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Review Article

Somatic Evolution of Cancer: A New Synthesis

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Out of the multiple interpretations of cancers, two predominant ones have been (i) somatic evolution of cheater cells that escape replication regulation and (ii) cancers as non-healing wounds. Both interpretations have substantial support as well as glaring anomalies, but the two, along with other possible interpretations, have not been put together to make a coherent synthesis. We argue here that mechanisms and pathways to escape the normal regulation of cell proliferation do not need to evolve *de novo*. Mechanisms to override the normal regulation have already evolved for wound healing and tissue regeneration. Almost all of the hallmarks of cancer are also seen in the wound healing process. This suggests that cancer develops not by any *de novo* gain of function but by exaptation of pre-evolved wound healing functions. Somatic evolution that makes the wound healing triggers constitutive is not mutation-limited but selection-limited, and the selective forces are dependent on the tissue microenvironment. Some mechanisms for such selection have been suggested. Many more need to be investigated. A series of mechanisms have evolved to minimize the risk of cancers, which may fail in an altered lifestyle context. We support our synthesis with multiple lines of evidence and also make differential testable predictions. This evolutionary perspective challenges multiple prevalent ideas, suggests novel lines of research, and also has translatable implications for cancer prevention.

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Introduction

Cancer is a phenomenon of uncontrolled growth of certain cells defying the regulation mechanisms of the body. Owing to the complexity of carcinogenesis and the rapidly accumulating details, a number of alternative interpretations have been made with respect to the why and how questions. There is a need for a comprehensive and inclusive synthesis that minimizes the apparent contradictions and creates a logically coherent framework on which the details can be appropriately interpreted. We attempt such a synthesis here. The article is organized as follows. First, we outline very briefly the available alternative interpretations, then evaluate their strengths and weaknesses vis-a-vis the complexity of cancers. On this background, we state the new synthesis on the platform of sound evolutionary logic, along with whether and how mechanisms to minimize the risk of cancer would have evolved. We then evaluate available evidence for the synthesis and also state more testable predictions that suggest new lines of research. Ultimately, we discuss how it can be translated to cancer prevention.

The complexity and multitude of possible interpretations

Development of cancer is perceived as a process of somatic evolution[1][2]. Conceptually, there are multiple ways of visualizing this evolution which are not necessarily mutually exclusive, but with some apparent mutual contradictions and incompatibilities. Somatic mutations are commonly assumed to be necessary for the transformation of a normal cell into a malignant cell, but the dynamics of mutation accumulation is complex. Since most differentiated cells undergo senescence and die, mutations in them are most unlikely to be relevant to tumorigenesis. Mutations in the population of adult stem cells (ASC) are the ones under focus[3][4][5]. A single mutation is generally not sufficient, and accumulation of mutations specific to each type of cancer is required for the transformation. One view is that of a purely chance-driven accumulation of the required set of mutations[5]. Since the probability of co-occurrence of multiple mutations is very small, a process such as clonal selection was thought necessary[6][7]. On the other hand lies the idea of chromothripsis, in which a large number of chromosomal changes happen simultaneously and

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explosively in a single shot[8][9]. The thinking in the field has been largely mutation-centered. The extensively debated Peto's paradox[10][11][12], the presumption of chromothripsis as well as the idea of cancer as "bad luck" arises from the assumption that the somatic evolution of cancer is mutation-limited.

The behavioral evolution and sociobiology school of thought views cancer cells as "cheater" cells[13][14][15][16] and assumes that a cheater or selfish mutant that does not comply with the social norm of tissue homeostasis would get selected in the somatically evolving cell population. However, the notion that a cheater would always get selected stands challenged. A nuanced view, supported by multiple lines of evidence, is that the somatic evolution of cancer is selection-limited rather than mutation-limited[1][17][2][18]. Despite the evidence for selection, which factors are responsible for the selection of the cancer-causing or driver mutations is underexplored.

Diametrically opposite to the mutation accumulation view lies the suggestion that mutations are not necessary for cancers. There is a theory of non-mutational malignant transformation of cells[19]. The observed mutations might be a consequence rather than a cause of malignant transformations.

Phytostratigraphy data showing that a significant number of protein domains involved in cancer predate or are connected to the origin of multicellularity[20][21] has been interpreted toward an atavistic theory of cancers[22][23][24]. By this view, cancer represents a reversal of certain cells to a quasi-unicellular ancestral behavior[25]. Multicellularity needs intricate tissue homeostasis and restraint on multiplication, but unicellular behavior escapes these constraints.

Another independent perspective is that of cancer as a non-healing wound[26][27][28][29][30][31]. This perspective is based upon the multiple similarities observed between the mechanisms and pathways involved in cancers and the wound healing cascade. The similarity is remarkable, although yet to be completely explored, and any interpretation of cancer cannot ignore this data.

Complexity of cancers and the limitations of individual interpretations

No single theory so far has the ability to accommodate all the well-demonstrated phenomena observed during the development of cancer. The simple view of cancer as an accumulation of chance mutations, serially or at once[4][5][8][9], which implies that cancer is only bad luck[4][5] is not compatible with the observed epidemiological patterns[18]. Furthermore, attempts to prevent DNA damage have not succeeded in preventing cancers[32]. The population-level predictions of clonal expansion theory are also not compatible with the epidemiological picture[18].

The main limitation of the cheater cell paradigm[14][15][16] is that cancer development and metastasis have extremely complex dynamics involving a number of characteristics and complex cell-cell cooperation processes. Whether the entire complexity arises *de novo* by mutations is questionable. Secondly, unlike its implicit assumption, experiments do not always demonstrate the selective advantage of the intermediate mutants. *In vitro*, the IGF-II concentration in culture media was found to markedly alter the selective advantage of an IGF-II over-expressing mutant in cell competition[33]. Also, this hypothesis does not account for the remarkable similarity between cancer and wound healing pathways.

