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*Review Article*

# All cancer hallmarks lead to diversity

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**Abstract:** The concept of cancer hallmarks is considered a major generalization of the principles of cancer biology. Many refinements of this concept were proposed based on the novel findings regarding the molecular and cellular features of cancer cells elucidated since 2000. Furthermore, in the last decade the rapid development of high-throughput omics technologies provided unprecedented insights into the evolutionary dynamics of cancer cell populations. Here, we proposed an extension of the cancer hallmarks concept based on the recent refinements of our understating of evolutionary mechanisms underlying cancer initiation and progression.

**Keywords:** Cancer, hallmarks, evolution, genetics, epigenetics, diversity

## Introduction

The two landmark papers by Douglas Hanahan and Robert Weinberg on the hallmarks of cancer summarized over a century of extensive research on cancer biology [1, 2]. Probably the acceptance of this theoretical generalization by the scientific community went far beyond authors' initial expectations and intentions. Usually widely accepted, this concept also faced some serious criticism being considered a logical continuation of the so called somatic theory of cancer and not being able to identify unique cancer features [3]. Some reports attempted to redefine and expand the cancer hallmarks concept emphasizing different aspects of cancer biology [4-8].

From a purely philosophical point of view, however, one can consider the cancer hallmarks as an obvious classical paradigm or disciplinary matrix as proposed by the American philosopher Thomas Kuhn in his influential treatise *The Structure of Scientific Revolutions* [9]. Taking this view, cancer hallmarks indeed represent a conceptual framework, which attempts to explain the already known natural phenomena of cancer biology. However, the cancer hallmarks story and its proponents do not function as a true normal science according to the original Kuhnian view. The second paper on hallmarks shows that Hanahan and Weinberg keep their views open for novel discoveries and accept that many currently unexplainable processes and phenomena exist [1].

This report neither intends to answer any open issue in cancer biology nor refutes the original work by Hanahan and Weinberg. It is rather an attempt to present and justify our view on the broad definition of cancer hallmarks and their interrelation. We acknowledge most of the definitions of Hanahan and Weinberg. We, however, accept a strictly Darwinian view on cancer development as proposed initially by Peter Nowell [10], i.e., through gradual selection and expansion of advantageous cancer cell clones with specific genetic aberrations. One of the absolute prerequisites [11] for this view is the ability of cancer cell populations to generate and sustain features that can be passed to daughter cells through genetic or epigenetic mechanisms [12-14]. Therefore, we propose that extreme proneness to diversification (or heterogeneity generation) of cancer cell population is its main hallmark allowing for an efficient cancer cell population evolution under the natural selection of the organisms' various microenvironments as well as under the conditions of anticancer therapy. In order to propose a logical

extension of the concept of cancer hallmarks from an evolutionary perspective, we defined the following hallmarks: (1) Extensive genomic and epigenetic diversification; (2) Sustaining proliferative signaling; (3) Evasion of tumor growth suppressors; (4) Enabling replicative immortality; (5) Resistance to cell death; (6) Modulation of modulatory microenvironment; (7) Enabling and adaptive metabolism; and (8) Metastatic potential and cellular plasticity.

Below we outlined the major characteristics of these hallmarks and explained in brief how all hallmarks contribute to the extensive genomic and epigenetic diversification of cancer cell populations. Our view on the interrelation of cancer hallmarks is schematically represented in **Figure 1**.

### Extensive genomic and epigenetic diversification

In 2011, Hanahan and Weinberg [1] proposed genomic instability as an enabling cancer hallmark. We further develop the idea of this hallmark and consider genomic instability as a prerequisite for the generation of clonal heterogeneity within the tumor tissue. Besides, we propose that epigenetic mechanisms also account for heritable diversity within the tumor. These heritable genomic and epigenetic diversities contribute to the establishment of phenotypic heterogeneity. Therefore, we prioritize this hallmark as the central (very core) hallmark of cancer. Furthermore, at least partly all other hallmarks can contribute to further diversification of the tumor tissue and ensure the "building material" for the clonal evolution of cancer (**Figure 1**).

With the advent of next generation sequencing (NGS), large-scale sequencing efforts such as the cancer genome (TCGA) project showed that every cancer is different and that there is no fixed genomic landscape. The cancer genome is characterized by heterogeneity between tumor types (intertumor) and within an individual tumor (intratumor), reflecting the action of the evolutionary forces of variation generation and natural selection. Intertumor heterogeneity is expressed by differences between tumors of the same origin in different patients. It is represented by different tumor subtypes with specific expression features and different biological behavior. For example, breast cancer, a well-studied example of intertumor heterogeneity, is subdivided into five subtypes - luminal A, luminal B, HER2-positive, triple negative and normal breast-like subtype [15]. However, NGS studies show that many tumors and their subtypes are phenotypically similar but can be genetically diverse. Sequencing studies show that very few mutations were observed in more than 5-10% of tumors of a particular tissue type [16]. Furthermore, efforts to define tumor subgroups based on specific mutations may also be confounded by epistasis, which implies the action of one gene on another: for instance, in acute myeloid leukemia (AML), *NPM1* mutations confer a favorable prognosis only in the presence of a co-occurring *IDH1* or *IDH2* mutation [17].

Another line of evidence for the central role of generation of tumor heterogeneity and through extensive genetic and epigenetic diversification is that the order of mutations matters for the acquisition of tumor phenotype at least in some instances. The classical example is the ordered acquisition of mutations in colon cancer. The initial *APC* gene mutations are usually followed by mutations in proliferation controlling genes such as *KRAS*, *NRAS*, *AKT1* and the final step is usually the loss of tumor suppressor *TP53* [18]. The acquisition of mutations in some genes can help the appearance of specific mutations in other genes. DNA methyltransferase 3A (*DNMT3A*) gene mutations are frequently the first genetic event in leukemia affecting hematopoietic stem cells and are frequently followed by the acquisition of indel mutations in *NPM1* and *FLT3* genes [19]. Furthermore, in the settings in myeloproliferative diseases the initial acquisition of JAK2 V617F mutation drives the phenotype to polycythemia vera development rather than to essential thrombocythemia [20]. It is therefore rational to believe that tumor cell populations early on in their development develop the ability for wide-spread mutability of their genomes so that it is likely to acquire a strong driver mutation. The extreme view on the mechanism of generation of somatic mutations in cancer is the so-called mutator phenotype of cancer as proposed by Larry Loeb [21].

