Review Article

# Somatic evolution of Cancer: A new synthesis

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**Cancers have been interpreted either as somatic evolution of cheater cells that escape replication regulation or alternatively as non-healing wounds. Both the interpretations have substantial support as well as glaring anomalies but the two 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. Development of cancer is perceived as a process of somatic evolution (Casás-Selves and DeGregori 2011, Rozhok and DeGregori 2017).Conceptually there are multiple ways of interpreting cancer generically. One school of thought views cancer cells as ‘cheater’ cells (Matapurkar and Watve 1997,

 doi.org/10.32388/IAELOG 

Aktipis and Nesse 2013, Aktipis et al 2015, Aktipis 2020). Another independent perspective is that of cancer as a non-healing wound (Schäfer and Werner 2008, Dvorak 2015, Sundaram et al 2018, Hua and Bergers 2019, MacCarthy-Morrogh, and Martin 2020, Deyell et al 2021,). Somatic mutations are commonly assumed to be necessary for transformation of a normal cell into malignant cell, but the dynamics of mutation accumulation is complex. The classical view of somatic evolution of cancer has been that of accumulation of a series of mutations. 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 (White and Lowry 2015, Tomasetti and Vogelstein 2015, Tomasetti et al 2017). 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 (Tomasetti et al 2017). Since the probability of co-occurrence of multiple mutations is very small, a process such as clonal selection was thought necessary (Nowell 1976, Greaves and Maley 2012).On the other hand is the idea of chromothripsis, in which a large number chromosomal changes happen simultaneously and explosively in a single shot (Forment et al 2012, Voronina et al 2020). The thinking in the field has been largely mutation centered. The extensively debated Peto's paradox (Nagy et al 2007, Noble et al 2015, Tollis et al 2017), the presumption of Chromothripsis as well as the idea of cancer as "bad luck" arises from the assumption that somatic evolution of cancer is mutation limited.

A nuanced view, supported by multiple lines of evidence is that somatic evolution of cancer is selection limited rather than mutation limited (Casás-Selves and DeGregori 2011, Vermeulen 2013, Rozhok, A. I. &DeGregori 2017, Vibishan and Watve 2020). 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 (Cao et al 2010). Several components of the tissue microenvironment are crucial in the development of cancer (Hu and Polyak 2007, Medema and Vermeulen 2011, Lu et al 2012, Quail and Joyce 2013, Pickup et al 2014, Schulz et al 2019, Liu et al 2020, Elgundi et al 2020). The malignant tissue also exhibits a number of complex "ecological" or "social" 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 (Tabassum and Polyak 2015, Adler andGordon 2019, Reynolds et al 2020, Paczkowski et al 2021, Somarelli 2021).Organs of future metastasis are not passive receivers of circulating tumor cells. A very intricate and sophisticated level of communication is involved in metastasis (Peinado et al 2017). The hallmarks and enabling characteristics

of cancer have kept on increasing with increasing research inputs (Hanahan and Weinberg 2000, 2011, Hanahan 2022). Of particular interest is the involvement of neurons in contributing to the hallmarks and enabling characteristics (Faulkner et al 2019, Zahalka and Frenette 2020, Ayala 2023, Hanahan and Monje 2023). If cancers arise by de novo gain of function and 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, 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.

At a different level lies the question of possible evolution of mechanisms to prevent cancer (Trivedi et al 2023). A number of tumor suppressor genes (Chen et al 2020, Sherr et al 2004, Kontomanolis et al 2020, Joyce et al 2022) 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 (Turan et al 2019). Nevertheless, some mechanisms for arresting cancer can be expected and are claimed to have evolved and the dynamics of their evolution also needs to be interpreted carefully.