The atavistic theory and its versions assume that cancer cells grow like unicellular organisms, but in reality, the malignant tissue exhibits a number of complex phenomena including cell-cell cooperation, cross talk between different cells, co-option of blood vessels, interaction with the immune system, responsiveness to the microenvironment, etc.[34][35][36][37][38]. Organs of future metastasis are not passive receivers of circulating tumor cells. A very intricate and sophisticated level of communication is involved in metastasis[39]. The hallmarks and enabling characteristics of cancer have kept on increasing with increasing research inputs[40][41][42]. Of particular interest is the involvement of neurons in contributing to the hallmarks and enabling characteristics[43][44][45][46]. If cancers are either like unicellular growth or are cheater cells, why should the nervous system take a pro-active role in their growth? If some cells arise as cheater cells by a set of mutations, or by adopting an ancestral genomic network, why should other normal cells proactively promote their growth? All these apparently well-coordinated phenomena are unlikely to arise *de novo* so frequently and reproducibly in the population. Cancers exhibit a complex and cooperative multicellular growth pattern and therefore cannot be said to be a reversal to a unicellular growth pattern. Also, the atavistic theory does not talk about how natural selection works on the complex networks; why the

ancient gene regulation networks have survived and remained conserved; whether they continue to have a normal physiological function; how and why they result in tumors; and how natural selection would act on the probability of tumorigenesis. It also fails to account for the large overlap between wound healing and cancer pathways.

The mutation-independent malignant transformation theory tries to explain mutations as downstream effects of genomic instability[19]. But this does not account for the fact that mutations in certain genes are disproportionately frequently associated with specific types of cancers, although not every time. Further, some of the non-mutational theories do involve polyploidy and DNA damage as essential elements. Therefore, whether cancers are possible without any changes in DNA is doubtful. At present, evidence for the non-mutational origin of cancers is limited.

The perspective of cancer as a non-healing wound[26][27][28][29][31] has a strong evidence base but does not explain what makes the wound healing pathways derail and give rise to cancer.

Based on the epidemiological as well as physiological patterns, some studies show that the somatic evolution of cancers is not mutation-limited but is selection-limited[1][2][18]. There is competition between normal and mutant cells as well as between different mutants[17][47]. The cancer-causing mutants get a selective advantage only under certain microenvironmental contexts. The microenvironment is variable across individuals based on their genetic, developmental, lifestyle, and age-related factors. The lifetime number of adult stem cell divisions is large enough so that the probability of each type of mutation is sufficiently large, but whether the mutant gets selected in competition with normal ASCs is the critical question that decides the development of cancer. Although this view is largely compatible with the epidemiological patterns[18], the details of the selective forces required for this hypothesis are still hazy. Further, rapidly accumulating molecular and cellular details reveal that cancer is much more than mutation accumulation. Cells with a set of mutations that might develop into a tumor in one set of conditions fail to do so in another[48][49][50]. Several components of the tissue microenvironment are crucial in the development of cancer[51][52][53][54][55][56][57][58] and the context-dependent selection theory proposes that the microenvironment generates the selective forces, but the details of it are largely unexplored.

At a different level lies the question of possible evolution of mechanisms to prevent cancer[59]. A number of tumor suppressor genes[60][61][62][63] have been identified, and they are believed to have evolved as mechanisms of cancer defense. However, each one of them has one or more normal physiological functions independent of cancer. Therefore, whether they evolved for preventing cancers or for their normal physiological functions is questionable. Since, barring a few exceptions, most cancers appear at later ages, selection for mechanisms of prevention is likely to be weak by the Peter Medawar principle[64]. Nevertheless, some mechanisms for arresting cancer can be expected and are claimed to have evolved, and the dynamics of their evolution also need to be interpreted carefully.

The new synthesis

In multicellular organisms with differentiated tissues, control of cell proliferation is needed at two distinct levels. One is the level of normal healthy tissue maintenance. The other is the occasional requirement of healing a wound or making up for the tissue lost or damaged for any reason. The latter needs increased dynamics of replication starting from ASCs at a different level of coordination and differentiation. Therefore, the mechanisms for surpassing the normal regulation of cell division are already present in the body. They are highly complex but very well coordinated with stage-specific mechanisms of regulation. All mechanisms of shifting between the two levels of coordination have evolved and preexist in the cell and can be activated by a set of triggers. By the new synthesis, cancer is not about escaping the regulation mechanisms by some novel mechanisms acquired by mutations. It is about wrongly triggering the healing and regeneration process without a genuine need. Normally, the signals coming from injured tissue provide the triggers for starting the process. Consequently, when healing is near completion, a different set of signals coming from the healed tissue downregulates the process. In cancers, since there is no real wound, the signals that control the process after healing are not generated at all. Therefore, the process of making new cells to replace the perceived damaged tissue continues without a full stop. Thus, cancer cells are not cheater cells, but are “cheated” or misled cells that are made to “believe” that there is a wound when in reality there may not be any.

The crucial question now is what constitutes the misleading signal to start the wound healing and cell replacement protocol. The wound healing process needs not a single but multitudes of signals to

get started. Therefore, a misled trigger would also need multiple signals. One possibility is that a set of mutations can make some of the inducible pathways of wound healing constitutive. We will exemplify this by the EGF signaling pathway. EGF signaling is one of the crucial mechanisms in the regulation of cell dynamics at both normal and wound healing levels of regulation. A basic level of EGF signaling is required for normal ASC and tissue dynamics[65]. The damaged tissue generates higher than normal levels of EGF, which is one of the many triggers to start the wound healing process[66]. Three types of mutations related to EGF signaling are known to occur in different types of cancers. One leads to the overexpression of the EGF receptor (EGFR)[67], another leads to the internal synthesis of EGF by cancer tissue[68] and the third makes pathways downstream of EGF signaling constitutive[69]. In all three, the cell becomes independent of or oversensitive to external EGF signaling. Therefore, in such a cell, the EGF signaling might be misread as injury signaling even when it is normal. The crucial question may not be whether one of the three types of mutations arises, but whether a cell with one of the mutations will survive and outcompete a normal cell. Differential selection acting on one of the EGF-related mutants, or more generally any growth factor signaling-related mutants, can be hypothesized as follows.