We, however, accept that genetic diversity in cancer is not generated exclusively by perturbation in DNA repair mechanisms but is established and sustained by a number of other over-

lapping mechanisms as discussed further below. Interestingly, human cancers differ dramatically based on the frequency of mutations per cancer genome. This difference, however, does not translate into the same level of variation in phenotypic heterogeneity. The changes that can compensate for the relatively lower number of mutations in certain tumor types might be epigenetic. In support of this idea is that acute myeloid leukemia (AML) genomes harbor a relatively lower number of mutations but up to one third of readily identifiable driver mutations affect epigenetics-related genes (e.g. *TET2*, *DNMT3A*, *IDH1/2*, *ASXL1*, etc.) [22]. Therefore, we make no difference whether genetic or epigenetic diversity is achieved through gradual stepwise acquisition of mutations or some kind of an extremely active variations generating process; the key feature remains only the ability of the cancer cell populations to generate heritable diversification exceeding the rate in normal tissues.

Intratumor heterogeneity manifests itself in the variability of genetic and epigenetic status, gene and protein expression, morphological structure, and other features of the tumor [23]. Such diversity is thought to develop either due to genetic/epigenetic disorders in tumor cells themselves or under the influence of the tumor microenvironment. Some of the epigenetic mechanisms causing tumor diversity include DNA methylation, chromatin remodeling, and post-translational modification of histones [24]. In fact, sequencing studies have shown that genetic abnormalities may even possibly bring about epigenetic abnormalities in certain instances [25]. Leaders in the field of epigenetics have already proclaimed epigenetic dysregulation as a pivotal event in cancer development [26, 27]. Furthermore, cancer metabolites and exosome secreted microRNAs can play a crucial role in oncogenic reprogramming within the entire tumor [28-30]. Whether genetic or epigenetic in nature, cancer-causing and driving events culminate in altered gene expression at single cell level. Recent advances in single-cell RNA sequencing (RNA-Seq) confirmed the expectations for unprecedented intratumor diversity at transcriptomic level [31, 32].

All these manifestations of variability become the source for the evolution and adaptation of the tumor (selective proliferation of subclones that have a phenotypic advantage) to changes in microenvironment and/or become a tool for triggering its metastatic potential. A clonal sweep, whereby a new clone takes over the entire population, replacing ancestral clones, will result in a homogenous cell population. But if not, branched tumor evolution, in which subclones evolve in parallel, will result in extensive subclonal diversity [14, 33]. For example, in clear-cell renal cell carcinoma, sequencing multiple biopsies from the same primary tumor revealed spatially separated subclones, harbouring heterogeneous somatic mutations and copy number events [34]. Likewise, multi-region sampling in glioblastoma documented heterogeneous copy number events between different regions of the same tumor [35]. Evidence for clonal diversity between primary and metastatic sites has also been demonstrated in breast cancer [36] and pancreatic cancer [37, 38] amongst others.

### Sustaining proliferative signaling

The proliferative advantage of cancer cell compared to a normal cell is often considered the principal hallmark of cancer growth. Indeed, more aggressive tumors conferring worse prognosis show higher proliferative capacity. We, however, believe that sustained proliferative signaling through major signaling cascades is not simply to ensure the presence of a bulk tumor tissue but rather a major contributor to other hallmarks. In the light of our proposal that the chief hallmark of cancer is the generation and sustaining of genomic and epigenetic heterogeneity we consider higher proliferation rate a major contributor to it. The direct consequence of higher proliferation is the increased DNA replication errors and replicative stress. As proposed recently by the Vogelstein group stochastic errors in DNA replication could be the major cause of cancer-initiating mutations [39, 40]. Furthermore, cancer incidence increases with age as well as the number of clonal DNA mutations that can initiate cancer. The latter has been elegantly shown for the hematopoietic tissue with the demonstration of the increased incidence of clonal hematopoiesis of indeterminate significance with age [41-44]. The most striking and conclusive evidence for the importance of DNA replication associated errors in tumorigenesis is the identification

of distinct somatic mutations signatures in human cancers. Among the defined 22 signatures at least seven were directly related to DNA replication, including age related signature, AID/APOBEC associated signatures, MSH related and BRCA1/BRCA2 related signature, etc. [45-47]. Moreover, many pro-proliferative oncogenes can cause increased replicative stress most notably through the collision of replication forks and transcription bubbles [48, 49], which coupled with replicative immortality, tumor suppressor genes evasion and apoptosis bypassing can contribute to genomic instability and further genetic diversification of the tumor tissue.

### Evading growth suppressors

We accept as a well-defined cancer hallmark the evasion of tumor suppressor genes. To a great extent this evasion supports the concept of constant contribution to the generation of extreme cancer cells diversity. For instance, the most popular tumor suppressor gene *TP53* has important roles as a sensor of DNA damage after chemicals exposure, UV irradiation, or oncogene activation. All these insults lead to p53 stabilization and subsequent binding to the promoter regions of proapoptotic genes such as *BAX* and *PUMA,* thus leading to cell cycle arrest, and apoptosis. *TP53* is one of the top ten most frequently mutated genes in human cancer leading to the loss of its DNA protective and apoptosis induction functions [50]. This allows the passage of newly acquired mutations and gross chromosome anomalies allowing for greater genomic heterogeneity in tumor tissues. Indeed, *TP53* mutated tumors usually show higher genomic complexity sometimes resulting from catastrophic genome rearrangement events including chromothripsis [51, 52]. It has recently been shown that *TP53* amplification is a major cancer resistance mechanism in long-lived animals such as elephants [53].

The other most widely studied genetic event allowing evasion of anti-proliferative signaling is the loss of the retinoblastoma (*RB1*) gene. Recent data show that pRB has a more a complex role in cell physiology than simply regulating the cell cycle progression. This is probably achieved through the simultaneous existence of different monophosphorylated forms of RB having a distinct set of interacting partner proteins [54]. Notably, it has been conclusively shown that loss of *RB1* is associated with increased levels of genomic instability in cancer cell lines [55]. In a final account, the loss of this important checkpoint mechanism in the cell cycle allows the cancer cell to progress to replication and cell division with further newly acquired DNA aberrations, and this ultimately leads to the increase of genomic instability and heterogeneity of cancer. Indeed, some authors consider increased proliferation and evasion of antigrowth signals a single hallmark of cancer as they both ultimately lead to replicative stress [56].

### Enabling replicative immortality

The ultimate proliferative potential of cancer cells has to deal with the limited DNA replicative potential of normal somatic cells because of the constant telomeres erosion. Interestingly, telomeres not only prevent the erosion of chromosomes ends and their entrance into the breakage-fusion-bridge (BFB) cycles that ultimately lead to gross chromosomal abnormalities [57] but can also serve as off-targets of endogenous mutators such as activation-induced cytidine deaminase (AID) that could trigger apoptotic response in case of over-activity of such mutators [58].

