. The uncertainty about the state of oncogenic pathways, with their promiscuous cross-talk and rewiring, leads to a stochastic perturbation of the cell's ability to process signals and environmental cues, driving as a result cell fate decision-making and metabolic control away from the regulation regime typical of normal cells. One of the critical functions of the cell signaling network and its underlying information processing capacity is the regulation of metabolic activities to meet the bioenergetic needs of the cell. The corresponding metabolic capacity is represented by the cell's energy or metabolic state, denoted by $E(t)$, and is defined as the instantaneous bioenergetic output of the cell at time t, representing the totality of biosynthesis and energy outputs, including proteins, lipids, amino-acids and Adenosine Triphosphate (ATP) molecules.

Cells are nonlinear, stochastic dynamical systems that can be described using the trajectories of their information and energy states. The cumulative increase of genetic alterations in cancer cells perturb signaling regulation and lead to a rise in signaling entropy and a higher instability of the metabolic output. On the other hand, an increase in signaling entropy induces a weakening of the cell information processing capacity, leading to a higher irregularity of cancer cell-fate decisions compared to normal cells. The corresponding stochasticity of information and energy states enables transformed cells to sample a large space of phenotypes and adapt their survival trajectories under the selective pressure of temporally and spatially changing nutritional and stimulatory conditions of the tumor microenvironment. Such cell-level stochasticity underlies the emergence of population-level (i.e., tumor) evolutionary dynamics, including therapeutic resistance. Evolutionary models of tumor progression often assume driver mutations to confer a fixed average selective advantage.[21] However, any regulatory constraints imposed by the feedback loops between signaling and metabolism on cell-fate decision-making and metabolic states will translate into constraints on the set of viable clonal growth and proliferation trajectories. This would modulate the selective advantage conferred by genetic alteration events, including passenger mutations, whose contributions are also implicated in tumorigenesis.[1] In particular, we propose that the increase of signaling entropy due to genetic alterations will lead to a decline of the information processing capacity of cancer cells and an increase of their bioenergetic capacity, which will eventually peak and begin declining when the cell information processing capacity becomes insufficient to support the normal regulation of cellular processes. This proposition, that we call the cell adaptive fitness, is an expression of a presumed imperative of growth that is hard wired in the genetic and proteomic circuitry of living organisms, whereby cellular bioenergetic processes evolve to transform all available nutrients unless otherwise regulated by the signaling network. In other words, cells optimize their energy production and consumption for metabolic sufficiency when their life-cycle processes are regulated, which corresponds to high cell information states. In contrast, cancer cells have varying degrees of dysregulated signaling pathways and obstructed flows of regulatory information that translate into relaxed metabolic regulation. This permits cancer cells to indulge in siphoning more nutritional resources through runway metabolic activities, achieving as a result higher metabolic states to support fast growth and proliferation. However, the inverse variation between cell information and energy states is expected to break down at lower information states. Indeed, as the entropy of the signaling network increases with the increasing burden of genetic alterations, the information processing capacity of corresponding clones and sub-clones will eventually dip below a putative minimum threshold necessary to achieve a homeostatic regulation of the cell life-cycle. Below such putative threshold, cell fate decision-making capability would become too compromised to sustain a stable growth and proliferation program. By the same token, the signaling-regulated enzymatic co-cooperativity of the metabolic network would also break down and would no longer be able to yield the high metabolic output needed by fast proliferating cancer cells. This transition

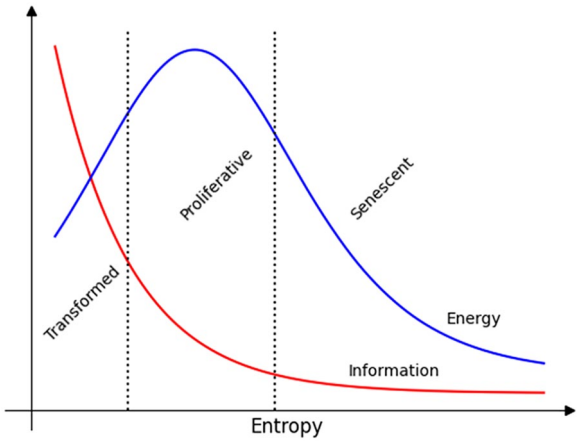

Figure 2. Cell information and metabolic/energy states as functions of the entropy of signaling pathways. In cancer cells, the increase of signaling entropy, driven by the accumulation of driver mutations, corresponds to a decline in the information processing capacity underling cell fate decision-making and metabolic regulation. This decline translates into relaxed control over metabolic activities leading to the reprograming of metabolism with a corresponding high metabolic output characterizing the proliferative phenotype of cancer cells.

point ushers the convergence of cancer cells toward lower energy and information states (see Figure 2), characterized by high genomic instability where successful replications would be rare.[22]