Since the growth factors are synthesized and regulated centrally, individual tissues or cells do not invest in their synthesis but receive the signal free of individual cost. However, if there is a chronic deficiency of a growth factor, a mutant that overexpresses or auto-activates a growth factor receptor, itself synthesizes the growth factor, or makes the downstream pathway constitutive, would be at a selective advantage. Since the cell has to pay some energy cost to do so[70], it would be at a disadvantage when the external supply of the growth factor is adequate (figure 1). However, when the external supply is deficient, normal cell replication would be suboptimal, and the mutant would get a selective advantage in competition. The investment in, say, overexpressing the receptor may be overcompensated by the unique benefit. The important point to realize is that the selective advantage to the growth factor-independent mutant cell is not an all-time advantage, but only a conditional advantage under long-term growth factor deficiency.

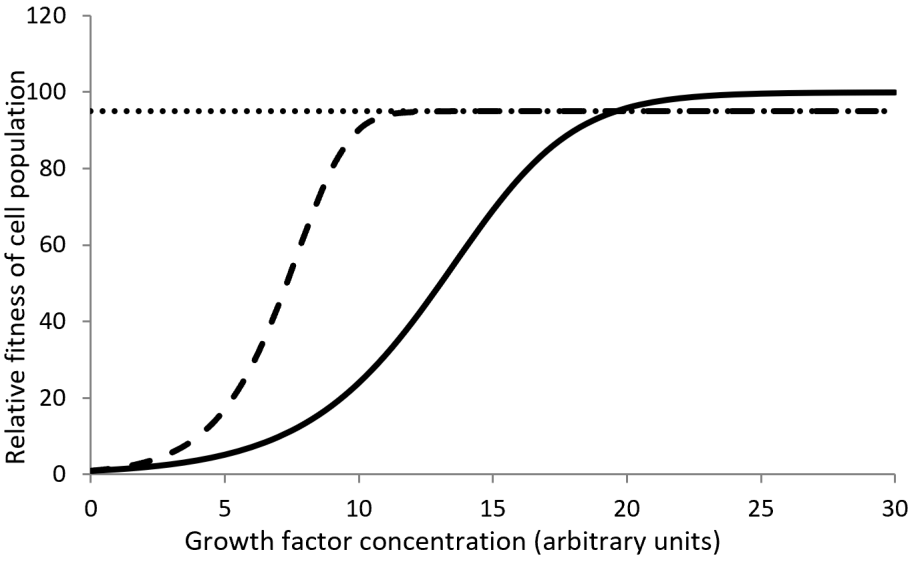

Figure 1. Expected growth responses of normal (solid line) and receptor-overexpressing (dashed line) mutants to different growth factor concentrations. At low growth factor concentrations, the mutant may gain a competitive advantage over the normal cell, but at high concentrations, they may lose it owing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

Owing to the tissue cell dynamics in higher animals, where somatic cells have a definite life span and inevitable senescence and death, any mutation in the differentiated tissue is unlikely to sustain over a long time. However, since growth factors are involved in the maintenance and self-renewal of adult stem cells[71][72][73], a stem cell mutant that becomes independent of growth factor signaling can

rapidly invade the stem cell population when the normal growth factor levels are depleted. From the tissue dynamics point of view, this is the most crucial phenomenon.

There are likely to be multiple mechanisms by which altered growth factor levels can create selective advantages for carcinogenic mutations. P53 is a known tumor suppressor but has multiple normal physiological functions as well. The involvement of EGF and p53 in adult stem cell dynamics suggests that a deficiency of EGF can select for TP53 mutants, potentially leading to cancer (figure 2). The normal dynamics of stem cells crucially depend upon symmetric or asymmetric division of stem cells. In symmetric division, both daughter cells are either renewed or differentiated. In asymmetric division, one of the daughter cells differentiates and the other gets renewed as a stem cell[74]. The renewal versus differentiation balance is crucial for ASC dynamics, which is under the control of multiple signals, including EGF and p53. While EGF signaling facilitates stem cell renewal[75][76][77], p53 facilitates differentiation and prevents dedifferentiation[78]. If the EGF signal is weak, the normal ASC would have a reduced probability of renewal. This would lead to a gradual depletion of the stem cell pool. Under these conditions, a TP53 mutant, which is less likely to differentiate, can have an increased probability of contributing to the stem cell pool. Thus, under EGF-deficient conditions, an EGF-independent mutant and a TP53 mutant, or both, get a selective advantage over a normal ASC. With normal EGF levels, the normal cell has a good rate of getting renewed in the ASC population, and the mutants would face tough competition from normal cells. Since p53 has multiple normal physiological functions in a cell, a TP53 mutant is likely to have suboptimal performance compared to a normal cell. If the mutants have to pay some cost for the mutation, they are more likely to lose out in the competition, unless some factor impairs the dynamics of normal cells.

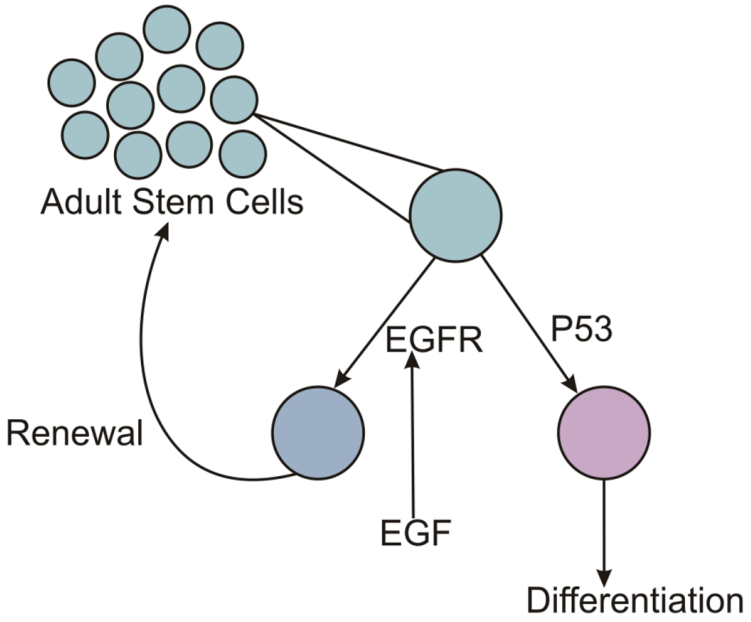

Figure 2. Effects of EGF and p53 on adult stem cell renewal and differentiation dynamics. In this dynamics, a weak input of the EGF signal can give a selective advantage to EGFR-overexpressing or p53 mutants, or both.

