Review Article

Mechanisms of Selection on Cancer-Causing Mutations

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The mainstream thinking in the somatic evolution of cancer is mainly mutation centered. In contrast, the evolutionary idea that selection rather than mutation is rate-limiting in cancers is a recent realization. So far, however, there are few insights into how selection works on cancer-causing mutations in the context of the tissue microenvironment. A cancer-causing mutant also causes one or more disruptions of normal cellular metabolism. Therefore, the mutant is unlikely to be selected in competition with normal cells. However, under specific contexts, when the normal adult stem cell dynamics are altered, the mutant is likely to gain a selective advantage and thereby outgrow normal cells. We suggest a battery of hypotheses about how context-dependent selection is likely to act at the cellular and molecular levels. We also weigh the hypotheses against available evidence and suggest a line of experiments that can test them.

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Introduction

It is a generally held view that cancer arises through somatic evolution that needs multiple mutational events. Mutational accumulation alone does not explain all the patterns observed, and an upcoming view attributes a substantial role to selection acting on potentially cancer-causing mutations, the selective forces being mediated by the microenvironment [1][2][3][4]. By the classical view, any mutation that escapes replication regulation and tissue homeostasis mechanisms should have a selective advantage in a population under regulation. Such mutants have been called cheater mutants [5][6][7]. Mutations that escape the regulation mechanisms should have an all-time selective advantage, but the epidemiological patterns expected by this view do not match the actual epidemiological patterns [1]. Given the number of

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lifetime stem cell divisions in the human body and the mutation rates, it is inevitable that almost every individual will have cancer driver mutations. If such mutants had an unconditional advantage, the incidence of cancer during the average human lifespan would be expected to be exceedingly high in the population [1].

A detailed look at the function of oncogenes and tumor suppressor genes reveals that apart from being associated with carcinogenesis, these genes have multiple normal vital functions, sometimes called "non-canonical" functions [8][9], that can be affected by the mutation. If a mutation removes the replication regulation mechanism on a cell but simultaneously cripples it in some other essential function, the cell may not get the presumed advantage of the removal of replication regulation in competition with the normal cell. However, if the replication of normal cells is suppressed further for any other reason, the mutant may get an advantage even with its crippled metabolic state. Therefore, it is illogical to expect these mutants to have an all-time selective advantage over normal cells. They can have an advantage under specific conditions. In this sense, the selection on potentially cancer-causing mutations is claimed to be "context-dependent," i.e., only under a set of microenvironmental conditions. In this sense, cancers are not mutation-limited but are selection-limited [1][2][3][4]. The context-dependent selection model explains the pathophysiological as well as epidemiological patterns in cancer very successfully [1], but the specifics of which context selects for which mutation and why are yet to be elucidated. There is one clear experimental demonstration of selection [10], and a few more are hypothesized [11]. Here, we broaden and generalize the potential contexts in which carcinogenic mutations can get a selective advantage.

The hypothesis framework

A large variety of mutations are implicated as drivers in different types of cancers, and if context-dependent selection is the keystone of cancer biology, we need a theoretical framework for how selection may work. As a general case representation (Table 1), the growth rate of normal adult stem cells (ASCs) in a healthy condition is denoted by $R_{n,\,h}$; mutant ASCs in healthy conditions by $R_{m,\,h}$; $R_{n,\,a}$ implies normal ASCs in an altered environment a; and $R_{m,\,a}$ implies mutant ASCs in an altered environment.

Condition	Normal ASCs(n)	Mutant ASCs(m)
Healthy micro-environment (h)	$R_{n,h}$	$R_{m,h}$
Altered micro-environment (a)	$R_{n,a}$	$R_{m,a}$

By the context-independent selection theory, mutant ASCs will have a greater R value than normal ASCs even in healthy microenvironmental conditions, i.e., $R_{m,h} > R_{n,h}$. By the context-dependent selection theory, the R value of mutant ASCs will be greater than the R value of normal ASCs only under altered microenvironmental conditions, i.e., $R_{m,a} > R_{n,a}$, and not under healthy microenvironmental conditions, i.e., $R_{m,h} <= R_{n,h}$. It is not necessary that $R_{m,a} > R_{m,h}$ or $R_{m,a} > R_{n,h}$.