Although direct measurements of cell energy and information states may not be currently feasible, the profiles of their trajectories as functions of signaling entropy provide an insight into the multi-stage clonal evolution shaped by accumulating genetic alterations. The proposed relationships between entropy, energy and information (see Figure 2) may be partially corroborated by reconstructed cancer mutational histories through whole-genome sequencing analysis.[9] For instance, only 9 genes are affected by 50% of early clonal driver mutations compared to 35 genes for 50% of late clonal driver mutations,[9] indicating that the arrow of tumor evolution corresponds to higher numbers of genes and signaling pathways being affected, driving as a result the increase of cell signaling entropy, and eventually affecting the viability of cancer cells[23]. In addition, mutational signatures such as defective mismatch repair exhibit a directed temporal increase from clonal to sub-clonal evolutionary stages of tumor progression.[9] Furthermore, while the increased diversity of genes affected in the late stages of tumor progression may be a source of clonal adaptation, high genomic instability compromises the viability of cancer cells. Taken together, these observations inspired the proposed phenomenological relationships between bioenergetics, signaling entropy, and information processing as an explanation of the potential mechanisms linking the accumulation of genetic alterations to the dynamics of clonal evolution.

Evolutionary Dynamics of Cancer

The nonlinear relationship between cell information and energy states is explored as a potential evolutionary constraint that modulates the selective advantage conferred to cancer cells by acquired genetic alterations. More specifically, clonal evolution is proposed to be characterized by a multi-stage progression trajectory where each stage is delineable by phenotypes that are determined by the dynamics of coupling between cell-fate decision making and metabolism. As cancer cell entropy increases with the number of driver mutations, the coupling between cell bioenergetics and cell-fate decision-making enforces an upper limit on clonal potential for expansion. While accumulating driver mutations are permissive of intensified bioenergetic activities, they are also the source of high genetic instability that leads to metabolic insufficiency and replication failures. This proposition is explored using an extension of the tumor progression model of Bozic et al.[21] The model is built on a Galton-Watson branching process,[24] starting with a single cell that either divides or takes an alternate fate of "stagnation," which may be differentiation, senescence or death.[21] The model tracks the number of cells having k driver mutations, after being initiated using one cell having a single driver mutation. Each division is assumed to yield a daughter cell that acquires an additional driver mutation with probability u, that is, assuming an average mutation rate $\boldsymbol{u}$. The probabilities of stagnation and division of a cell with k mutations were set to $d_k = \frac{1}{2}(1-s)^k$, and $b_k = 1 - d_k$, respectively, where s is the selective advantage assumed to be conferred by a driver mutation.[21] Unlike the original model, the proposed extension uses a clone-dependent selective advantage to account for the varying degrees of fitness associated with the phenotypic heterogeneity of cancer cells. This leads to the probability of stagnation $d_k = \frac{1}{2}(1-s_k)^k$, where s_k is the selective advantage assumed to be conferred by a driver mutation on the k-clone, that is, clone with k driver mutations, defined based on the conjectured constraint imposed by the coupling between cell fate decision-making and metabolism as follows:

$$s_k = s_0 E_k H_k \tag{3}$$

Here, E_k and H_k are the average metabolic and information processing capacities of the k-clone and s_0 is a constant chosen so that the founding clone, that is, having a single driver mutation, will have an average selection equal to the one used in the tumor progression model of Bozic et al.[21] The clone selection coefficient is defined as the product of the energy and information capacities, representing the first order dynamics of their coupling. It is objectively grounded in the dynamics of signaling and metabolic networks which constitute the biophysical support of cell life. Furthermore, the proposed definition of the clone selection coefficient embodies a tangible link between signaling pathways, which are the primary objects of therapeutic interventions, and the phenotypic realm upon which evolution acts. The conjectured relationships between signaling entropy, cell metabolic capacity and information processing capacity, illustrated in Figure 2, are modeled for clone k as follows:

$$E_k = 2E_{0k}\left(\frac{1}{1+e^{-Q_k+Q_2}} - \frac{1}{1+e^{-Q_k+Q_{10}}}\right) \quad (4)$$