If the new mutant has any selective advantage owing to altered levels of any other internal environmental factor, its population will rise, making the stage available for any further spontaneous genomic change. This way, the improbable nature of the coming together of many chromosomal changes necessary to give rise to a cancerous cell alters substantially.

A natural question to follow is what causes chronic alterations in the levels of EGF and other growth factors that can give a selective advantage to mutants. A Stone Age ancestral hunter-gatherer is likely to have experienced minor injuries such as pricking, pinching, bruises, blunt impacts, and the like at a high frequency. It is therefore not surprising that the injuries, as well as the anticipation of injuries, stimulate a variety of growth factors[79][80][81][82][83]. The regulation of growth factor production

would have evolved to suit the natural and inevitable frequency of injuries. As compared to Stone Age or agricultural societies, the modern urban lifestyle has a substantially lower frequency of cutaneous injuries. In addition, acts of physical adventure that anticipate injuries are becoming increasingly deficient owing to multiple reinforced measures of safety and physical risk avoidance. Since, in ancestral populations, the injury-induced growth factor release would be frequent, the mean growth factor levels in normal Stone Age life would have been sufficient for all normal functions of growth factors. Therefore, it is likely that no other mechanisms for maintaining healthy growth factor levels in the absence of injury stimulus would have evolved.

In a non-injury-prone and non-adventurous modern lifestyle, a cumulative deficiency of growth factors may develop. Current data on population levels of growth factors are scanty, but available studies show that the levels of EGF, NGF, and many other growth factors are altered in many lifestyle-related disorders[84][85][86].

The wound healing process needs multiple triggers, and therefore making only one of the triggers constitutive does not make the mutant cell malignant. Until a minimum number of triggers are altered by mutation or epigenetic or physiological changes, the process will not begin. Therefore, either a series of mutations or a concerted genetic, epigenetic, and physiological changes are required for malignancy[87][88][89][90][91][92]. It is also likely that when only some of the triggering pathways are constitutive, the presence of an actual wound provides the necessary stimuli, and a tissue regeneration process begins. This is the likely reason why many tumors initiate only after a local injury or inflammation[93][94][95][96]. However, owing to the mutations, the down-regulation at the right time is disabled, and as a result, the cell process fails to stop, leading to cancerous growth. If the wound healing process can be falsely triggered by mechanisms other than mutations, then malignancy can potentially begin without mutations. Thus, the non-mutational origin theory is compatible with our synthesis, although evidence for non-mutational origins is debatable.

Evolution of mechanisms for cancer prevention

Classically, cancer is considered to be somatic evolution that needs to reinvent itself every time[97]. All characteristics of cancer have to evolve de novo by this perspective. By this view, a number of mechanisms have evolved to minimize the risk of cancer[97][98]. Our synthesis necessitates a rethinking of this perspective. The mechanisms and pathways that characterize cancers do not need to evolve *de novo*. Almost all of them have already evolved for the wound healing and tissue regeneration process, and somatic evolution only needs to make their expression constitutive or out of context.

The mutation-limited view of cancers has emphasized strategies to reduce the chances of mutations on the one hand and to detect and eliminate the transformed cells by metabolic or immune mechanisms on the other. The tumor suppressor genes that have been identified get a different interpretation by our synthesis. If the so-called tumor suppressor genes and mechanisms are a normal part of the regulation and closure of the wound healing process (Supplementary table 1), they may not have evolved specifically as a defense against cancer. Instead, their normal role in regulating and terminating the wound healing cascade will make them suppress cancers too. Our synthesis identifies many other efficient mechanisms of preventing cancers and also identifies the conditions in which such mechanisms can fail.

There are five classes of strategies to prevent cancers: (A) strategies to ensure that potentially cancer-causing mutants do not pass on to the next generation, (B) strategies to reduce the chances of somatic mutations, (C) strategies to prevent erroneous triggering of wound healing, (D) strategies to regulate and terminate the wound healing cascades, and (E) strategies to ensure that the mutants are at a selective disadvantage.

A. To prevent cancer-related mutations from passing on to the next generation: A combination of two strategies can ensure this almost completely (i) a single cell stage in the life cycle and (ii) pleiotropy between adult tissue regulation and gametogenesis or early embryonic development. In social cheating, individual isolation at some stage of the lifecycle is known to arrest cheating[13]. In multicellular organisms in which the life cycle needs to go through a single cell stage, if mechanisms in this cell are defective, it will simply not develop into an organism. The only possibility of passing on cancer-related mutations to the next generation is if the mutants are individually neutral and become cancerous only in combination with others. However, if the genes are involved in the early developmental process, any mutation altering its expression will impair development itself. Evolution of pleiotropy between gamete development or early embryonic developmental mechanisms and adult cell replication regulation mechanisms can

ensure that cancer-causing mutations do not pass on to the next generation. It is easy to see that the growth factors, in particular, have important roles in early embryonic development[99][100][101][102][103] as well as in wound healing[104] and whose mutants are often related to cancers[105]. Similarly, many cancer-related genes play important roles in gamete development, sperm competition, and fertilization[106] including EGF signaling[107][108], Notch[109], RB1[110], and p53[111]. Civetta and Ranz[112] list genes implicated in sperm competition in mice, most of which have roles in cancers as well. Thus, gamete-level mutational selection[113] can arrest germline inheritance of cancer-causing mutations.