This resistance is elegantly bypassed by tumor cells by the well-studied overexpression of the components of the telomerase complex. Recent whole genome sequencing studies conclusively showed that a large proportion of cancers harbor mutations in the human telomerase promoter leading to its re-expression. Recent data showed that telomerase re-expression is not only pivotal for securing telomere length in cancer cells but is rather contributing to other recognizable hallmarks [59]. The first observations suggesting that telomerase may play a non-canonical role in cancer were those of the unexplained need for its overexpression in several mouse tumor models. Telomerase reverse transcriptase (Tert) can suppress the important anti-proliferative signaling of the TGF-β pathway [60]. Catalytically inactive Tert can promote tumor cell proliferation through induction of WNT and MYC signaling pathways [59]. Tert has also been shown to provide anti-apoptotic signals through activation of the

NF-kB pathway [61]. Interestingly *TERT* is also actively involved in epithelial-mesenchymal transition through TERT-mediated Wnt/b-catenin signaling, leading to the upregulation of Snail-1 (snail family zinc finger 1) and vimentin [62]. In the light of our view on the hallmarks of cancer, however, most interesting are the findings that TERT can regulate DNA damage signaling through ataxia telangiectasia mutated (ATM), breast cancer 1 (BRCA1), and gamma-H2A histone family, member X (γH2AX) therefore reducing the number of newly acquired mutations during rapid DNA replication associated with tumor growth [63, 64]. In this way, telomerase is playing a protective role for the genetic integrity and propagation of a given advantageous cell clone. However, very recent experimental evidence suggested that the most frequent noncoding mutations across various cancer subtypes those in the *TERT* promoter initially lead to bulk telomere shortening, and afterwards the critically short telomeres cause genomic instability and telomerase upregulation to ensure immortalization [65].

### Resisting cell death

In the last three decades, distinct pathways for cell death known as necrosis, apoptosis, necroptosis and autophagy have been defined at cellular and molecular level. The intuitive thinking of cancer implied that cell death through any natural mechanism should work as a barrier to cancer development. The classical examples of perturbation in anti-apoptotic mechanisms include deregulation of the B-cell lymphoma-2 (BCL2) family proteins in various cancer types [66]; the most notable example being the chromosomal translocation t(8;14) driving Bcl2 over-expression in follicular lymphoma under the control of the IgH locus [67]. We accept that in a large number of cancers perturbation of apoptosis is a hallmark of paramount importance directly affecting cancer cells survival. However, there are several lines of evidence that this view might indeed be an oversimplification and that under certain circumstances enhanced apoptotic death can serve as a tumor promoting event [68]. To support that latter idea are the observations that in mouse models BCL2 overexpression causes lymphomas and eventually other cancers only with long latency and requires the acquisition of mutations in other oncogenes and tumor suppressors [67]. Even stronger evidence is the fact that BCL2 overexpression in some solid cancers is not invariably linked to worse prognosis [69]. To explain these counterintuitive observations that apoptosis may enhance tumorigenesis, a recent hypothesis has been coined that apoptosis may serve as a strong trigger for clonal selection because dying out tumor cells provide a niche for expansion of more highly proliferating clones. A similar normal process is observed during the thymic development of T cells in mammals when autoreactive clones undergo rapid apoptosis providing sufficient space for the expansion of non-autoreactive T cells [70]. Perturbation of this natural competitive selection process in the thymus has been shown to lead to T cell lymphoma development [71, 72]. Other studies showed that the loss of the proapoptotic BH3-only protein, PUMA, can abrogate T cell lymphoma development and carcinogen-induced liver cancer in mice [73]. Finally, it has recently been showed that BCL2 overexpression in a mouse model of myelodysplastic syndrome can improve macrocytic anemia and delay leukemia transformation [73]. If one sticks to the classical view on the role of apoptosis in cancer development its evasion is a major prerequisite for the sustained survival of cancer cell clones already having a proliferative advantage and increased genomic instability [74]. On the other hand, the non-canonical view of apoptosis induction as a trigger for the proliferation of other advantageous clones would imply that it indirectly contributes to the enhanced generation of genetic heterogeneity in cancer cell populations as discussed above.

Autophagy mediated cell death has also been to shown to have tumor suppressor and tumor promoting role [75]. Interestingly, in the hypoxic tumor areas autophagy is up-regulated and contributes to tumor survival [76]. A number of studies have shown that RAS-driven tumors may by autophagy addicted [77, 78]. A key mechanism for this is probably the suppression of p53 activation [79, 80]. Therefore, autophagy as a tumor-promoting process is mechanistically linked to other hallmarks and also with induction of cancer cells heterogeneity as discussed above. Necrosis can also contribute to cancer progression through induction of tumor-promoting inflammation via the release of the High mobility group 1 (HMGB1) protein from the

necrotic cells [81]. Necroptosis may also have a significant contribution to cancer promotion at least in some instances [82].

### Modulation of modulatory microenvironment

We define a broad hallmark of *Modulation of modulatory microenvironment*. This hallmark in our view comprises the versatile mechanisms through which cancer cells interact with the cellular and acellular components of the microenvironment. Notably, cancer cells can modulate microenvironment and vice versa microenvironment can directly affect tumors. Therefore, we propose the inclusion within this broad hallmark such key processes as neoangiogenesis and tumor vascularization, interaction with extracellular matrix as well as immune system interaction. Notably, under certain circumstances the various components may act as cancer-promoting or anticancer mechanisms. The most notable examples in this respect are the tumor-promoting inflammation and the cancer immunoediting.

The tumor microenvironment is a complex habitat in which the cancer cells exist. It comprises cells of hematopoietic origin, cells of mesenchymal origin and non-cellular components [83]. Cells of hematopoietic origin including myeloid-derived cells (macrophages, neutrophils, dendritic and myeloid-derived suppressor (MDSC) cells), lymphoid-derived cells (CD4+, CD8+ T cells, T regulatory cells (Tregs) and innate lymphoid cells (ILCs)) [83]. Cells of mesenchymal origin include mesenchymal stem cells, myofibroblasts, endothelial cells and adipocytes. The non-cellular component includes the extracellular matrix. It consists of proteins, glycoproteins, proteoglycans, type IV collagen, laminin and fibronectin [83]. The diversity of the cellular populations and the production of different signals, cytokines, growth factors and the interaction of all these components promote tumor development and angiogenesis. A major environmental context for the development of this is hypoxia, which is the trigger for a plethora of signaling pathways and regulatory networks in both cancer cells and tumor microenvironment. A general line of thought is that rapid tumor growth and unstable tumor vasculature render significant parts of the tumor tissue hypoxic. Indeed, hypoxic response is orchestrated by the relatively simple signaling HIF-1 pathway [84]. HIF-1 (Hypoxia-inducible factor 1) is a transcription factor that is ubiquitously expressed and is composed of two subunits, HIF-1α and HIF-1β subunits. The HIF-1α subunit is regulated by $O_2$-dependent hydroxylation by prolyl hydroxylase domain protein 2 (PHD2), which promotes binding of the von Hippel-Lindau protein (VHL), leading to ubiquitination and proteasomal degradation. The hydroxylation reactions utilize $O_2$ and α-ketoglutarate as substrates and generate $CO_2$ and succinate as by-products and provide a direct link between metabolic state and signaling to the nucleus (see below). Under hypoxic conditions, hydroxylation is inhibited, leading to HIF-1α accumulation and its dimerization with HIF-1β with subsequent transcriptional activation of target genes. Thousands of genes are under the transcriptional regulation of HIF-1 and are implicated in virtually all other cancer hallmarks, including angiogenesis and metastatic potential [85]. Most importantly, HIF-1 directly links hypoxia to inhibition of DNA damage response genes and contributes to genomic instability, including microsatellite and chromosomal instability [86, 87]. Hypoxia may also drive genetic instability via the alteration of transcription and translation of the DNA damage response and repair genes [88]. It would ultimately promote metastasis. Furthermore, hypoxia directly affects gene expression in MDSCs, tumor associated macrophages and Tregs with a net effect of suppression of antitumor response [89].