## Limitations and criticism of existing perspectives of cancer

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 accumulation of chance mutations serially or at once (Tomasetti and Vogelstein 2015, Tomasetti et al 2017, Forment et al 2012, Voronina et al 2020), which imply that cancer is only bad luck (Tomasetti and Vogelstein 2015, Tomasetti et al 2017) is not compatible with the observed epidemiological patterns (Vibishan and Watve 2020). Furthermore attempts to prevent DNA damage have not succeeded in preventing cancers (Cockfield and Schafer 2019). The population level predictions of clonal expansion theory are also not compatible with the epidemiological picture (Vibishan and Watve 2020). The main limitation of the “cheater cell” paradigm (Aktipis and Nesse 2013, Aktipis et al 2015, Aktipis 2020) is that cancer development and metastasis has 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 IFG-II over-expressing mutant in cell competition (Archetti et al 2015). Also this hypothesis does not account for the remarkable similarity in cancer and wound healing pathways. The perspective of cancer as a non-healing wound (Schäfer and Werner 2008, Dvorak 2015, Sundaram et al 2018, Hua and Bergers 2019, Deyell et al 2021) 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 in not mutation limited but is selection limited (Casás-Selves and DeGregori 2011, Rozhok, A. I. &DeGregori 2017, Vibishan and Watve 2020). There is competition between normal and mutant cells as well as between different mutants (Vermeulen 2013, Colom et al 2021). The cancer causing mutants get a selective advantage only under certain microenvironmental contexts. The microenvironment is variable across individuals based on their genetic, developmental, life style and age related factors. The life time number of adult stem cell division is large enough so that the probability of each type of mutations 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 (Vibishan and Watve 2020), the details of the selective forces required for this hypothesis are still hazy.

## The new synthesis

In multicellular organisms with differentiated tissues, a control on 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 on 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 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 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 (Krishnan et al 2021). The damaged tissue generates higher than normal levels of EGF which is one of the many triggers to start the wound healing process (Leydon et al 2014). Three types of mutations related to EGF signaling are known to occur in different types of cancers. One leads to overexpression of EGF receptor (EGFR)(Uribe et al 2021), another leads to internal synthesis of EGF by cancer tissue (Garvey et al 2020) and the third makes pathways downstream of EGF signaling constitutive (Pino et al 2006). In all the three, the cell becomes independent 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 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 (Oña and Lachmann 2020), it would be at a disadvantage when 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.