B. Strategies to reduce mutational burden: The stem cell and asymmetric division system by itself is efficient in reducing the chances of mutation accumulation. The adult stem cells undergo asymmetric division and thereby one of the daughter cells differentiates and the other adds back to the ASC pool. The differentiated cells may replicate, but ultimately undergo senescence and die. The mutation rate in the stem cell is substantially smaller than that in cells at other stages[114]. Therefore, any mutations accumulated in the differentiated cells vanish along with cell death. New lines start again from ASCs. This mechanism arrests mutation accumulation considerably, if not completely. The other side of the coin, however, is that a mutation in the ASC will persist. Further, in normal cell cycles, there are checkpoints and apoptosis that can trigger self-destruction in a cell with DNA damage[115][116].
C. Strategies to prevent erroneous triggering of wound healing: If the wound healing process were to get triggered by a single trigger, a single mutation could have been sufficient to cause cancer. But the beginning of wound healing involves complex signaling, including the ones released by cell lysis, degraded collagen, calcium signaling, and growth factors released by platelets and cells[117][118][119][120]. The advantage of multiple signaling pathways is that a single mutation making a pathway constitutive will not initiate cancer. Further, the multiple triggers may also contain signatures of the site and type of tissue that needs regeneration. In the absence of selection, it is highly unlikely that a cell can have multiple mutations to internalize all the necessary triggers and start the wound healing process in the absence of a wound.
D. Strategies for effective termination of wound healing: Equally critical for wound healing is to terminate proliferation, migration, and other responses at the right stage. This process is also regulated by a number of well-coordinated signals and pathways. Interestingly, many so-called “tumor suppressor genes” are involved at this stage of wound healing (supplementary table 1). Evolution of multiple mechanisms of regulating the process simultaneously ensures cancer prevention, unless there is selection for one or more mutants affecting the regulatory mechanisms.
E. Strategies to ensure that the mutants are at a selective disadvantage: A mutant cell that can internalize a signal under normal circumstances pays a greater cost than cells responding to external growth factor signals, as described earlier. Therefore, mutants internalizing one of the multiple necessary wound healing signals are unlikely to gain a selective advantage and proliferate. They are more likely to undergo negative selection owing to their higher cost.

Almost all proto-oncogenes or tumor suppressor genes have multiple normal physiological functions. A mutant cell is therefore very likely to be deficient in one or more of its normal vital functions, leading to a strong or weak negative selection. Unless the contextual positive selection on the mutant is strong enough to overcome the functional deficiency, the mutant may not survive.

The signaling pathways within a cell are often branched, and the branches are linked to different vital functions (figure 3). We argued above that when the external signal is inadequate, any mutation making the pathway constitutive may get selected. Potentially, any signal along the pathway towards triggered cell proliferation can mutate to become constitutive or overexpressed. However, if it is downstream of the branching point, it will not upregulate the other vital function, and as a result, the mutant cell may die instead of proliferating. The structure of the signaling pathways, particularly its branching, might have evolved to minimize the types of mutations that can lead to successful proliferation of the cell.

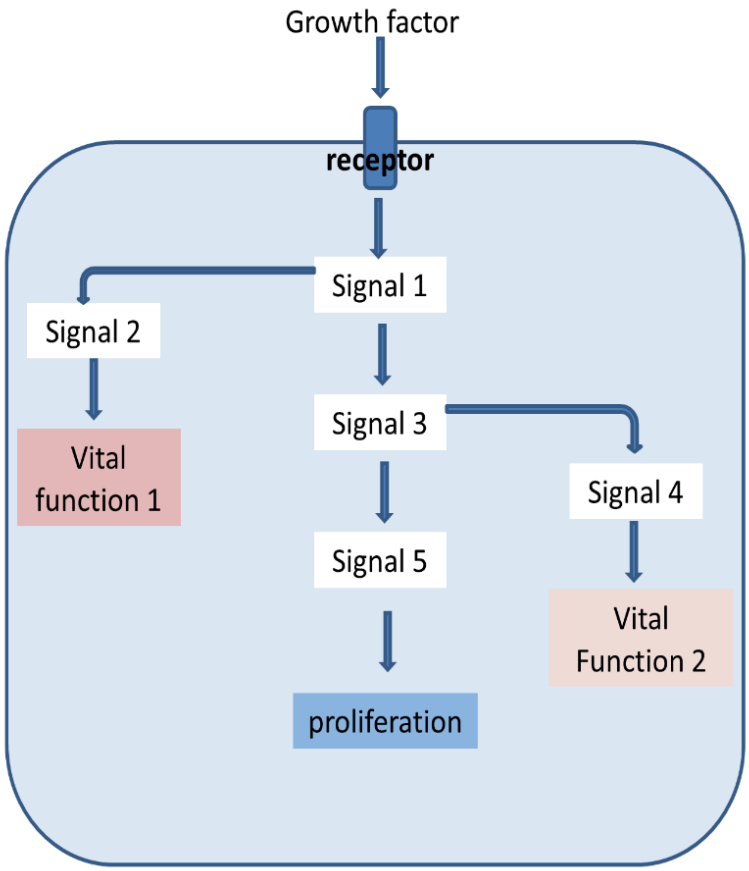

Figure 3. The signaling pathways may have evolved to minimize the possible number of mutations that can trigger uncontrolled cell proliferation. Linking a vital function of the cell as a branch of the proliferation signaling pathway is a potential preventive mechanism. In the hypothetical signaling pathway above, if the external signal is weak, a constitutive or overexpressing mutation at the receptor or signal 1 level can lead to uncontrolled proliferation, but a mutation making signal 3 or signal 4 constitutive cannot. In reality, the signaling pathways are often branched and linked to many different functions of the cell.

Optimization of the anti-cancer defenses: The cancer defense mechanisms come at a cost and enforce certain constraints on cellular and physiological processes[121]. Therefore, an optimization is expected to evolve in the cancer defense mechanisms. We discussed above that a subnormal level of growth factors can lead to the selection of a signal-internalizing mutant. However, growth factors have a cost[70]. Apart from the cost of making and maintaining the growth factor levels, the metabolic rate and rate of cell replacement also increase with growth factor levels. Therefore, having higher levels of growth factors under normal conditions is energetically costly. There should be an optimum level of growth factors that keeps the energy cost to a minimum but does not increase the risk of selecting mutants considerably. The net cost with varying levels of growth factors is likely to follow a cliff-edge fitness function (figure 4)[122]. The optimum should ideally lie near the tip, but some variations being inevitable in biological systems, some individuals may drift towards a propensity to develop cancers normally. Because of the cliff-edge fitness function, a small probability of developing cancer may exist in a population growing in its natural habitat. But if growth factor expressions are suboptimal due to a mismatched lifestyle, the risk can increase substantially. A growth factor-independent mutant is only an example. A similar function can be expected for selective factors for other cancer-causing mutations. There is also likely to be a trade-off between adult stem cell numbers and maintenance mechanisms with growth rate, and accordingly, the ASC number could have been optimized by evolution.