As discussed in the previous hallmarks of cancer papers, angiogenesis is important for the tumor progression, invasion and eventually metastasis. The activation of the angiogenesis switch via HIF, VEGF, PDGF, FGF pathways leads to the formation of tumor neovasculature [1]. The immune inflammatory cells, endothelial cells, pericytes, and the altered extracellular matrix within the tumor microenvironment play a major role in angiogenesis and vascular remodeling [90]. Other suggested forms of new vessels formation such as intussusceptive angiogenesis are triggered by platelet derived growth factor-B, angiopoietins, ephrins and EphB receptors [90-93]. Vasculogenic mimicry is also suggested as a phenomenon by which tumor cells act similar to endothelial cells and form vascular channels themselves. It was demonstrated in multiple solid tumors like

uveal melanoma, glioblastomas, and hepatocellular and breast carcinomas [90-94]. In the light of our proposal the extreme example of the role of the tumor microenvironment on induced genetic heterogeneity in cancer cells came from David Scadden's lab with the demonstration that Dicer1 deletion in mouse osteoprogenitors causes myelodysplasia and transformation to overt acute leukemia [95]. Notably, tumor stroma can support the emergence of therapeutic resistance without the need for genetic changes. This paracrine interplay between tumor and stromal cells has been demonstrated for melanoma, prostate cancer and lymphoma models [96-100].

The complex mammalian immune system is an indispensable player in cancer initiation, promotion, evolution and spread [101]. The interplay between the mechanisms of the innate and adaptive immunity (including humoral and cellular elements) is an important protective mechanism resulting in inflammation [70]. The current general paradigm in cancer immunology is that chronic inflammation is frequently associated with cancer initiation and progression whereas acute inflammation usually has an anti-oncogenic effect [102, 103]. The innate response is rapid, nonspecific against foreign antigens, short-lived and is not able to form an immunological memory. It includes proteins (such as cytokines complements, chemokines) and cells (such as natural killer (NK) cells, mast cells, eosinophils, basophils, macrophages, neutrophils, and dendritic cells). On the other hand, the adaptive immunity is a slower response that involves immune components more specific for the targeted antigens and can establish immunological memory. It includes T cells, B cells and antigen presenting cells. The role of the innate immunity in cancer is to ameliorate the inflammation caused by the tumor tissue. This process also triggers adaptive immune responses for targeting cancer via more specific immune mechanisms. Complement activation has multifaceted role leading to either activation of pathways that help in the eradication of cancer cells or the inhibition of pathways that would defend cancer cells from complement-mediated injury.

The genetic and epigenetic modifications can change the cell surface markers expression. For example, the expression of MHC class I become altered or reduced in cancer cells. It activates the NK cell by stimulating receptors present on its cell surface. This triggers apoptosis via TNF-α, antibody dependent complement cytotoxicity, and cytokines release [104, 105]. Neutrophils and their contents (proteases) also play a role in cancer growth, invasion and metastasis. Other immune cells such as dendritic cells and macrophages bridge the innate and the adaptive immunity serving as phagocytes in the innate immune responses, and as antigen-presenting cells for adaptive immunity. The γδ-T cells control cancer progression by leading to tumor lysis via secretion of IFN-γ, and antibody-dependent complement cytotoxicity [106].

There are several mechanisms through which tumor associated inflammation can increase genetic heterogeneity at tumor initiation or progression. It has been conclusively shown that inflammatory milieu is a rich source of reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI). Both of them can accumulate within the extracellular space and diffuse into cancer cells and directly damage DNA. Alternatively, ROS can suppress mismatch repair enzymes and microsatellite instability [102, 107]. Various cytokines and toll-like receptor (TLR) agonist can directly induce the expression of DNA damaging enzymes such as Activation-induced cytidine deaminase (AID). AID is naturally expressed in germinal center B cells which seem to be protected from its off-targeting and collateral damage [108], which could be overcome in the absence of p53 [109]. Prolonged action of the potent pro-inflammatory cytokine IL-6 causes AID associated translocations and plasmacytomas in mice [110-112]. Ectopic expression of AID can be induced by various microorganisms and viruses and leads to rapidly growing cancers even in tissues from mesenchymal and epithelial origin [113-117].

The main concept of the role of adaptive immunity role in cancer revolves around the formation of neoantigens/neoepitopes. T cell activation plays a crucial role in cancer immunity. It triggers a cascade of pathways and cytokines production and the formation of immune checkpoints via the CD4+ T cells and CD8+ T cells. Depending on the signals present in the tumor environment, these mechanisms can lead either to the killing of the cancer cells or their

proliferation [118]. Programed cell death protein 1 (PD-1) expression by the T cells plays a role as an immune checkpoint in cancer immune evasion. Another important immune checkpoint molecule is the cytotoxic T lymphocyte-associated antigen 4 (CTLA4). It is expressed on regulatory T cells (Tregs) but is upregulated only in activated T cells.The role of CTLA-4 is the modulation of T cell responses. The understanding of the above signals has led to the discovery of immune checkpoint blockade based therapies [119, 120]. Understanding the role of T cells in cancer led to the evolution of the concept of chimeric antigen receptors (CARs) on T cells (CAR-T cells) therapy, which has been proven to be effective in hematological malignancies [121, 122].