We now develop a few example hypotheses for the altered microenvironmental conditions under which the mutant is likely to have a selective advantage over a normal ASC. Further, we also indicate which of the cancer driver mutations are likely to get selected under such contexts. As preliminary support for the hypothesis, we examine whether the hypothesis is compatible with known epidemiological patterns. As a logical next step, we suggest how the hypotheses can be empirically tested *in vitro* or *in vivo*. Making and testing such hypotheses opens up novel potential lines of research to understand the fundamentals of the somatic evolution of cancer.

1. Growth factor deficiency and growth factor-independent mutants: This line of thinking exists in the literature, and there is one example of an empirical test as well. Growth factor signaling is one of the crucial mechanisms in the regulation of cell dynamics at both normal and wound-healing levels of regulation [11]. Three types of mutations related to EGF signaling are known to occur in different types of cancers. One leads to overexpression of the EGF receptor (EGFR), another leads to the internal synthesis of EGF by cancer tissue, and the third makes pathways downstream of EGF signaling constitutive. In short, the cell becomes partly independent of external EGF signaling. But this implies a higher investment for the cell [12]. If the external EGF signal is normal, this extra investment would put the mutant at a slight disadvantage, making $R_{m,h} < R_{n,h}$. But if the external signal is weak, any of the three types of mutants will gain a selective advantage, as shown in Figure 1, i.e., $R_{m,a} > R_{n,a}$. Therefore, a chronically subnormal level of EGF is the context required for the selection of any of the three types of mutants.