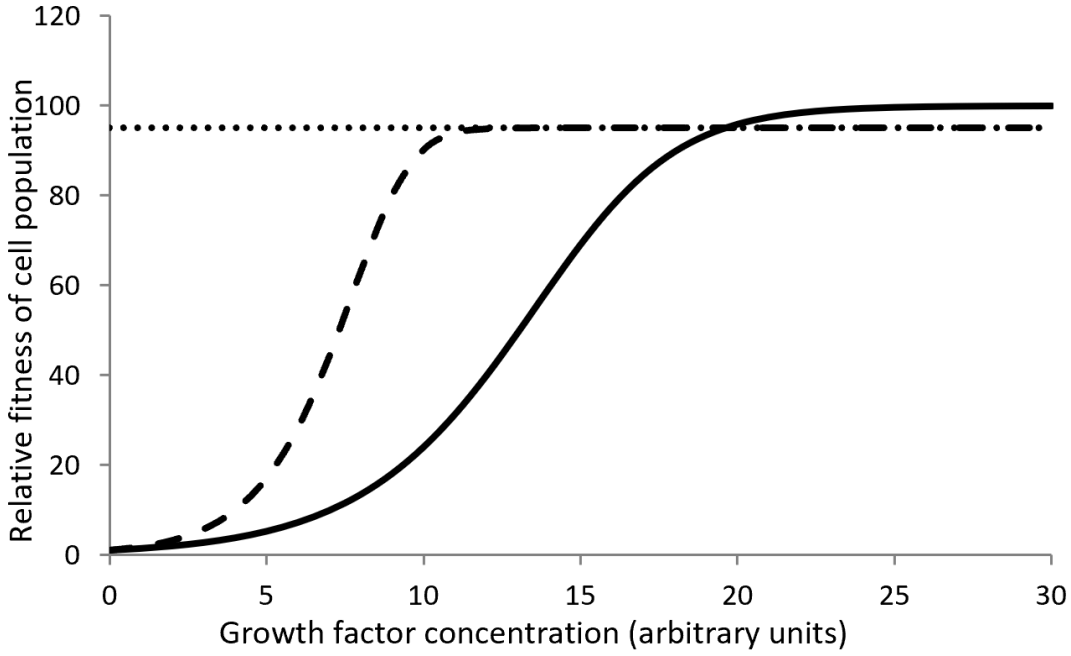


**Figure 1.** Expected growth responses of normal (solid line) and receptor overexpressing (dashed line) mutant to different growth factor concentrations. At low growth factor concentrations, the mutant may gain a competitive advantage over the normal cell, but at high concentration they may lose it 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 (Shi et al 2008, Discher et al 2009, Coutu, D. L., & Galipeau 2011), 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 the adult stem cell dynamics suggests that a deficiency of EGF can select for TP53 mutant potentially leading to cancer (Figure 2). The normal dynamics of stem cells crucially depends 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 (Sunchu and Cabernard 2020). The renewal versus differentiation balance is crucial for the ASC dynamics which is under control of multiple signals including EGF and p53. While EGF signaling facilitates stem cell renewal (Tamama et al 2010, Piryani et al 2016, Wang et al 2019), p53 facilitates differentiation and prevents dedifferentiation (Yu et al 2014). If EGF signal is weak, the normal ASC would have a reduced probability of renewal. This would lead to a gradual depletion of 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, 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 a tough competition from normal cells. Since p53 has multiple normal physiological functions in a cell, a TP53 mutant is likely to have suboptimal performance as compared to a normal cell. If the mutants have to pay some cost of the mutation, they are more likely to lose out in the competition, unless some factor impairs the dynamics of normal cells.

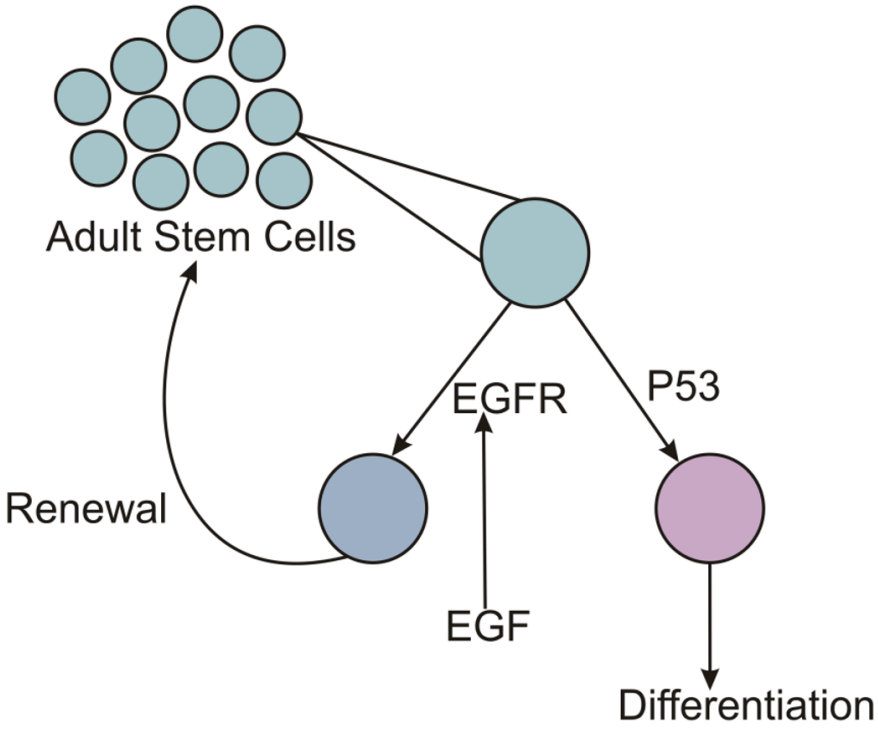


**Figure 2.** Effects of EGF and p53 on adult stem cell renewal and differentiation dynamics. In this dynamics a weak input of EGF signal can give selective advantage to EGFR overexpressing or p53 mutants or both.