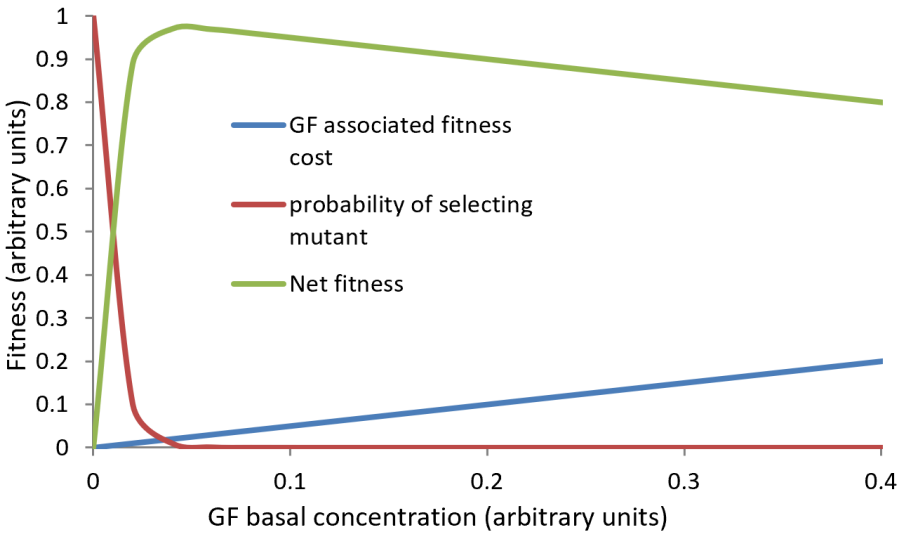

Figure 4. Cliff edge fitness function in optimizing mechanisms of cancer prevention. Continuing with the example of growth factor independence mutations discussed above, at low basal GF levels, the probability of selecting a mutant increases. On the other hand, a high basal level of GF comes with some cost. The peak fitness at the optimum is highly asymmetric, with a steep decline on the side of cancer risk. Since multiple factors result in individual phenotypic variability in any character, when the optimum is selected genetically, a small chance of cancer will remain. Subnormal GF expression due to lifestyle factors can increase the chance rapidly.

Evidence for the synthesis

Our synthesis accounts for a number of well-known patterns and phenomena in cancer that have been unexplained or paradoxical with prior perspectives. This can be treated as existing support for the synthesis, before any novel testable predictions can be stated.

1. The parallels between wound healing and cancer: Many authors have pointed out the similarities between mechanisms and pathways involved in cancer and in wound healing[28][123][30][31] (Supporting information tables 1 to 3). In vitro wound healing assays have been commonly used to assess cell proliferation, migration, and metastasis in cancer[124][125][126] as well as in wound healing[127]. But the parallels between the two are not restricted to what is reflected in wound healing assays. All of the hallmarks and enabling characteristics of cancers[40][41][42][46] namely proliferative signaling, evading growth suppressors, replicative immortality, inducing angiogenesis, altered cellular metabolism, avoiding immune destruction, genome instability or increased rates of mutations, and tumour-promoting inflammation are demonstrable in some or other stages of the wound healing process as described under and in supplementary information.
   The process of wound healing and tissue regeneration has been divided into six phases, namely (i) hemostasis, (ii) inflammatory phase, (iii) growth and neovascularization phase, (iv) re-epithelization, and (v) tissue maturation and remodeling. When a wound causes serious damage or loss of tissue, the first defense from invading pathogens and removal of damaged cells and debris is needed. This involves inflammatory cells, oxidative burst, and other mechanisms of defense. Then certain cells from the surrounding tissues need to proliferate more and make up for the loss. This requires proliferation beyond the normal regulated levels by evading growth suppressors, dedifferentiation, epithelial to mesenchymal transition (EMT), altered dynamics of ASCs, coordinated and directed migration to the site of damage, cell-cell communication, and cooperation between different cell types, co-opting blood vessels and enhancement of angiogenesis, and a rapid metabolic burst needed to supply energy for the proliferation and repair process. Thus, these phenomena are not unique to cancer cells. All the mechanisms witnessed in the development of cancer have evolved for a normal healing, regeneration, repair, and tissue homeostasis process (Supplementary table 1). Out of the 264 genes listed by the COSMIC catalogue of genes whose mutations are causally implicated in

cancers, 243 genes have some or other role in wound healing (Supplementary table 2). Conversely, out of the 554 genes differentially expressed in wound healing, 462 were evidently involved in tumorigenesis; only 16% were not (Supplementary table 3).

Mechanisms to prevent ectopic growth of cells, such as anoikis, as well as mechanisms to become anoikis resistant, are required for normal tissue dynamics and wound healing processes[128][129]. Therefore, the phenomenon of anoikis resistance[130] is not unique to cancer cells.

But since the coordination of wound healing is dependent upon gradients of locale-specific signals which are absent in cancer, cancer proliferation lacks the superb site-specific coordination and regulation seen in wound healing. For example, the migration of cells to the site of damage is well directed by chemoattractant gradients in wound healing[131][132][133]. Some of these chemoattractants are active in cancers as well, but the absence of site specificity in these signals can result in metastasis to unrelated tissues. Further, as the healing is near completion, another coordinated cascade for terminating the proliferation, remodeling the tissue, destruction of the now unwanted cells, cleaning, and wound closure is activated. It can be noted from Table 1 that many of the important genes and mechanisms involved in the later phases of wound healing are also known to be tumor suppressors. This offers a new interpretation of the evolution of tumor suppressor genes. They might have primarily evolved to regulate and appropriately terminate the wound healing process and not as tumor suppressors.

A wound healing process requires coordination and cross-talk between different types of cells, tissues, blood vessels, and nerves. A number of such complex interplays have been demonstrated[134][135][136][137][138][139]. It's no wonder, therefore, that such complex cross-talks are seen in cancer development too[140][141]. Injuries and behavior have a necessary two-way relationship. Injuries potentially affect social hierarchies and foraging behavior, and therefore an injured animal needs to fine-tune its behavior according to the severity of injury. The behavior, in turn, feeds back to the process of healing. Therefore, complex neuronal interaction with the healing tissue is expected to have evolved normally[139] and they contribute to the interaction between nerves and tumors as well[46].