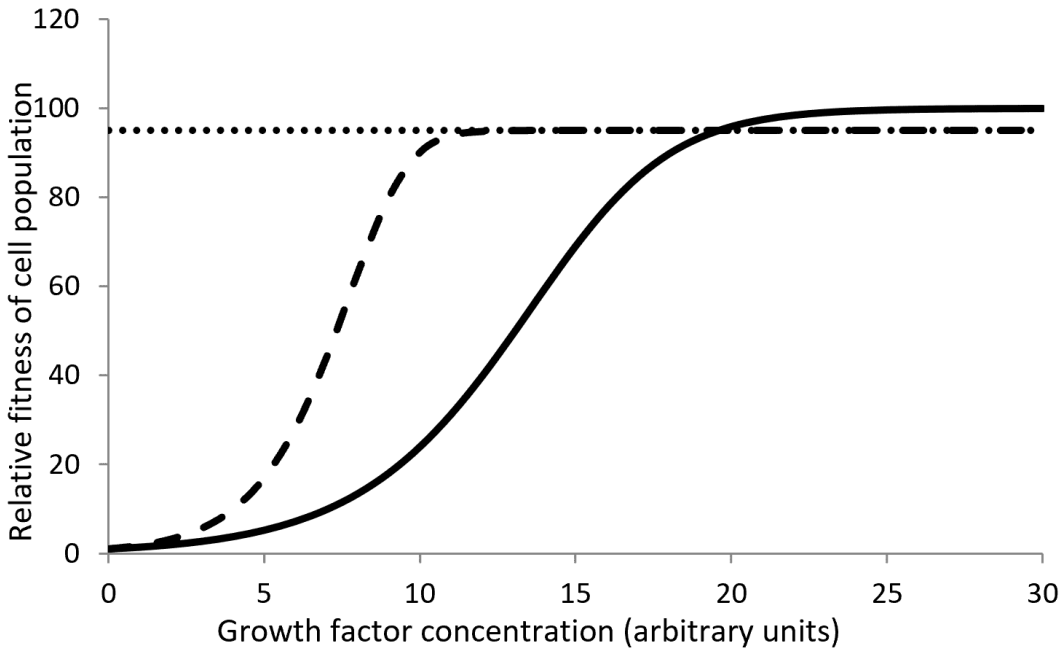

Figure 1. *(Adopted from Baig et al., 2023) Expected growth responses of normal (solid line) and receptor-overexpressing (dashed line) mutants to different growth factor concentrations. At low growth factor concentrations, the mutant may gain a competitive advantage over the normal cell, but at high concentrations, it may lose it owing to the extra cost it pays for overexpressing the receptor.*

- A similar case with IGF has been demonstrated experimentally by Archetti et al. [10]. In an *in vitro* experimental competition between IGF-II producer and non-producer cells, at low external IGF-II, the producer grew better, but at higher IGF-II, the non-producer outcompeted the producer. This is a clear empirical demonstration of context-based selection.

2. The stem cell renewal-differentiation balance: Stem cell dynamics need asymmetry in the fate of daughter cells. One of them takes the differentiation pathway and another renews to join back the pool of adult stem cells (ASCs) [13]. Multiple signaling pathways are involved in maintaining this balance. For example, P53 facilitates differentiation whereas EGF facilitates renewal. Baig et al. [11] hypothesized a context-based selection on the EGF-P53 balance. If there is a chronic deficiency of EGF signaling, more cells are likely to take the differentiation path and gradually deplete the stem cell pool. Under such circumstances, a P53 mutant is more likely to go to renewal, in spite of low EGF, because of which the stem cell pool will get enriched in P53 mutants. But when EGF signaling and stem cell renewal are normal, P53 mutants are less likely to compete with normal

stem cells, i.e., $R_{m,\ h} <= R_{n,\ h}$, because the normal functions of P53, including maintenance of mitochondrial efficiency, [14][15] are lost. Chronic deficiency of EGF signaling is a possible specific context in which P53 mutants might get selected.

Notch signaling is known to facilitate differentiation [16][17] and bone morphogenetic protein (BMP) antagonizes Notch signaling in deciding the daughter fate determination after stem cell division [17] [18]. BMP is also involved in iron metabolism, and deficiency of iron leads to lower expression of BMP. In addition, BMP expression is also responsive to injury and impacts because that necessitates strengthening of bones [19][20][21]. A combination of sedentary life and iron deficiency is therefore expected to lead to lower BMP expression, making Notch-induced differentiation excessive. In this context, a Notch under-expressing mutant is likely to get enriched in the ASC population. In contrast, when BMP is normal, both the normal ASCs and Notch-inactivating mutants would contribute to the stem cell pool. However, Notch-inactivating mutants would have a selective disadvantage due to the necessity of Notch in multiple normal cellular pathways [22][23].

One more example is that of Beta-catenin, which stimulates stem cell renewal, pluripotency, and mesenchymal transition. WNT signaling is known to stimulate and APC to degrade beta-catenin, and a balance in these signaling pathways keeps the stem cell dynamics normal. IGF1 increases expression and stability of beta-catenin [24][25][26]. A combination of stress and subnormal IGF signaling will keep beta-catenin suppressed, due to which stem cell renewal is likely to be subnormal. Under this condition, a cell overexpressing beta-catenin, either by mutated APC or mutated beta-catenin itself, is more likely to follow the renewal path and therefore get enriched in the stem cell population.

3. Cell cycle and proliferation regulation: The cell cycle is a highly regulated process, and the regulation is crucial for tissue homeostasis. Different signaling pathways can facilitate or arrest a given stage of the cell cycle. It is tempting to assume that any mutant that relaxes the regulation and allows the cell to proliferate will always get selected. But we see with examples that this is not the case.