$$E_{0k} = 1 - \sum_{j \neq k} \frac{n_j}{K} \quad (5)$$

$$H_k = e^{-Q_k} \quad (6)$$

$$Q_k = -\frac{k\log\left(\frac{k}{m}\right)}{1+\log(m)} \quad (7)$$

Here n_j is the size of clone j, while K is the carrying capacity, that is, the total number of tumor cells that can be supported by the environment. Given k driver mutations affecting m directed graph paths in the cell signaling network, the probability π_j that path j is an oncogenic driver is estimated as $\pi_j = k/m$. Substituting this estimate of π_j in equation (1) lead to the average entropy Q_k of the k-clone. Q_2 and Q_{10} are the entropies of clones having 2 and 10 driver mutations respectively. Drawing a parallel to Knudson two-hit hypothesis,[25] the occurrence of the second driver mutation is assumed to be a critical event that ushers a phase of accelerated replication of cancer cells and a corresponding rise of their energy states. On the other hand, given the range of 1 to 10 driver mutations carried by tumors,[10] reaching the cumulative level of 10 driver mutations corresponds to a second critical event associated with the commencement of a tumor progression phase characterized by high genomic instability, metabolic insufficiency and rare clone replications. E_{0k} represents the maximum metabolic capacity that can be harnessed by tumor clone k. It is defined on a scale of 0 to 1 as a function of the carrying capacity K. H_k and E_k are normalized quantities with values ranging from 0 to 1. They represent average values over the set of cancer cells making up clone membership. At zero entropy, the cell information processing capacity is at its highest, that is, 1, whereas its metabolic output is 0.36, or 36% of its maximum potential E_{0k}. At very high entropy, both information processing and metabolic capacities converge to 0. These boundary conditions reflect the two starkly distinct phenotypes: the normal phenotype, endowed with a high information processing capacity judiciously using about a third of its metabolic capacity, and the senescent phenotype where the high entropy resulting from extensive genetic alterations drives the information processing and metabolic capacities to 0, abrogating as a result the cell's capacity to maintain a normal life-cycle. This model reflects the existence of a spectrum of cancer transformed and proliferative phenotypes flanked by normal and senescent phenotypes. The phenotypic spectrum as modeled above is discrete and tied to the number of driver mutations which represents the clone average state. In reality, however, there is an inherent diversity within each clone membership due to the stochasticity of genetic alterations. The accumulation of passenger mutations that are different and acquired at different rates within the same clone is one potential generator of such diversity. Contrary to the strongly held notion that passenger mutations do not confer fitness advantage, a recent study shows that passenger mutations have an aggregated effect on tumorigenesis and cancer progression.[1] This corroborates the proposed evolutionary model of tumor progression, whereby genetic alterations of any type would affect cell signaling and lead, under the pressures of an evolving, heterogeneous TME, to phenotypic diversity of cancer cells and a corresponding variability of their capacity to survive and proliferate.

Simulating the tumor evolutionary model using $u = 0.000034$ with each generation set to 3 days as was done in the original model,[21] yields the tumor progression dynamics illustrated by 4 examples shown in Figure 3, obtained after 3000 simulation runs of the model. The number of directed graph paths in the cell signaling network is set to $m = 64$ based on the consideration of 10 canonical pathways[26] (cell cycle, Myc, Hippo, Notch, Nrf2, PI-3Kinase/Akt, RTK-RAS, TGFB signaling, p53 and B-catenin/Wnt) involved in cross-talk, where each receptor (input) of the 10 canonical pathways reaches 64% of the downstream (output) nodes of these canonical pathways.[27] The number of oncogenic directed paths having a significant impact on tumor progression dynamics may vary depending on the cancer type. However, such number is significantly larger than the presumed maximum number of driver mutations, justifying hence the assertion that $k/m \ll 1$ and that entropy Q_k is monotonically increasing with the accumulation of new driver mutations and the progression through cancer stages.

The simulation illustrates the working of the conjectured cell-inherent adaptive fitness as a potential source of constraints on evolutionary dynamics of tumor progression. In particular, the overwhelming majority of simulation runs did not yield any tumors, highlighting the challenge of predicting cancer occurrence based on genomic profiling. The model recapitulates the variability of tumor progression trajectories and points to a constrained clonal expansion. For instance, the final tumor size for the overwhelming majority of patients rarely reaches the carrying capacity K which was set to 10^9, while the most probable number of clones across all simulation runs is 4 and does not exceeds 6. This limitation on the number of emergent clones is in line with the observation of phenotypic convergence in multifocal lung cancer.[28] The second corollary of the conjectured cell adaptive fitness is the predicted increase of the average tumor entropy Q_T accompanying tumor growth progression (see Figure 4). The average entropy of a tumor is defined as $Q_T = \frac{1}{N}\sum_{k=1}^{Nk} n_k Q_k$, where n_k is the size of the k-clone, Nk is the total number of clones and $N = \sum_{k=1}^{Nk} n_k$ is the total number of cancer cells in the tumor. According to the