At the level of chromosomes and nucleic acids, some of the mechanisms are adaptive and functionally important in wound healing. A few others appear to be inevitable effects of rapid proliferation. For example, RNA splicing has a specific role in wound healing, and there is considerable overlap between the altered splicing agents in wound healing and cancers[142][143][144]. Involvement of circular RNA and specifically circ-Amotl1 is common to wound healing and cancer[145][146].

The speed of replication being the priority in wound healing, more mutations and chromosomal abnormalities may accumulate in the proliferating cells[147][148]. In addition, some of the mechanisms involved in inflammation and proliferation are known to be mutagenic[149][147][150]. Genomic instability also may result from inflammatory mechanisms[151]. Therefore, the rate of mutation and chromosomal abnormalities is expected to be high in the healing tissue. Therefore, active apoptotic mechanisms are needed in the later phases of wound healing to detect and eliminate defective cells. However, since differentiated cells are subject to senescence and death, normally there would be a reasonable amount of mutation tolerance in this process. Further, mutations may also generate neoantigens, and such cells will be cleared by the immune system normally. Therefore, increased rates of mutation and chromosomal alterations may not cause long-term problems in wound healing. However, if mechanisms including apoptosis and macrophage-mediated clearance are impaired, accumulation of mutation and chromosomal anomalies may result.

A plausible alternative interpretation also exists for the chromosomal alterations. Some of the phenomena have been speculated to have a functional significance. For example, polyploidization and cell fusion are suggested to have useful functions in wound healing[152][153][154] and therefore they may be a normal part of the wound healing process and not unique to cancer.

Macrophages have a dual role in both wound healing and cancer. Although somewhat oversimplified, there is a macrophage polarization paradigm that classifies them into M1 and M2 types. During wound healing, M1 macrophages clear invading pathogens as well as apoptotic or effete cells. Conversely, M2 macrophages suppress inflammation and promote cell proliferation during repair and regeneration[155]. Similarly, in tumor development, M2 promote proliferation[156] and M1 appear to attack and clear tumor cells[157].

The expected high rate of mutations in inflammation and healing processes raises the possibility that neoantigens will be created in the process. This is a possible threat or hurdle at certain stages of wound healing. It is possible, therefore, that the PD-1, PD-L1, CTLA-4/B7-1/B7-2 driven immune checkpoints[29][158] evolved for this purpose. They regulate the immune mechanisms during critical phases of cell proliferation for tissue regeneration. In some of the healing-associated disorders, macrophages appear to be activated by antigens[159][160], but the origin of these antigens is not known. Activating immune checkpoints facilitates wound healing. Given the probability of generating new antigens during wound healing, mechanisms for contextual and short-time suppression of the immune response to new antigens are needed. Therefore, these mechanisms may have evolved to accompany wound healing. If cancers were only invasion by cheater cells, it is difficult to explain why immune checkpoint mechanisms are turned on in cancers.

Owing to multiple similarities between wound healing and tumor growth, most cancer therapies interfere with wound healing mechanisms[161][162] as expected. This is not a "side effect" of cancer therapy; it is the main effect according to our perspective.

If there is a large overlap between cancer and wound healing pathways at the genomic as well as functional level, and phylostratigraphy has shown affiliations with ancient genomic networks, it is likely that the wound healing pathways evolved from these ancient networks and remained conserved because of the indispensable survival importance of the wound healing and tissue regeneration processes. This accounts for the phylostratigraphy data without involving the atavistic interpretation.

2. The relationship between mutations and cancer: Our synthesis expects to find many potentially causal mutations existing in non-cancer tissues since cancer is not a mutation-limited process and multiple triggers are needed to start a misguided wound healing response. Also, since the selective conditions for different mutants can be different, it is likely that some of the mutants get selected but do not become carcinogenic in the absence of other necessary triggers. This is indeed a finding of many studies[49][50][163].
3. Epidemiological patterns: Vibishan and Watve[18], using multiple lines of epidemiological evidence, argue that cancers are not mutation-limited but selection-limited, and a selection-limited view explains the epidemiological patterns better. Our synthesis makes further suggestions on how the selection works. This explains why there can be non-mutagenic carcinogens, why the relationship between the number of stem cell divisions and cancer incidence is non-linear, why the incidence of cancer reduces at late age, and why cancer incidence does not increase with the size of the organism.
4. Importance of tissue microenvironment: The tissue microenvironment has dual importance. On the one hand, it shapes the selective pressures on the mutants, and on the other, it influences the triggers for wound healing pathways. Therefore, it is expected that to a large extent, the tissue microenvironment will shape the history of developing cancer at all stages. This is compatible with empirical findings[164][165][51][52][53][54][56][57].
5. Accounting for Peto's paradox: Since the somatic evolution of cancer is not a mutation-limited process, Peto's paradox[10][11][12] simply does not exist. The paradox was created by a mutation-centric view. In our synthesis, the perspective is radically different. Cancers are selection-limited rather than mutation-limited, and there is no reason why cancer incidence should increase with body size or the number of cell divisions.
6. Lifestyle factors and cancer incidence: Since lifestyle factors can influence the body's internal environment, they can influence cancer incidence in a significant way. Many studies show the effects of several lifestyle factors[166][167][168][169][170][171]. But so far, the detailed causal links have been underexplored. Our synthesis gives a theoretical platform on which the pathways and links between lifestyle factors and tumorigenesis can be elucidated in detail.
7. Behaviorally rich environment suppresses implanted tumor growth: Perhaps potentially the most important and so far ignored lifestyle factor is behavior. In our synthesis, behavior has a central role in shaping the tissue microenvironment. An important experiment highlighting the importance of behavior is that by Cao et al[48] which showed that by providing a behaviorally rich environment, the progression of an implanted tumor could be effectively suppressed. Many experiments have reproduced the results, although they differ in detail[172][173][174][175][176]. Our synthesis demands a revival of this line of work to trace the multiple molecular links between behavior and carcinogenesis.