The interactions between the tumor tissue and immune system have been generalized by the model of immune editing recognizing three phases of the process called Elimination, Equilibrium and Escape [123]. The Elimination phase involves immune cells targeting and eradication of the cancer cells. The Equilibrium phase is characterized by a dynamic balance between cancer progression and elimination by the immune system; here, the tumor enters a functional dormancy state. Finally, during the Escape phase, the immune system can no longer limit tumor growth and tumor cells evade the immune recognition causing clinically apparent disease [124]. At this phase, the processes through which cancer cells evade the immune system include genetic, epigenetic changes and selective pressure [123-125]. For example, in certain cancers, the epigenetic silencing of JAK1 kinase leads to the tumor's unresponsiveness to IFN-γ, therefore losing its antitumor immune response. The "selective pressure" on the cancer cells by the immune system represents another escape process. It includes cancer cells inhibition of apoptosis by the upregulation of Bcl-XL and FLIP [123, 124]. The secretion of factors such as IL-4 and IL-13 would recruit macrophages that express TGF-β, IL-10 and VEGF; these would have inhibitory effects on the immune cells.

### Enabling and adaptive metabolism

In 2010 Hanahan and Weinberg proposed an emerging hallmark, reprogramming energy metabolism [1]. The strongest arguments in support of the inclusion of such a hallmark are the classical observations of the shift of cancer metabolism to the glycolytic utilization of glycose rather than to oxidative phosphorylation ("Warburg effect") and the strong dependence of cancer metabolisms on glutamine utilization [126, 127]. The major counterargument against the definition of altered metabolism as a hallmark of cancer is the idea that all alteration might be just downstream effects of major pathways altered in cancer [1]. Our current understanding is that the "metabolic reprogramming" in cancer serves not just to satisfy the energetic demands of the this fast proliferating tissue but to provide versatile intermediates for the various anabolic processes as well as to ensure proper redox potential within the tumor tissue [128, 129]. It is also evident that in a vast majority of cases this reprogramming is a result of the altered signaling through oncogenes or tumor suppressor genes such as *PI3K*, *MYC* and *TP53* [130-134].

Another emerging feature of cancer metabolism that particularly supports our idea of the central role of genetic and epigenetic heterogeneity of cancer is the provision of so called "oncometabolites". This term refers to metabolites whose abundance increases significantly in specific tumors and their emergence can be linked to specific mutations as well as have a defined role in oncogenesis [128]. Recent evidence showed that a class of enzymes known as α-ketoglutatrate dependent dioxygenases play pivotal roles in hypoxic cellular responses and epigenetic modifications in the cells [129]. This class includes enzymes such as TET enzymes (TET1-3), histone demethylases (Jumonji C family), prolyl hydroxylases (PHDs), etc. α-ketoglutarate (α-KG) serves as a cofactor of these enzymes undergoing concurrent oxidation to succinate [135] rendering these enzymes particularly sensitive to variations in the amounts of the available α-KG. This dependence appears to be a potent oncogenic mechanism. For example, some of the familial cases of paragangliomas and pheochromocytomas have biallelic loss of the succinate dehydrogenase (*SDH*) gene, whereas other subsets of these tumors as well the familial cancer syndrome leiomyomatosis and renal cell cancer (HLRCC) have loss of the fumarate hydratase (*FH*) resulting in low levels of α-KG resulting in global DNA methylation increase [136-140].

Another prominent example of oncometabolite generation is the presence of gain-of-function mutations in isocitrate dehydrogenase 1 (*IDH1*) and 2 (*IDH2*) genes. Such mutations have been found in gliomas, cholangiocarcinomas and AML [141, 142]. Notably, these mutations lead to neomorphic catalytic activity of the enzymes leading to the preferential generation of 2-hydroxyglutarate (2-HG) rather than α-KG [143]. 2-HG serves as a competitive inhibitor of the α-ketoglutarate dependent dioxygenases and cause CpG islands hypermethylation [144]. 2-HG can also cause histone hypermethylation and block in differentiation [25, 145-147].

Taken together the examples of "oncometabolites" prove that cancer-related metabolic changes must be considered as a separate hallmark. Besides, this hallmark has the potential to affect at least epigenetic heterogeneity within the tumor either directly or in a paracrine fashion [30, 148] and therefore can consistently feed the core hallmark as proposed by our model (**Figure 1**).

**Metastatic potential and cellular plasticity**

From a clinical point of view, the importance of the metastatic potential of cancer cells is illustrated by the fact that metastatic disease is the leading cause of mortality in cancer patients [149]. The classical view on metastasis was heralded by the 1889 Stephen Paget's "seed and soil" hypothesis which entails that a tumor cell metastasizes ("seeds") when it reaches the appropriate soil, i.e. the organ which can sustain its growth [150]. Currently, metastasis is understood as a more complex process of orchestrated molecular and biochemical events. The invasion-metastasis cascade was proposed to better describe the metastatic process and it involves six steps. Below we briefly outline the molecular and cellular events underlying this cascade and finally discuss how metastatic process contributes to the core hallmark - tumor heterogeneity.

Epithelial-mesenchymal transition (EMT) enables tumor cells to undergo migration and invasion by down-regulating E-cadherin, a protein involved in cell to cell adhesion, in response to transcription of EMT regulating genes Snail, Slug, Twist and zinc-finger E-box-binding 1/2 (ZEB1/2) as a result of EMT signals (hypoxia, growth factors, signaling pathways, metabolic, mechanical stress and matrix stiffness) [151, 152]. Specific miRNAs (e.g., miR-200) suppress transcription of ZEB1/2 preventing EMT, ZEB1/2 suppress miR-200 transcription as well [153, 154]. After EMT and BM invasion, tumor cells invade the extracellular matrix (ECM) by secretion of matrix metalloproteinases (MMP)-1, -2, and -9 and activation of the proteolytic urokinase-type plasminogen activator system (uPA/uPAR) [155].

Intravasation of the metastasizing cells can be hematogenous (active or passive) or lymphatic. The process is not efficient and the blood shear forces and immune system can destroy the cells in the bloodstream. It is caused by factors similar to those involved in local invasion including TGF-β, EGFR family and proteases like MMP-1, -2 and -9 and activation of uPA/uPAR [155]. Hematogenous intravasation depends on access to the vasculature and microvessel diameter, so the expression of angiogenic factor VEGF correlated with the presence of liver metastasis [155, 156]. FGFs are also angiogenic and their expression in MCF7 breast cancer increased intravasation [157]. VEGF-B can reduce the efficacy of blood perfusion resulting in hypoxia that stimulates invasion. It also increases vessel leakiness [158].

Most of circulating tumor cells (CTCs) flowing in the blood every day will die with less than 1% surviving and having a chance to produce distant metastasis [159]. To avoid that, CTCs reform its integrin expression profile and activate cellular signaling as the Akt signal transduction pathway [160]. In avoiding the immune system, the tumor cells upregulate different surface protein population groups. Examples of such proteins are CD47 [161, 162], PD-L1 [163], and vascular cell adhesion molecule 1 (VCAM-1) [164], which bind to macrophages to evade phagocytosis. The reduced NADPH - generating enzyme present in the folate pathway is increasingly relied on in order to avoid oxidative stress [165]. Such stress can also be tolerated by expressing tissue factor protein on their surfaces. These then tend to attract platelets [166] that stimulate reversible metabolic changes in the tumor cells and link them with CD11b+ macrophages, thus establishing micro-clots to protect CTCs in the bloodstream [167].