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 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 anticipation of injuries stimulate a variety of growth factors (Roberts 1974, Nexo et al 1981, 1984, Aloe et al 1994, Wilson et al 1999). The regulation of growth factor production would have evolved to suit the natural and inevitable frequency of injuries. As compared to the stone age or agricultural societies, modern urban life style has substantially lower frequency of cutaneous injuries. In addition acts of physical adventure which 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 (Kasayama et al 1989, Rasmussen 1995, Mraz et al 2009).

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 (Miranda-Gonçalves *et al* 2018, Saggese *et al* 2020, Crispo *et al* 2019, Izzo*et al* 2021, Sun *et al* 2022, Thakur and Chen 2019). 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 (Walter et al 2011, Kuraishy et al 2011, Arwert et al 2012, Lee et al 2018). 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.

## Evolution of mechanisms for cancer prevention

Classically cancer is considered to be somatic evolution that needs to reinvent itself every time (Gatenby et al 2010). 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 (Gatenby et al 2010, Nedelcu and Caulin 2016). 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 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 on strategies to reduce the chances of mutations on the one hand and detect and eliminate the transformed cells by metabolic or by 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 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 mechanism 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 and (C) strategies to prevent erroneous triggering of wound healing (D) strategies to regulate and terminate the wound healing cascades (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 lifecycle is known to arrest cheating (Matapurkar and Watve 1997). 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 (Spanos et al 2000, Teruel and Smith 2000, Guzeloglu-Kayisli et al 2009, Llobat 2021, Allan et al 2001) as well as in wound healing (Vaidyanathan 2021) and whose mutants are often related to cancers (Witsch et al 2010). Similarly many cancer related genes play important roles in gamete development, sperm competition and fertilization (Sabetian and Shamsir 2015) including EGF signaling (Jaldety et al 2012, Michailov et al 2014), Notch (Huang et al 2013), RB1 (Yang et al 2013), and p53 (Hu 2009). Civetta and Ranz (2019) list genes implicated in sperm competition in mice most of which have roles in cancers as well. Thus gamete level mutational selection (Haig 2023) 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 is cells at other stages (Brazhnik 2020). 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 the ASC will persist. Further in normal cell cycles there are check points and apoptosis that can trigger self destruction in a cell with DNA damage (Roos and Kaina 2006, Aitken and Koppers 2011).

C. Strategies to prevent erroneous triggering of wound healing: If the wound healing process was to get triggered by a single trigger, a single mutation could have been sufficient to cause cancer. But 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 (Niethammer2016, Shannon et al 2017, Yamakawa and Hayashida 2019, Ghilardi et al 2020). 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 selected owing to its 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 to overcome the functional deficiency, the mutant may not survive.

The signaling pathways within a cell are often branched and the branches 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 to 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.