   The retinoblastoma protein pRb regulates the cell cycle mainly by preventing the entry of the cell cycle into S phase and thereby arrests cell proliferation [27]. This is antagonized by growth factors including IFG I, EGF, and PDGF acting through CDKCs [28][29][30]. A pRb mutant will not be able to arrest the cell cycle, and the mutant cell would proliferate. However, whether this mutant gets a selective advantage depends upon the growth factor signaling. In the presence of adequate growth

factor signals, both normal and mutant cells can proliferate. But pRb has many other functions in the cell, including mitochondrial respiration, the electron transport chain, alterations in the mitochondrial polarity, and a preference towards glutamine uptake [31]. Therefore, when both can proliferate, a *Rb* mutant might be at a substantial disadvantage, making $R_{m,\,h} < R_{n,\,h}$. But when growth factor signals are chronically subnormal, normal cells would remain suppressed, making $R_{m,\,a} > R_{n,\,a}$.

PTEN is a tumor suppressor gene that is frequently mutated or lost in many human cancers. PTEN regulates cell proliferation, and a mutation inactivating it may be expected to have an advantage. However, PTEN is also important in normal cell functions, including mitochondrial functions and genomic stability [32][33]. So it is likely that this disadvantage offsets the possible proliferative advantage to PTEN mutants. Only when the cell cycle remains abnormally suppressed due to some kind of stress or deficiency can PTEN mutants outcompete.

Similarly, p16 is a tumor suppressor gene which, when inactivated, can contribute to cancer development. It is primarily involved in DNA damage repair, maintenance of genome stability, cell cycle, and cell proliferation regulation. Under oxidative stress, normal cells respond by upregulating p16 expression [34]. This upregulation leads to a temporary arrest of cell proliferation, allowing the cell to repair oxidative damages. The p16 mutant cell, in contrast, continues to proliferate even in the presence of oxidative stress. Therefore, under chronic oxidative stress, $R_{m,\,a} > R_{n,\,a}$. In the absence of oxidative stress, while normal cells maintain regulated proliferation, a P16 mutant will be deficient in mitochondrial biogenesis and many other normal functions [35][36], making $R_{m,\,h} <= R_{n,\,h}$.

4. Facilitation of angiogenesis: Angiogenesis is affected by a number of growth factors and other signals, and in a sedentary lifestyle, many of these signals are deficient. As a result, capillary density reduces, and so does transport of nutrients and oxygen [37][38][39]. Below a threshold, the supply of nutrients, oxygen, or growth factors through blood would become growth-limiting. In this context, if a mutant cell expresses angiogenic signals, it can increase local capillary density and thereby is able to proliferate more than others. This advantage may be shared by some of the neighboring normal cells too, and this is a game-theoretical problem [10]. In this situation, the mutants are expected to get a frequency-dependent selective advantage.

   For example, PTEN mutants are known to stimulate angiogenesis through VEGF. This raises the possibility that when angiogenesis is grossly subnormal, a PTEN mutant cell stimulates capillary

formation around it and gets a greater nutrient supply [40][41]. Such a cell can get selected over the severely nutrient-limited normal cell.

5. Glucose supply for cell proliferation: Apart from a pro-proliferation signal, cell proliferation also needs an adequate energy supply. Therefore, restricting glucose uptake or the process of glycolysis can also keep proliferation in check. Insulin is a mitogen as well as a facilitator of glucose uptake, but the two functions are executed by different pathways. The insulin receptor INSR-A triggers cell proliferation signals, whereas INSR-B is responsible for the pathway leading to glut-4 docking and thereby glucose uptake [42]. In chronic hyperinsulinemia, both pathways are expected to be upregulated, but that is prevented by a feedback operating through P53 [43][44]. P53 induces insulin resistance, because of which glucose uptake remains normal in spite of high insulin. This becomes a case where there is a mitogenic signal but energy restriction puts a limit on proliferation. This is the context in which a P53 mutant can get a selective advantage because it will have upregulated glucose uptake as well. When insulin signaling is normal, this mutant is unlikely to experience any advantage. Instead, the normal functions of P53 being impaired, it will be at a disadvantage.
6. Telomerase expression: In stem cell dynamics, TERT induces enhanced resistance to cell death under cellular stresses. So TERT overexpression will be beneficial under conditions of stress, but in the absence of stress, cells overexpressing TERT would be paying an extra cost for the overexpression and thereby become less competitive than normal cells.