Testable predictions and suggested lines of experimental research

A number of testable predictions emerge from our synthesis, which may guide certain novel lines of research and lead to greater insights into the fundamental biology of cancer.

i. One cell stage in life cycle: Organisms in which cancers can be fatal should have a mandatory one cell stage in the life cycle. Organisms that have other mechanisms due to which cancers are either very infrequent or not always fatal may have the single cell stage optional. For example, plants can shed a diseased part and grow new tissues. The cancer-like conditions in plants are not necessarily fatal, and therefore plants can have a single cell stage optionally in the life cycle. They may reproduce vegetatively. Animals like hydra reproduce vegetatively, but there is no report of cancer in vegetatively reproducing hydra. Whether this is a generalized statement needs to be evaluated across the diversity of life.

ii. In vitro cell competition experiments: The concept of context-dependent selective advantage to specific driver mutations involved in different types of cancers can be tested using in vitro competition experiments. One such demonstration comes from Archetti et al[33] studies. These experiments mark a line of work by which the selective conditions for different mutations thought to be drivers of carcinogenesis can be identified.

iii. Extension of Cao et al (2010) experiments: The in vivo counterpart of selection experiments should follow the experimental design exemplified by Cao et al[48] and replicated by many others[172][177][174]. Although the findings were largely reproducible, the mechanisms by which behavior influences tumor growth remain underexplored. Our suggestion that behavior alters the selective landscape in tissues is testable in vivo on the background of such experiments.

iv. Behavior-centered lifestyle studies: The concept of lifestyle has been largely restricted to diet and physical activity. The nature of physical activity and behavior is an important component of lifestyle according to our synthesis. Many links between behavior and physiology that could potentially alter the microenvironment are reviewed by Watve[178]. Association between behavioral traits and cancer incidence is potentially testable using epidemiological designs similar to the earlier studies, but with data on behavioral traits. There are indications that metabolic diseases as well as cancers are rare in hunter-gatherer and agri-horticultural societies[179]. How far the behavioral component contributes to the difference is an open question that can be pursued through careful cross-cultural studies.

v. Looking for cancer-specific phenomena in wound healing: We have seen that a large number of molecular, cellular, and system-level phenomena, once thought to be unique to cancer, have been detected during wound healing (table 1). However, a few more are thought to be cancer-specific, and wound healing has not been explored for the presence of them. We predict that most of such phenomena would be found to be operative during wound healing in some form. Hunting for such phenomena in the wound healing process with functional relevance can serve as empirical tests for our synthesis.

   A good example is the question of whether neoantigens are generated during wound healing. Neoantigens in cancer are not only a result of mutations. There appear to be specific mechanisms to increase the chances of forming new epitopes on the cell surface. The phenomena of codon reassignment and frameshift polypeptides happening at the ribosomal level without any mutational change[180] is evidently a context-specific and highly regulated process. Its occurrence across many different types of tumors suggests that it is unlikely to arise *de novo* in the somatic evolution of cancer, but it may have evolved for some specific contextual function in normal physiology which expresses itself during cancer. We expect that this function would be crucial during some stage of the wound healing process. Macrophages need to remove damaged, exhausted, and effete cells[181][182][183] during wound healing, and how they selectively identify such cells is an open question. The codon reassignment and frameshift can help generate novel peptide epitopes on the cell surface which enable an immune response to such cells in addition to some known “eat me” signals[184][185]. What we already know is that the IDO1 pathway that triggers the codon reassignment in cancer[180] is active during wound healing and has a role in antimicrobial activity as well as immune regulation to avoid autoimmune complications, both being crucial in wound healing[186][187][188][189][190].

   There are other specialized mechanisms for generating neoantigens, including mRNA splicing[191] that are currently thought to be unique to cancers. But the splicing proteins

SFRS6[142] and SFRS3[192] are already known to be active in wound healing. We speculate that such mechanisms of generating novel surface epitopes will help macrophage-mediated clearance of exhausted, effete cells and cells whose role in the healing process is over[193] from the wound healing site. Even in tumors, cell senescence is associated with antigen expression[194] further supporting the hypothesis that it is an evolved normal physiological mechanism for removing senescent cells. An experimental demonstration of one or more of such phenomena during wound healing is a testable prediction that would give strong empirical support to our synthesis.

vi. The expected limitations of immunotherapy: Cancer immunotherapy has attracted much attention and research investment currently. Our synthesis predicts very limited success for this approach. If the immune response is mediated by neoantigens generated by mutations, there will be strong selection acting against such mutants, and in the rapid somatic evolution, macrophage action will quickly select against cells carrying neoantigens or neoepitopes[195][196][197]. Since most neoantigens originate in passenger, rather than driver mutations, there is likely to be a rapid succession of different neoantigens, but immunotherapy is less likely to clear the tumor entirely. Only if an essential or driver mutation is associated with a neoantigen, or if a back mutation from the neoantigen is lethal[197], can therapy such as CAR-T have sustained benefit.

If, on the other hand, antigens are generated by the built-in process of ribosomal level codon reassignment and frameshifted polypeptides, these processes are presumably evolved for removing specific cells, and they will continue to do so in tumors as well. They are unlikely to destroy the entire tumor. Compatible with our expectation is the extremely limited success of immunotherapy alone[198][199][200]. At most, it may be useful in supporting other lines of treatment.

Relevance of our synthesis to cancer research and clinical applications

Although many lines of evidence point to the evolution of cancer being selection-limited rather than mutation-limited, so far we have very little understanding of microenvironmental factors that would select specific driver mutants. This needs to become a major focus of research in the near future. Which lifestyle and environmental variables affect the microenvironmental factors is the next critical question that would follow. Normalizing the microenvironment to prevent selection for driver mutations can potentially prevent cancers to a large extent. Among the lifestyle factors, the behavioral environment is an interesting possibility that needs to be explored seriously[48][178]. If behavioral deficiencies are central contributors to cancer proneness, sports, exercise, and activities that act as appropriate behavioral supplements should be able to prevent cancers to a significant extent. This is potentially an important public health implication of our synthesis.

There is possible bad news for immunotherapy, but at the same time, we predict that studying the pathways that regulate and terminate the wound healing process might give useful novel breakthroughs in controlling tumor growth.

Statements and Declarations

Conflict of interests

The authors have no conflict of interest.

Data availability

All data used are included in the supplementary material.

Author contributions

UB and MW conceptualized and developed the thinking. UB and RK reviewed and analyzed literature and compiled the supplementary information. MW wrote the paper.

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