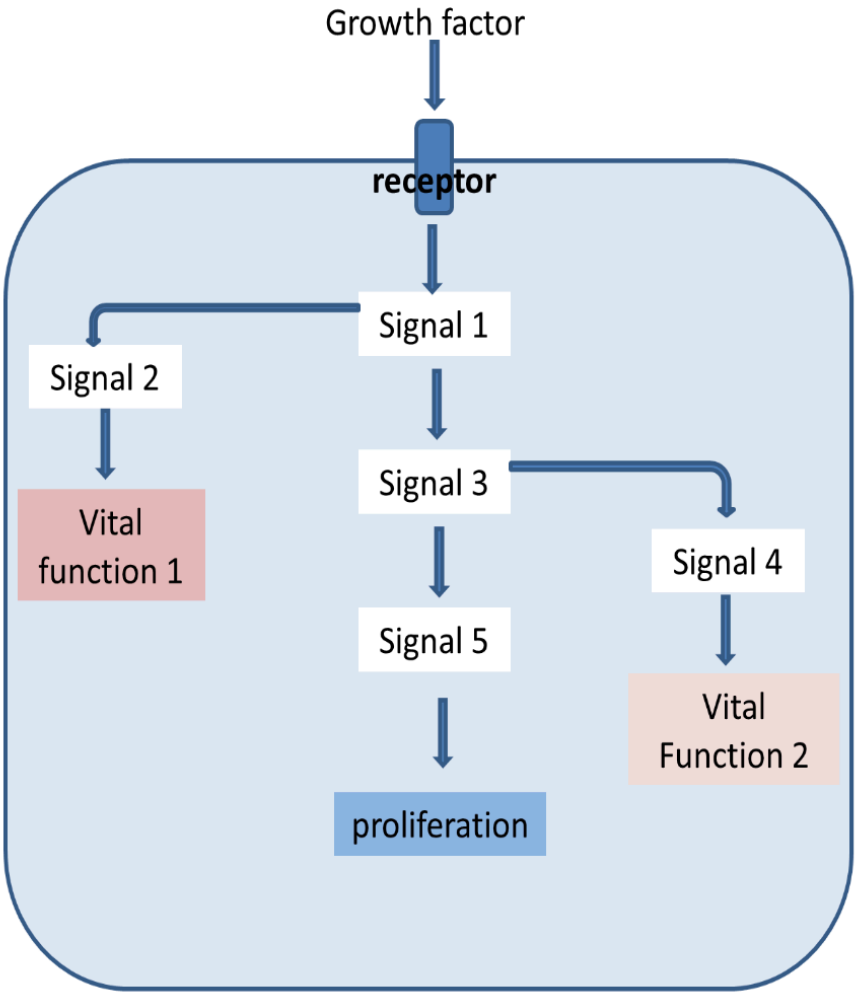


**Figure 3.** The signaling pathways may have evolved to minimize the possible number mutations that can trigger uncontrolled cell proliferation. Linking a vital function of the cell as a branch of the proliferation signaling pathway is a potential preventive mechanism. In the hypothetical signaling pathway above, if the external signal is weak, constitutive or overexpressing mutation at the receptor or signal 1 level can lead to uncontrolled proliferation but mutation making signal 3 or signal 4 constitutive cannot. In reality the signaling pathways are often branched and link 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 (Boutry et al 2020). 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 selection of a signal internalizing mutant. However growth factors have a cost

(Oña andLachmann 2020). Apart from the cost of making and maintaining the growth factor levels, the metabolic rate and rate of cell replacement also increases with growth factor levels. Therefore having higher levels of growth factors in normal conditions is energetically costly. There should be an optimum level of growth factors that keep the energy cost to a minimum but do 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) (Nesse 2004). 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 suboptimum due to a mismatched lifestyle, the risk can increase substantially. Growth factor independent mutant is only an example. Similar function can be expected for selective factors for other cancer causing mutations. There is also likely to be a trade-off of adult stem cell numbers and maintenance mechanisms with growth rate and accordingly the ASC number could have been optimized by evolution.