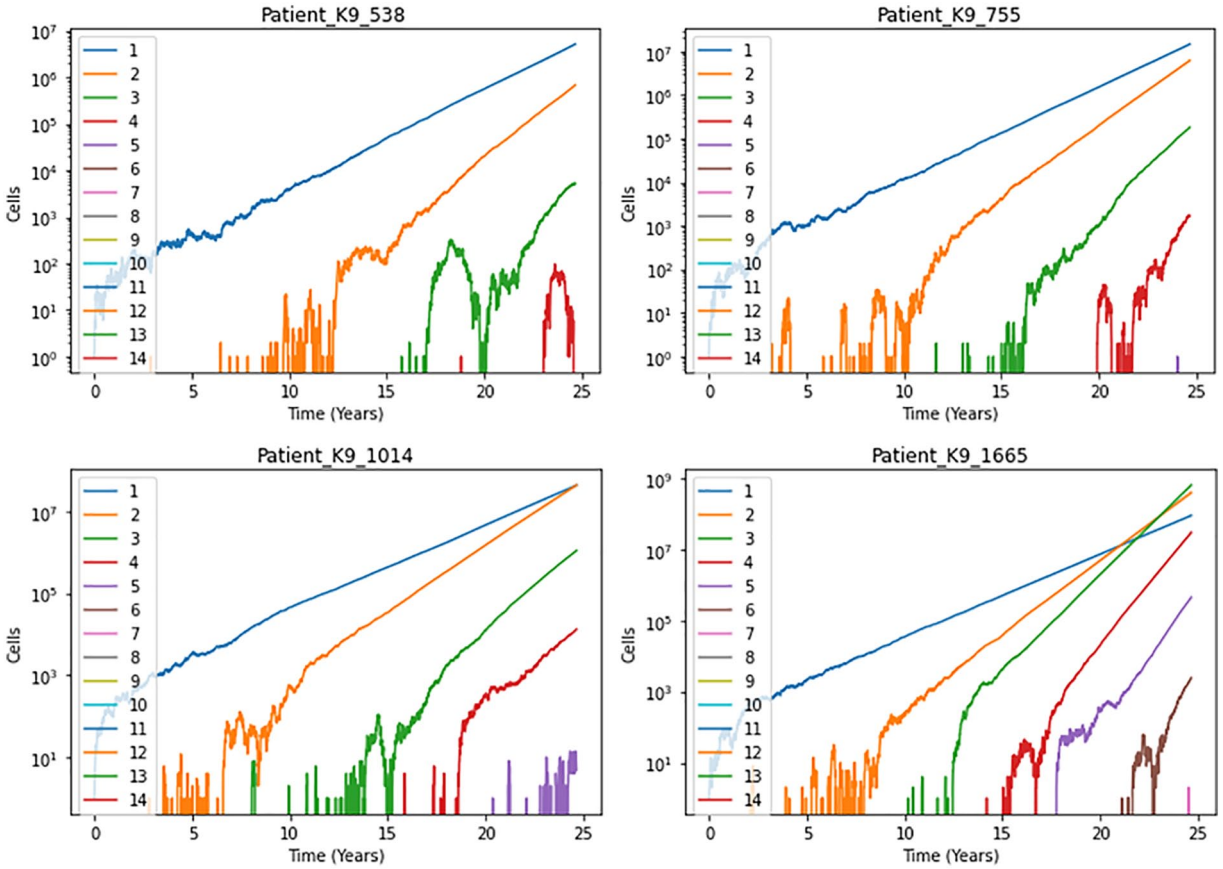

Figure 3. Constrained evolutionary dynamics of tumor progression. Clone size (number of cells with a given number of driver mutations) versus the age of the tumor. Four simulation runs of the extended tumor progression model with a clone-dependent selective advantage. The widely varying dynamics of tumor growth is distinguished by a marked constraint on the number of emerging clones. Simulation runs are labeled as hypothetical patients.

simulation's results, tumor progression is accompanied with a monotonically increasing average tumor entropy. However, there are short intervals of time such as those near year 5 and year 10 for the hypothetical patients Patient_K9_1897 (Figure 4a) and Patient_K9_993 (Figure 4d), respectively, where the average tumor entropy experienced transient local peaks before resuming its trend of monotonic increase. These instances correspond to the emergence of new clones that did not survive, leading to a transient contribution to the average tumor entropy. Given the highly differentiated patterns of tumor average entropy across patients, the rate of entropy change may be used to monitor tumor progression dynamics. This may be of particular utility to the design of cancer adaptive therapies, where the average entropy of a tumor could be estimated based on circulating tumor DNA (ctDNA) to serve as a proxy biomarker for tumor burden.

Implications for Therapeutic Strategies

The proposed perspective on tumor evolutionary dynamics has the potential to support the design of therapeutic strategies that are based on eco-evolutionary principles such as adaptive therapies.[8] Adaptive combination therapies are promising approaches for the management of drug resistance and residual disease. Their effectiveness hinges on the accurate monitoring of tumor burden and requires, at a minimum, a one-step ahead prediction of clonal composition. Such monitoring enables the consideration of the disease's evolutionary potential which leverages genetic diversity and epigenetic plasticity to sustain robust trajectories of growth under therapeutic targeting.[6,29-31] Indeed, tumors with highly diverse clonal compositions are more likely to harbor malignant cell phenotypes,[32,33] and are associated with worst outcomes for various cancers.[34-39] Estimating cancer evolutionary dynamics is therefore necessary for the development of effective therapies, including adaptive therapies aiming to control cancer based on ecological principles of clonal competition.[40,41] Although the nonlinear dynamics of cancer and the uncertainty on the knowledge of the initial conditions of carcinogenesis limit the predictability of cancer dynamics,[42-45] the postulated existence of a cell-inherent adaptive fitness may enable the estimation of clonal dynamics up to a time horizon that may be sufficient to support effective adaptive therapies. Monitoring tumor clonal and sub-clonal compositions using ctDNA liquid biopsy[46] would provide the mean to estimate clonal and tumor average entropies. Given the multi-stage clonal evolution, conjectured to be marked by a monotonically increasing clonal entropy, a one-step-ahead prediction of stage-transitions could serve as a feedback for the adaptation of cancer therapy. In this context,