Before extravasation CTCs get entrapped in the first capillary bed they encounter. This is determined by the blood flow in the body and the origin of the CTCs [168]. The entrapped cells grow within the vessel resulting in its rupture or extravasate by breaking through the vessel wall. Genes involved in the process of extravasation of CTCs that metastasize in lung cancer include protein Fascin-1, invadopodia, epiregulin and Wnt ligands [169]. Furthermore, humoral factors such as angiopoietin-like 4 (ANGPTL4), VEGF, COX2, MMP1 and osteonectin increase vessel permeability [170-172]. Another tumor-derived factor, SPARC, increases vascular permeability and extravasation by endothelial VCAM1 signaling [173]. Platelets that are attached to CTCs also enhance extravasation by TGF-β and triggering EMT in the cancer cells [174] or by secreting adenine nucleotides, which relax endothelial cell junctions. Additionally, tumor cells induce programmed necrosis (necroptosis) of endothelial cells, thus increasing vascular leakiness and tumor cell extravasation and metastasis [175].

Extravasated cancer cells need specific conditions in order to survive and initiate tumor growth in the new microenvironment they are exposed to. They locate themselves in specific niches which form before the seeding of CTCs. These so-called premetastatic niches are formed by factors released from the primary tumor thus providing the “soil” to the future metastasis. These factors lead to up-regulation of VEGF-A, PlGF, TGF-β and inflammatory proteins S100A8/-9 [176, 177]. Tenascin C or TGF-β released from the extravasated cancer cell itself after arrival results in the formation of an Ad hoc niche by amplifying Notch and Wnt signaling [178, 179]. Perivascular niche form in perivascular areas and support extravasated cancer cells in capillary BM [180, 181].

Tumor dormancy occurs through two mechanisms, cellular and tumor mass dormancy. In cellular dormancy the disseminated tumor cells (DTCs) becomes quiescent. However, during tumor dormancy the DTCs are kept in check by vascular insufficiency or immune system [182]. TGF-β, bone morphogenetic proteins (BMPs) and autocrine Wnt inhibition can induce dormancy in DTCs [183-185], but microenvironments rich in type 1 collagen or fibronectin inhibit it [186, 187]. For the metastatic colonization to occur the DTCs must have a tumor initiating ability by residing in a cancer stem cell state [178, 179, 188] and undergo a mesenchymal-to-endothelial transition (MET) in order to restore cellular traits of the primary tumor [189]. DTCs must create adaptive organ specific colonization programs [190] that enable them to survive in the microenvironment of the distant organ and to shape the supportive niches aiding colonization [179].

It is widely accepted that most cancers exhibit some degree of intratumor heterogeneity and intrinsic genetic diversity increases the probability of selecting cells that are intrinsically better in overcoming the biological and physical constraints during the process of metastasis. There is growing evidence that cancer cells behave as communities and there is cooperative dynamics between tumor subpopulations that can influence disease progression. It was already recognized as early as in the 1970s [191-193] that heterogeneous subclones within tumors possess differing capacities for growth and metastatic ability. Studies have shown evidence of such heterogeneity and cooperative dynamics contributing to greater metastatic potential. Using a xenograft zebrafish model it was demonstrated how an inherently invasive (MITF-high) melanoma cells can cooperate with poorly invasive (MITF-low) cells. The protease activity and ECM deposition caused by the MITF-high around the primary tumor allowed for a co-invasion with MITF-low through the solid tissue surrounding the tumor site [194]. In another study, a model was developed for studying subclonal competition and cooperation in *Drosophila melanogaster* [195]. Eichenlaub et al. used a *Drosophila melanogaster* model of epithelial tumor formation to show that overexpression of both epidermal growth factor receptor (EGFR) and miR-8 in wing imaginal disc cells results in super competitive cells that engulf those surrounding them. These super competitive cells drive tumorigenesis and metastasis, whereas cells overexpressing either EGFR or miR-8 alone do not [196, 197].

Cellular plasticity provides cells with the ability to epigenetically adapt to conditions of stress as well as to changes in the microenvironment. Tumor cells can reversibly undergo transition between epithelial and mesenchymal states (EMT and MET). While EMT is a fundamental

biological process in embryogenesis and wound healing, EMT activation during cancer promotes disease progression and enhances the metastatic phenotype by providing the previously locally growing carcinomas migratory and invasive capacities. These mesenchymal traits cooperate to enable cancer cell to disseminate and seed metastatic deposits [198]. However, different populations of cancer cells possess different epigenetic patterns that drive these changes, and each pattern may have different clinical significance. The complexity of EMT and metastasis lies in the heterogeneity of the population: not all cells will undergo EMT simultaneously, and not all cells that have undergone EMT will successfully metastasize [199]. For instance, minimal induction of EMT may not be sufficient to promote metastasis; however, the maximum induction of EMT may otherwise end up in stable mesenchymal cancer cells resulting in the suboptimal outgrowth of metastases. In contrast, induction of partial EMT could optimize tumor-initiating potential while still maintaining cell plasticity (the ability to reverse EMT process and undergo MET), thus generating more epithelial progeny which significantly raises the odds for a successful of metastatic colony formation [198]. Cancer progenitor cell characteristics, together with environmental factors, extracellular and intracellular signaling, and epigenetic changes all influence the choice of whether a cell would undergo EMT and would eventually metastasize [199]. Finally, Comaills *et al.* [200] showed how epithelial cells induced to undergo EMT exhibited mitotic errors and genomic instability during the process, although the EMT process was reversible upon withdrawal of the inducing factors, the genomic changes and the heterogeneity that resulted persisted and were heritable. This was supported by assessing the prevalence of genomic instability in mesenchymal and epithelial CTCs from breast cancer patients showing higher prevalence in the mesenchymal lineage.

## Discussion

In his Pulitzer-winning book The Emperor of All Maladies Dr. Mukherjee used the metaphor Cancer's life is a recapitulation of the body's life, its existence is a pathological mirror of our own [201]. Here, we agreed with it and proposed and stated that in order to survive within the fitted environment of our bodies cancer cells rely on the universal principles of evolution. Early on in its ontogenesis the cancer clone has to acquire the ability to create an extreme diversity of genetic and epigenetic features resulting in specific phenotypic variations that are further positively or negatively selected. In fact under normal conditions our bodies have constrained such a hazardous process of genomic diversification to the development of T and B lymphocytes [70]. During immune response the immune cells are positively selected among billions of preexisting types of their specific receptors generated through the random recombination of the immunoglobulin or T-cell receptor genes. Positively selected cells undergo clonal expansion and proliferation and eventually become long lived memory cells. Notably, only B cells can undergo further rounds of somatic hypermutation of their genes and further sub-clonal selection. Obviously, the key feature of this process remains the initial generation of extreme genetic diversity.