   Vitamin D deficiency impairs normal telomerase expression [45]. Therefore, TERT overexpression may get selected under extreme vitamin D deficiency.

We have listed above a number of hypothetical contexts in which a cancer-causing mutant might get a selective advantage. More mechanisms are certainly likely, and a good understanding of the pleiotropy of gene functions will be required to reveal them.

Evidence from published literature

An immediate but preliminary test of our hypothesis would be to see what epidemiological predictions can be made from the specific examples and whether they match observed patterns.

i. Many of our hypotheses depend upon altered growth factor expression. The expression of growth factors is behavior-responsive [46][47] and therefore a behavioral mismatch between the ancestral lifestyle in which human physiology evolved and the modern lifestyle can be a crucial element in

the proneness to many modern lifestyle-related disorders [48]. A sedentary lifestyle, in particular, is likely to create chronic growth factor underexpression and thereby increased chances of cancers. Epidemiological information about growth factor levels is scanty, but available studies are compatible with our hypothesis [49][50]. Further, other effects of a sedentary lifestyle, such as obesity, are associated with increased cancer risk [51]. Infants with very low birth weight seem to have lower concentrations of IGF-I and IGFBP-3 [52]. As expected by our hypothesis, sporadic retinoblastoma is more prevalent in such infants and underweight mothers [53][54].

ii. Of particular importance is the Cao et al. [55] experiment showing that behavioral enrichment leads to tumor regression. This effect of a behaviorally enriched environment has been found to be reproducible by many [56].

iii. As expected by our series of hypotheses, chronic stress and a deficiency of iron and of certain vitamins are associated with cancer incidence [57][58][59].

iv. A specific anomaly in cancer incidence is that if the somatic evolution of cancers is not mutation-limited, then why many mutagenic agents are also carcinogenic is a riddle, although not all carcinogens are mutagenic [60][61]. Our hypothesis potentially resolves this anomaly. DNA damage also suppresses the cell cycle, thereby giving time for the DNA repair mechanisms to act. Chronic exposure to mutagenic agents can keep the cell cycle unduly suppressed, giving a selective advantage to a mutant escaping the suppression in spite of any metabolic defect the mutation may have induced. In addition to being mutagenic, radiation exposure and other chronic mutagenic exposures also create the selective environment, and that completes the causal relationship between mutagens and cancers. Increasing the mutation rate alone is not likely to be a sufficient cause of cancer.

v. Non-mutagenic carcinogens: The presence of non-mutagenic carcinogens [61] itself indicates that something other than mutations is crucial for the somatic evolution of cancer. Whether and how the non-mutagenic carcinogens shape the selective landscape needs to be investigated in detail.

How to test the hypotheses empirically

It is possible to test our hypotheses empirically. One test already done by Archetti et al. [10] gives a prototype experimental design. Experiments for every specific molecular mechanism need to be designed based on this principle. Such experiments can be designed using the appropriate cell lines, with

specific induced mutants competing with non-mutants under controlled environmental conditions. In vivo experiments are also possible on the lines of the Cao et al. [55] experiment.

Implications for understanding cancer, prevention, and possible treatment

If the lifestyle factors that influence the selective microenvironment for cancer-causing mutations are identified, better cancer prevention strategies can be envisioned. The selection is a long-term process, and the chronic presence of the selective context is important. Therefore, as a general rule, monotonicity of the lifestyle-related risk factors is crucial for cancer development. As a general rule, avoiding monotonicity of lifestyle can be a good generic strategy for cancer prevention.

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