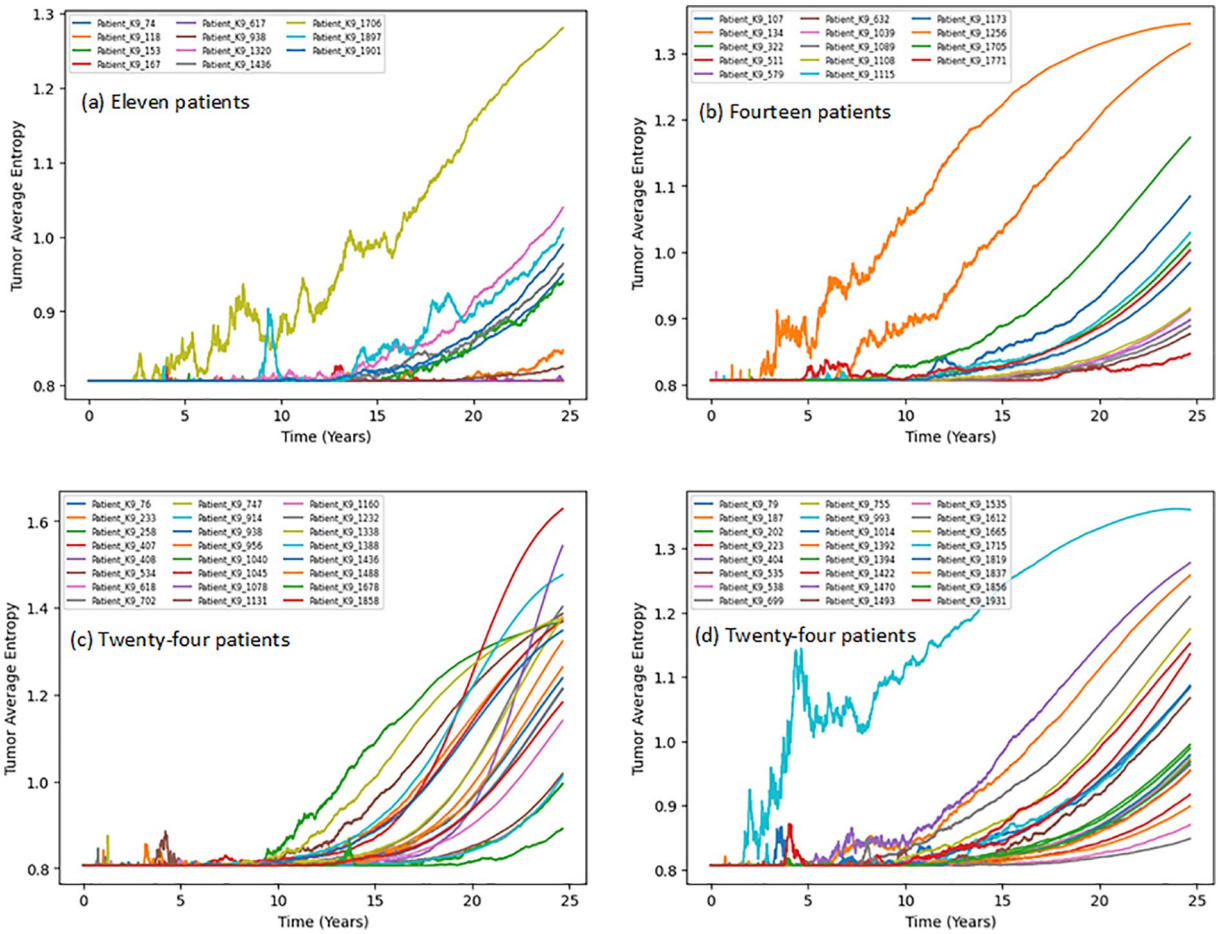

Figure 4. Tumor average entropy. (a) 11 patients, (b) 14 patients, (c) 24 patients, and (d) 24 patients. Four simulation runs (a–d) of the stochastic tumor progression model yielding different numbers of tumors, labeled as hypothetical patients. Each color represents the tumor average entropy as a function of time for one hypothetical patient. Patients are differentiated by starkly distinct trends of the tumor average entropy.