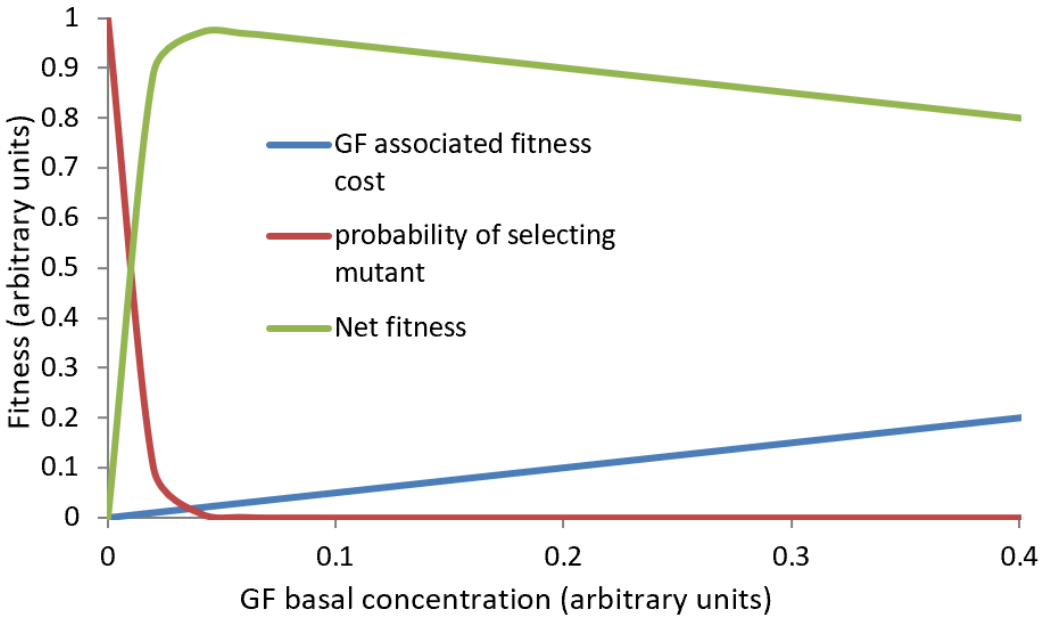


**Figure 4.** Cliff edge fitness function in optimizing mechanisms of cancer prevention. Continuing with the example of growth factor independence mutations discussed above, at low basal GF levels, the probability of selecting mutant increases. On the other hand high basal level of GF comes with some cost. The peak fitness at the optimum is highly asymmetric with steep decline on the side of cancer risk. Since multiple factors result into individual phenotypic variability in any character, when the optimum is selected genetically, a small chance of cancer will remain. Subnormal GF expression due to life style 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 to 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 (Sundaram et al 2018, Foster et al 2018, MacCarthy-Morrogh and Martin 2020, Deyell et al 2021) (Supporting information tables 1 to 3). In vitro wound healing assays have been commonly used to assess cell proliferation migration and metastasis in cancer (Wang et al 2019, Freitas et al 2021, Kauanova et al 2021) as well as in wound healing (Stamm et al 2016). 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 (Hanahan and Weinberg 2000, 2011, Hanahan 2022, Hanahan and Monje 2023) 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 the 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 (v) tissue maturation and remodeling (Rodrigues et al 2019). When a wound causes serious damage or loss of tissue, 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, 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 the 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 (Malagobadan and Nagoor 2019, Yin et al 2022). Therefore the phenomenon of anoikis resistance (Weems et al 2023) 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, the cancer proliferation lacks the superb site specific coordination and regulation seen in wound healing. For example migration of cells to the site of damage is well directed by chemoattractant gradients in wound healing (Brubaker et al 2013, Ansorge et al 2016,

Ridiandries et al 2018). Some of these chemoattractants are active in cancers as well but the absence of site specificity in these signals can result into 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 to 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 (Ashrafi et al 2016, Brazil et al 2019, Zhou et al 2020, Bird 2021, Gupta et al 2022, Beura et al 2022). It's no wonder therefore that such complex cross-talks are seen in cancer development too (Pascut et al 2020, Su et al 2021). 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 his 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 are expected to have evolved normally (Beura et al 2022) and they contribute to the interaction between nerves and tumors as well (Hanahan and Monje 2023).

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 specific role in wound healing and there is considerable overlap between the altered splicing agents in wound healing and cancers (Jensen et al 2014, Anczuków and Krainer 2016, She et al 2021). Involvement of circular RNA and specifically circ-Amotl1 is common to wound healing and cancer (Yang et al 2017, Li et al 2022).

The speed of replication being the priority in wound healing, more mutations and chromosomal abnormalities may accumulate in the proliferating cells (Zhang and Xu 2017, Bielas and Heddle 2000). In addition some of the mechanisms involved in inflammation and proliferation are known to be mutagenic (Kiraly et al 2015, Zhang and Xu 2017, Kay et al 2019). Genomic instability also may result from inflammatory mechanisms (Butin-Israeli et al 2019). 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 is suggested to have useful functions in wound healing (Alvarez-Dolado, and Martínez-Losa 2011, Losick et al 2013, Dornen et al 2020) 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 (Krzyszczyk et al 2018). Similarly in tumor development M2 promote proliferation (Cassetta and Pollard 2023) and M1 appear to attack and clear tumor cells (Boutilier, A. J., & Elsawa 2021).

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 (Hua and Bergers 2019, Hohnson et al 2022) 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 (Weyand et al 1994, Watanabe et al 2017), but the origin of these antigens is not known. Activating immune checkpoints facilitates wound healing (Su et al 2019, Wang et al 2022). Given the probability of generating new antigens during wound healing, mechanisms for contextual and short time suppression of 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 in wound healing mechanisms (Haubner et al 2012, Deptula et al 2019) as expected. This is not a “side effect” of cancer therapy, it is the main effect according to our perspective.