The strategy employed by cancer cells is virtually identical. The most striking example of the utilization of this selection model in cancer is probably the use of stereotypic B cell receptors in certain B cell malignancies such as chronic lymphocytic leukemia (CLL) with cognate autoantigens [202, 203]. The cancer cell population is intrinsically prone to constant generation of phenotypic diversity resulting from numerous epigenetic and genetic events. The elegant demonstration of clonal heterogeneity in both primary and metastatic cancer demonstrates that extreme heterogeneity in cancer populations appears selected as advantageous in various microenvironments. More interestingly cancer cells and microenvironments seem to co-evolve [204]. Certain features of microenvironment and immune system may favor the selection of specific cancer clones and vice versa specific clones may lead paracrine preformation of the tumor niche [205]. Other evidence that increased mutability provide evolutionary advantage stems from the field of virology. RNA viruses (including HIV) undergoing high levels of hypermutation of their genomes can acquire a pool of beneficial mutations though at the expense of generation of a large number of dead viruses [206, 207].


**Figure 1.** Definition of eight cancer hallmarks and their interdependence. The central (core) hallmark is the ability of cancer cell populations to sustain extensive genomic and epigenetic diversity. This hallmark enables the emergence of all others and their propagation to subsequent cell generations. All other hallmarks provide competitive advantages to the cells but most importantly can contribute to further generation of genomic and epigenetic diversification. The outer circle symbolizes the direct and indirect interdependence of the hallmarks.

We assume that the most important hallmark of cancer is the ability to generate and sustain genetic and epigenetic diversity (**Figure 1**). All other hallmarks defined by Hanahan and Weinberg contribute to this key feature (**Figure 1**). Therefore, in our view any order of hallmarks acquisition can lead to cancer and sustain its growth. We accept that any genetic or epigenetic event [208] or even slight genetic predisposition [209] or transiently acting change in gene expression [210] could potentially trigger the acquisition of even a slightly advantageous feature (that can be seen as an element of any given hallmark) (**Figure 2**). As proposed by us all hallmarks can contribute to the increased genetic/epigenetic diversification of the tumor tissue (**Figure 1**). That would inevitably lead to the appearance of novel phenotypic features and hallmarks that would be put under selective pressure from the organism's own mechanisms or external challenge (chemotherapy, radiation therapy or targeted therapy). Selected features and hallmarks within some of the cancer clones would themselves sustain the diversification process so that they could perpetuate the cycle of cancer diversification, phenotypic variation and selection (**Figure 2**). Theoretically, such a cycle of adaptive variability can perpetuate cancer survival provided a minimum of nutrients supply. Probably on the organismal level this idea is evidenced by the cross species cancer transmission in invertebrates and in rare cases of mammals with immune compromise [211-216]. A model similar to ours has been proposed by Ye et al. based on the analysis of non-clonal chromosome aberrations cell line models [217].

The logical counterargument against our proposal that the sustainable ability of cancer to diversify and survive can last forever would be that the gradual mutational process would ultimately lead to cancer population extinction because of accumulation of too many deleterious passenger mutations [218]. In fact carcinogenesis is quite an ineffective process with only 0.1% of the premalignant lesions developing a full blown cancer [219]. Evidence to support this notion comes from mathematical modeling of the rate of mutations accumulation as well as in vitro cell lines experiments [218, 220, 221]. Other studies on the real-time evolution of small-sized malignant breast cancer lesions suggested that a number of them can regress spontaneously (i.e., without apparent therapeutic intervention) [222, 223]. It is not clear whether this is due to cancer inability to progress because of a deleterious mutation within the sole dominant clone or due to a drastic change in the microenvironment (such as abrupt non-specific inflammation) rendering cancer clones unable to adapt because of lack of heritable advantageous features at least in minor sub-

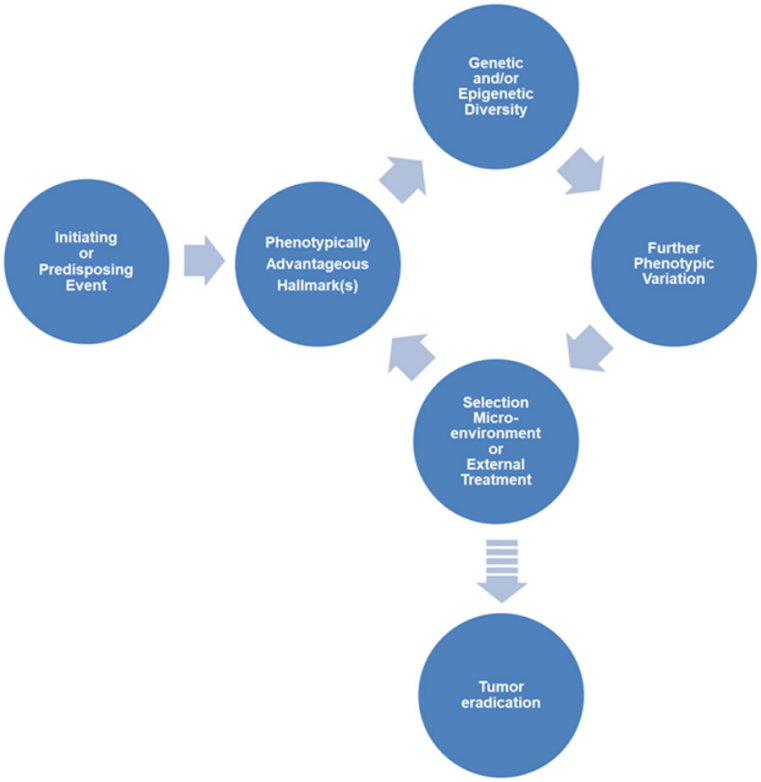


**Figure 2.** Proposed model of cancer initiation and progression. Any predisposing or initiating event can lead to phenotypically advantageous feature(s) (hallmark(s)). The latter increase the genetic or epigenetic diversity through various mechanisms. This ultimately leads to further phenotypic variation between the cancer clones that are subjected to selective process. The selected advantageous hallmark(s) close the cycle and lead to novel levels of diversity. This vicious cycle could potentially be broken if cancer cell population is eradicated when being unable to adapt to changes after therapeutic intervention.

clones or even single cells [224, 225]. Indeed, there exist real life evidence that gross genomic rearrangement can compensate for a disease causing mutation and prove beneficial for the patient [226]. Collectively, the high cost of extreme genetic plasticity is justifiable and acceptable as it is estimated that only 0.1% of species on Earth have ever adapted fast enough to avoid extinction [227]. All these observations raise the hypothesis that the ideal scenario for a tumor to progress is the "just right" level of cell-to-cell variation [228].