multiple drugs may be combined sequentially, concurrently or using a mixed schedule thereof to control the disease and prevent the emergence of therapeutic resistance. Monitoring the patterns of expansion-stagnation of specific clones, would inform precision therapeutic targeting that needs to be applied at each round of therapy. This may involve continuing with the same drugs, switching between drugs used in previous rounds of therapy or introducing new drugs, based on the observed evolution stages of tumor clones. For example, when a clone is predicted to enter a stagnation stage based on their estimated signaling entropy and energy-information profile, targeting a driver mutation using TKIs (tyrosine kinase inhibitors) would increase toxicity without significant therapeutic benefits. On the other hand, targeting clones before an anticipated commencement of expansion would have a more significant effect on outcome. However, given the evolutionary dynamics of tumor progression, every therapeutic action will have an adaptive tumor survival reaction. Therein lies the potential utility of the proposed evolutionary model as a predictive component of clinical decision-support systems that may be conceived to assist oncologists in the design of adaptive cancer treatment strategies that leverage the advantage of anticipating cancer evolution toward thwarting therapeutic resistance.

The prediction of clonal, evolutionary stage transitions would also be of utility to adjuvant therapies, which are designed to eliminate small residual populations of cancer cells associated with minimal residual disease (MRD). For instance, colorectal cancer (CRC) cells were shown to have an equal potential to become drug-tolerant persister (DTP) in response to therapy,[47] and that such transitions to the DTP state is fostered by an increase of mutation rate.[48] In light of the proposed conjecture, the timing of clonal expansion would coincide with an increase of clonal signaling entropy induced by heightened mutability and a corresponding switch to a proliferative state. Given this observation, longitudinal MRD monitoring, using ctDNA liquid biopsies, could include the tracking of clonal signaling entropy to distinguish between high entropy clones converging toward senescence from the low entropy clones having a higher potential for drug resistance. This would inform the design of more effective adjuvant therapies that focus on the latter population of residual cancer cells (i.e., having lower entropy) to preempt the emergence of DTP clones. Such therapeutic approach, which may be qualified as a precision adjuvant therapy, would be an improvement on current adjuvant therapies used for various cancers to prevent recurrence and metastasis.

Discussion

The proposed cell adaptive fitness conjecture implies that clonal architecture is characterized by an increasing average entropy and is shaped by a selective advantage $s_k = s_0 E_k H_k$ that leads to phenotypic convergence toward three broad cancer cell phenotypes, namely: (1) stem-like potentially therapy-resistant tumor cells characterized by low signaling entropy with a fitness similar to that of normal cells, (2) proliferating cancer cells with entropy levels that yield a high energy/metabolic state, and (3) a high-entropy senescent cancer cells with limited information processing capacity and a low energy state that abrogate their ability to replicate. The convergence toward PTEN loss in distinct metastatic sites having different PTEN alterations[49] and the convergent activation of the MTOR pathway in clear cell renal cell carcinomas[50] are examples of phenotypic convergence whose emergence may be explained by the proposed notion of cell adaptive fitness selecting for the loss of PTEN and the activation of the MTOR pathway as routes leading to the emergence of the proliferative phenotype. Recurrent evolutionary trajectories identified for different cancer types[11] may also be explained by the cell-inherent adaptive fitness which would hence be universally relevant to all cancers. On the other hand, senescent tumor cells being present in the leading fronts of tumors,[51] lends support to the prediction of the model that senescence is associated with high-entropy tumor cells from late clone variants. The conjectured directionality of tumor progression along an increasing entropy of newly emerging clones and sub-clones suggests that early clone variants are likely to be harboring cancer cells that would be therapeutically resistant. Their low entropy afforded them with a wide-mouth funnel of potential evolutionary trajectories of adaptation to therapeutic interventions. Furthermore, given that most common cancer treatments involve the use of cytotoxic drugs that target fast proliferating cancer cells, that is, those with high energy/metabolic states, therapeutic strategies should include resistance management plans that focus on early clone variants that harbor stem-like low-entropy cancer cells.

The conjecture is an attempt to explain evolutionary dynamics of tumor growth through the lens of the coupling between signaling and metabolic pathways as the mediator of dynamic interactions between the tumor and its co-evolving heterogenous microenvironment. It is also an attempt to offer analytic insight into the causal chain linking pathways as targets of therapeutic actions, and tumor growth dynamics as indicators of clinical outcome. Full evidentiary support for the conjecture will ultimately rest on future clinical validations of its characterization of clonal evolution and the extent to which such characterization is successful in enabling improvements of cancer treatment strategies. In this respect, longitudinal monitoring of tumor mutational changes using liquid biopsies and next-generation sequencing (NGS) may be used in future efforts to build clinical support for the proposed conjecture and validate the corresponding model of tumor evolutionary dynamics. Data obtained through longitudinal tumor monitoring may be used in conjunction with known patterns of cancer evolutionary histories[9] and key oncogenic pathways to track clonal architecture and corresponding clonal and tumor entropies. Conjecture-supported tumor evolutionary trajectories would then be analyzed in relation to disease progression states, to be asserted using currently applicable protocols, as a first step toward developing supporting evidence for the clinical validation of the proposed conjecture.