2. Epidemiological patterns: Vibishan and Watve (2020), 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 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.
3. 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 (Wang et al 2017, Hu and Polyak 2008, Medema and Vermeulen 2011, Lu et al 2012, Quail and Joyce 2013, Pickup et al 2014, Liu et al 2020, Elgundi et al 2020).
4. Accounting for Peto's paradox: Since the somatic evolution of cancer is not a mutation limited process, the Peto's paradox (Nagy et al 2007, Noble et al 2015, Tollis et al 2017) 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.
5. Lifestyle factors and cancer incidence: Since life style factors can influence body's internal environment, they can influence cancer incidence in a significant way. Many studies show the effects of several lifestyle factors (Anand et al 2008, Katzke et al 2015, Wolin et al 2010, Avgerinos et al 2019, Singh et al 2022, Pati et al 2023). But so far the detailed causal links have been underexplored. Our synthesis gives a theoretical platform on which the pathways and links between life style factors and tumorigenesis can be elucidated in detail.
6. Behaviorally rich environment suppresses implanted tumor growth: Perhaps potentially the most important and so far ignored life style 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 (2010) which showed that by providing a behaviorally rich environment progression of an implanted tumor could be effectively suppressed. Many experiments could reproduce the results although they differ in the detail (Li et al 2015, Takai et al 2019, Watanabe et al 2020, Xiao et al 2021, de Sousa Fernandes et al 2022). 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 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 (2015) 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 (2010) and replicated by many others (Li et al 2015, Foglesong et al 2019, Watanabe 2020). Although the findings were largely reproducible, the mechanisms by which behavior influences tumor growth remains 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 (2013). 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 (Eaton et al 1994). 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 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 a functional relevance can serve as empirical tests for our synthesis.

A good example is the question whether neoantigens are generated during wound healing. Neoantigens in cancer is 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 (Bartok et al 2020, Pataskar et al 2022) 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 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 (Peng et al 2007, Westman et al 2020, Vignali et al 2022) during wound healing and how they selectively identify such cells is an open question. The codon reassignment and frame shift can help generate novel peptide epitopes on cell surface which enable immune response to such cells in addition to some known “eat me” signals (Lemke 2019, Birkle and Brown 2021). What we already know is that the IDO1 pathway that triggers the codon reassignment in cancer (Pataskar et al 2022) 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 (Nino-Castro et al 2014, Bandeira et al 2015, Ito et al 2015, Lemos et al 2020, Bello et al 2021).

There are other specialized mechanisms for generating neoantigens including mRNA splicing (Merlotti et al 2023) that are currently thought to be unique to cancers. But the splicing protein SFRS6 (Jensen et al 2014) or SFRS3 (Li-Korotky 2006) 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 who’s role in the healing process is over (Riwaldt et al 2017) from the wound healing site. Even in tumors, cell senescence is

associated with antigen expression (Hanna and Balko 2023) 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 to this approach. If 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 (Anagnostou et al 2017, Nagel et al 2022, Niknafs et al 2023). Since most neoantigens originate in passenger, rather than driver mutations, there is likely to be 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 (Niknafs et al 2023), therapy such as CAR-T can have sustained benefit.

    If, on the other hand, antigens are generated by the built in process of ribosomal level codon reassignment and frame shifted 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 (Ventola 2017, Sambi et al 2019, Taefehshokr 2022). At the 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 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 life style factors, behavioral environment is an interesting possibility that needs to be explored seriously (Cao et al 2010, Watve 2013). 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 a 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 Interest*

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.

### *Acknowledgements*

Discussions at an early stage of concept development with Ruby Singh, Ruchika kaul-Ghanekar, Preirna Raina, Vibishan B., Nazneen Gheewala were useful.

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**Supplementary data:** available at https://doi.org/10.32388/IAELOG

## Declarations

**Funding:** No specific funding was received for this work.

**Potential competing interests:** No potential competing interests to declare.