However, our proposal does not imply only genetic mutations for generation of heterogeneity but also epigenetic modifications as well as non-constant rate of accumulation of alterations during cancer evolution. Furthermore, in our model it does not make any difference whether the genetic/epigenetic variation is acquired gradually or abruptly through the so called punctuated equilibrium [14]. The genetic diversity necessary to provide a reasonable chance of successful adaptation might be well below the actual number of somatic mutations that a given genome can tolerate [229, 230]. On the other hand, abruptly acting mutational processes such as chromothripsis and kataegis can completely reorganize cancer genome and reset the evolutionary process [231, 232]. Besides, many mutations may remain masked for a long time and become evident only under stress conditions accounting for rapid adaptive response after external challenge as described for Hsp90 mutants in Drosophila [233]. So, even if not perpetual, the diversification and selection cycle in our view can sustain tumor growth well beyond individual lifespan [14].

Therapeutically managed cancers are under strong selective pressure. The apparent limitations of chemotherapy, radiation therapy and targeted therapy to eradicate cancer cells suggest that driver genetic lesions are not entirely responsible for the therapeutic resistance and escape. Indeed, initially non-clonal and passenger mutations or epigenetic changes can provide a minor competitive advantage in the affected cells that become of importance under the settings of specific therapy [234]. Moreover, conventional chemotherapy and radiation therapy contribute to the major hallmark themselves, namely the generation and sustainable cancer cell population diversity. Notably, chemotherapy, radiotherapy and targeted therapy can also cause epigenetic changes and therefore epigenetic heterogeneity. At first sight our proposal of cancer diversity as a major hallmark contradicts the idea of leukemia and cancer stem cells [235]. The counterarguments would be that extensive genetic and epigenetic heteroge-

neity within a bulk tumor is of limited importance as only a very minor fraction of cancer cells can re-establish tumor tissue and constantly sustain tumor growth [14, 236]. However, recent experiments showed that well-differentiated epithelial normal and malignant cells could reverse their phenotype to stem cell like properties [237, 238] and therefore could propagate the acquired genetic and epigenetic changes to the clones originating from the putative cancer stem cell pool [236].

Our model suggests that to eradicate a resistant cancer one has to target its core hallmark, the sustained genetic and epigenetic diversification, or the aspects of other hallmarks that actively contribute to it. It has already been proposed that targeting the diversification and evolutionary processes of cancer development are the rational approach to the management of aggressive cancers [239, 240]. Some of the rationally proposed approaches include targeting clonal events, attenuation or enhancement of genome instability, enhancing subclonal competition, forcing cancer populations to reach evolutionary constraints [228, 239].

The obvious first question is whether modulation of genomic and epigenetic heterogeneity is a working strategy. The most prominent results that support the idea of increased mutational load can be a successful strategy in cancer is the introduction of PARP inhibitors in the treatment of BRCA1/2 deficient cancers [241, 242]. Mutational signatures associated with AID/APOBEC enzymes are found in a large proportion of human cancers [46, 243] and their endogenous activation could potentially increase the tumor mutational load to levels that cannot be tolerated by the cancer cells [244, 245]. Epigenetic therapy through methyltransferase inhibitors has already reached the clinic [246, 247] and seem to have a complex effect on clonal evolution myeloid malignancies [248, 249]. IDH2 mutant specific inhibitor has just been approved by FDA for AML treatment [250, 251]. Much hope is put in the clinical development of BET bromodomain and DOT1L inhibitors [252]. Interestingly, in vitro studies suggest that higher mutational load can make cancer cells more susceptible to common drugs [253].

Another rational approach is to target the truncal mutations within the cancer population. The most notable success with this strategy has been achieved with imatinib in chronic myeloid leukemia (CML) [254]. However, targeting the same genetic event in acute lymphoblastic leukemia (ALL) did not improve the long term results significantly because of various resistance mechanisms [255-257]. Another successful example is the use of BRAF inhibitors in BRAF mutation positive melanoma [258, 259]. High resistance rate to this treatment is supposed to be due to high tumor heterogeneity [260, 261] requiring intermittent or combined treatment strategies [262, 263].

Combinatorial targeted therapy is another rational approach to overcome the resistance because of tumor heterogeneity [264]. It could be implemented as a treatment after the identification of novel drivers or as a preventive therapy. It is believed that the so-called liquid biopsies, i.e., identification of various mutations from cell free DNA could be translated into wide clinical use and could overcome the limitations of genetic testing from limited number of sites of disseminated solid cancers [265, 266]. This could help the individual tailoring of targeted therapies upfront or optimized control of the residual or relapsed tumors. Some successful examples with this approach include the recent add-on of FLT3 inhibitor, midostaurin, to conventional induction therapy in AML [267]. Other viable approaches include combination of EGFR and MEK inhibitors in colorectal cancer and EGFR-mutated lung cancer [268, 269].

Finally, in theory, the adaptive immune response has longed been considered the ideal approach for safe and effective cancer elimination. Despite the evidence for active immunoediting in numerous experimental and clinical settings, it has also been clear that tumors develop a number of strategies to escape restriction by the adaptive immune response [270]. As mentioned above PD-1 and CTLA-4 inhibition prove to be an effective strategy of deblocking cytotoxic T cell specific immune responses to cancer cells. However, the large number of tumor driver and passenger mutations provide a large pool of individual cancer-specific neoantigens (the so called “mutanome”) that could be used to design patient-tailored cancer vaccines [271]. Their combination with checkpoint inhibitors might be a

viable approach to overcome the previous failures of cancer vaccines to produce durable immune responses. This approach has recently been demonstrated as feasible and effective in melanoma patients by two independent groups [272, 273].

For almost half a century after the pathetic announcement of the War on Cancer the biomedical community and the society had to face many moments of inspiring success, bitter disappointment and devastating human suffering [201, 274, 275]. It took the biomedical community decades to realize that cancers exploit a broad variety of molecular, cellular and ecological models to secure the virtual perpetuation of their propagation. Years of research and billions of dollars spent helped us to learn a lot not only about cancers but also about biological principles defining life as a phenomenon. If we are to end this report with yet another metaphor, we would say that the War on Cancer is a Clash of Titans - two products of the evolution on Earth of spectacular complexity - our intelligence and the evolving living matter gone rogue. The paradox is that they are both result of the same chemical building blocks and biophysical principles. In a final account, cancer is also a test of the maturity of our system biology thinking and a major stimulus for its perfection.

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## Disclosure of conflict of interest

None.

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