Conclusions

The cell adaptive fitness conjecture embodies, to the author's knowledge, the first ever proposition put forth about the existence of an inherent cell adaptation mechanism wired in the coupling between cell signaling and metabolism to maintain the cell potential for survival, growth and replication. Although driver mutations underly oncogenesis and tumor evolutionary dynamics, their accumulation will ultimately engender the emergence of evolutionary constraints driven by the coupling between signaling and metabolism, and manifested as a cell adaptive fitness that confers a varying clonal selective advantage and leads to phenotypic convergence. One of the consequences of cell adaptive fitness is that the increasing entropy shapes the phenotypic landscape of clonal evolution with clear implications for therapy. Low-entropy early clone variants are likely to harbor stem-like therapy resistant tumor cells, while high-entropy late clone variants are overwhelmed with senescence. The focus of cancer treatments on the proliferating phenotype, that is, having an entropy that maximizes the proliferation potential, should therefore be complemented with resistance management strategies that target the stem-like, low-entropy early clone variants.

Author Contributions

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ORCID iD

Youcef Derbal https://orcid.org/0000-0003-3317-9417

REFERENCES

1. Kumar S, Warrell J, Li S, et al. Passenger mutations in more than 2,500 cancer genomes: overall molecular functional impact and consequences. *Cell*. 2020; 180:915-927.
2. Beroukhim R, Mermel C, Porter D, et al. The landscape of somatic copy-number alteration across human cancers. *Nature*. 2010;463:899-905.
3. Bielski CM, Zehir A, Penson AV, et al. Genome doubling shapes the evolution and prognosis of advanced cancers. *Nat Genet*. 2018;50:1189-1195.
4. Loeb LA, Kohrn BF, Loubet-Senear KJ, et al. Extensive subclonal mutational diversity in human colorectal cancer and its significance. *Proc Natl Acad Sci U S A*. 2019;116:26863-26872.
5. Nowell PC. The clonal evolution of tumor cell populations. *Science*. 1976;194: 23-28.
6. Greaves M. Evolutionary determinants of cancer. *Cancer Discov*. 2015;5: 806-820.
7. Enriquez-Navas PM, Wojtkowiak JW, Gatenby RA. Application of evolutionary principles to cancer therapy. *Cancer Res*. 2015;75:4675-4680.

8. Gatenby RA, Brown JS. Integrating evolutionary dynamics into cancer therapy. *Nat Rev Clin Oncol*. 2020;17:675-686.
9. Gerstung M, Jolly C, Leshchiner I, et al. The evolutionary history of 2,658 cancers. *Nature*. 2020;578:122-128.
10. Martincorena I, Raine KM, Gerstung M, et al. Universal patterns of selection in cancer and somatic tissues. *Cell*. 2018;173:1823.
11. Caravagna G, Giarratano Y, Ramazzotti D, et al. Detecting repeated cancer evolution from multi-region tumor sequencing data. *Nat Methods*. 2018;15:707-714.
12. Ward PS, Thompson CB. Signaling in control of cell growth and metabolism. *Cold Spring Harb Perspect Biol*. 2012;4:a006783.
13. Wang YP, Lei QY. Metabolite sensing and signaling in cell metabolism. *Signal Transduct Target Ther*. 2018;3:30.
14. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646-674.
15. Billingsley P. *Ergodic theory and information*. Wiley; 1965; xiii, 193.
16. Demetrius L, Manke T. Robustness and network evolution—an entropic principle. *Physica A*. 2005;346:682-696.
17. West J, Bianconi G, Severini S, Teschendorff AE. Differential network entropy reveals cancer system hallmarks. *Sci Rep*. 2012;2:802.
18. Teschendorff AE, Sollich P, Kuehn R. Signalling entropy: a novel network-theoretical framework for systems analysis and interpretation of functional omic data. *Methods*. 2014;67:282-293.
19. Derbal Y. On signaling dysregulation in cancer. In: Proceedings of the 2021 International Conference on Computational Science and Computational Intelligence (CSCI), 2021:318-323.
20. Banerji CR, Miranda-Saavedra D, Severini S, et al. Cellular network entropy as the energy potential in Waddington's differentiation landscape. *Sci Rep*. 2013;3:3039.
21. Bozic I, Antal T, Ohtsuki H, et al. Accumulation of driver and passenger mutations during tumor progression. *Proc Natl Acad Sci U S A*. 2010;107:18545-18550.
22. Andor N, Maley CC, Ji HP. Genomic instability in cancer: teetering on the limit of tolerance. *Cancer Res*. 2017;77:2179-2185.
23. Janssen A, Medema RH. Genetic instability: tipping the balance. *Oncogene*. 2013;32:4459-4470.
24. Athreya KB, N PE. *Branching Processes*. Springer; 1972.
25. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci USA*. 1971;68:820-823.
26. Sanchez-Vega F, Mina M, Armenia J, et al. Oncogenic signaling pathways in the cancer genome atlas. *Cell*. 2018;173:321-337.
27. Rowland MA, Greenbaum JM, Deeds EJ. Crosstalk and the evolvability of intracellular communication. *Nat Commun*. 2017;8:16009.
28. Ma P, Fu Y, Cai MC, et al. Simultaneous evolutionary expansion and constraint of genomic heterogeneity in multifocal lung cancer. *Nat Commun*. 2017;8:823.
29. Mroz EA, Rocco JW. The challenges of tumor genetic diversity. *Cancer*. 2017;123:917-927.
30. Dagogo-Jack I, Shaw AT. Tumour heterogeneity and resistance to cancer therapies. *Nat Rev Clin Oncol*. 2018;15:81-94.
31. Derbal Y. The adaptive complexity of Cancer. *Biomed Res Int*. 2018;2018:5837235.
32. Greaves M, Maley CC. Clonal evolution in cancer. *Nature*. 2012;481:306-313.
33. Noble R, Burley JT, Le Sueur C, Hochberg ME. When, why and how tumour clonal diversity predicts survival. *Evol Appl*. 2020;13:1558-1568.
34. Maley CC, Galipeau PC, Finley JC, et al. Genetic clonal diversity predicts progression to esophageal adenocarcinoma. *Nat Genet*. 2006;38:468-473.
35. Martinez P, Timmer MR, Lau CT, et al. Dynamic clonal equilibrium and predetermined cancer risk in Barrett's oesophagus. *Nat Commun*. 2016;7:12158.
36. Schwarz RF, Ng CK, Cooke SL, et al. Spatial and temporal heterogeneity in high-grade serous ovarian cancer: a phylogenetic analysis. *PLoS Med*. 2015;12:e1001789.
37. Jamal-Hanjani M, Quezada SA, Larkin J, Swanton C. Translational implications of tumor heterogeneity. *Clin Cancer Res*. 2015;21:1258-1266.
38. Park SY, Gönen M, Kim HJ, Michor F, Polyak K. Cellular and genetic diversity in the progression of in situ human breast carcinomas to an invasive phenotype. *J Clin Investig*. 2010;120:636-644.
39. Rye IH, Trinh A, Saetersdal AB, et al. Intratumor heterogeneity defines treatment-resistant HER2+ breast tumors. *Mol Oncol*. 2018;12:1838-1855.
40. West J, You L, Zhang J, et al. Towards multidrug adaptive therapy. *Cancer Res*. 2020;80:1578-1589.
41. Gatenby RA, Silva AS, Gillies RJ, Frieden BR. Adaptive therapy. *Cancer Res*. 2009;69:4894-4903.
42. Dalgleish A. The relevance of non-linear mathematics (chaos theory) to the treatment of cancer, the role of the immune response and the potential for vaccines. *QJM*. 1999;92:347-359.
43. Uthamacumaran A. A review of dynamical systems approaches for the detection of chaotic attractors in cancer networks. *Patterns*. 2021;2:100226.
44. Coffey DS. Self-organization, complexity and chaos: the new biology for medicine. *Nat Med*. 1998;4:882-885.
45. Lipinski KA, Barber LJ, Davies MN, Ashenden M, Sottoriva A, Gerlinger M. Cancer evolution and the limits of predictability in precision cancer medicine. *Trends Cancer*. 2016;2:49-63.
46. Porras TB, Kaur P, Ring A, Schechter N, Lang JE. Challenges in using liquid biopsies for gene expression profiling. *Oncotarget*. 2018;9:7036-7053.
47. Khaleel Rehman S, Haynes J, Collignon E, et al. Colorectal cancer cells enter a diapause-like DTP state to survive chemotherapy. *Cell*. 2021;184:226-242.
48. Russo M, Crisafulli G, Sogari A, et al. Adaptive mutability of colorectal cancers in response to targeted therapies. *Science*. 2019;366:1473-1480.
49. Juric D, Castel P, Griffith M, et al. Convergent loss of PTEN leads to clinical resistance to a PI(3)Kα inhibitor. *Nature*. 2015;518:240-244.
50. Fisher R, Horswell S, Rowan A, et al. Development of synchronous VHL syndrome tumors reveals contingencies and constraints to tumor evolution. *Genome Biol*. 2014;15:433.
51. Park SS, Choi YW, Kim JH, Kim HS, Park TJ. Senescent tumor cells: an overlooked adversary in the battle against cancer. *Exp Mol Med*. 2021;53:1834-1841.