Cancer memory as a mechanism to establish malignant phenotypes

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Abstract

Cancers during oncogenic progression hold information in epigenetic memory which allows flexible encoding of malignant phenotypes and more rapid reaction to the environment when compared to purely mutation-based clonal evolution mechanisms. Cancer memory describes a proposed mechanism by which complex information such as metastasis phenotypes, therapy resistance and interaction patterns with the tumor environment might be encoded at multiple levels via mechanisms used in memory formation in the brain and immune system (e.g. single-cell DNA methylation changes and distributed state modifications in cellular ensembles). Carcinogenesis might hence be the result of physiological multi-level learning mechanisms unleashed by defined heritable oncogenic changes which lead to tumor-specific loss of goal state integration into the whole organism. The formation of cancer memories would create and bind new levels of individuality within the host organism into the entity we call cancer. Translational implications of cancer memory are that cancers could be engaged at higher organizational levels (e.g. be "trained" for memory extinction) and that compounds that are known to induce amnesia in patients could be investigated for their potential to block cancer memory formation or recall. It also suggests that diagnostic measures should extend beyond sequencing approaches to functional diagnosis of cancer physiology.

Introduction

Oncogenic progression can be seen as a learning process with cancers adapting their physiology to promote survival and spread. The present work formulates and explores the cancer memory hypothesis which states that cancers are learning agents that form and retrieve memories via epigenetic mechanisms, at several physiological scales and at varying degrees of complexity, to more efficiently grow and spread within the organism (Fig. 1). The cancer memory hypothesis suggests that oncogenic features can be encoded and stored in epigenetic cell states and cell network modifications, thereby implying that commonly used molecular approaches such as genomic sequencing and protein expression assays might miss important determinants of malignancy. If one looks at cancer functionally, it needs a mechanism to acquire, store and recall phenotypes such as resistance to growth inhibition and therapeutic interventions. Yet, there is no reason that these have to be exclusively encoded via DNA mutations and theories that relate oncogenesis solely to genomic mutations are limited in explanatory power [1-3]. Indeed, recent experimental results suggest that tumors and cancer can be induced and maintained entirely epigenetically [4,5]. The cancer memory hypothesis entails new theoretical concepts (e.g. cancer

as a memory-based agent), experimental avenues (e.g. cancer engram detection) and treatment concepts (e.g. cancer memory recall interference and extinction), and illuminates potential evolutionary tradeoffs with regard to organismal intelligence in light of the adaptation-maladaptation dilemma [6,7], informally stated as “everything that makes an organism more intelligent, also makes its cancer more intelligent”.

Cancers and cancer precursor cells hold carcinogenic epigenetic memory

Recent work has shown that cancer cells and their precursors can hold phenotypic states in epigenetic memory which encode malignancy via means that are not based on DNA sequence alterations.

Transient transcriptional downregulation of Polycomb proteins induces an irreversible epigenetic transition to a cancer cell fate in Drosophila without genomic driver mutations [4]. Melanoma cells display long-term fluctuating gene expression patterns encoding for therapy resistance phenotypes via PI3K- and TGF-beta- pathways and hold these cell states in memory [8]. Inhibiting PI3K renders these malignant cells susceptible to subsequent BRAF and MEK inhibition therapy [8]. Epigenetic memory induced by the plasticity response after tissue damage predisposes epithelial cells towards subsequent carcinogenesis [9]. After skin injury, distant epithelial stem cells implement an epigenetic memory mechanism that primes them towards enhanced wound repair in the future and this cell state change facilitates subsequent tumorigenesis [10]. Cancer cells also display metastatic latency [11] in which disseminated cancer cells re-enter the malignant state after extended periods of dormancy (i.e. a potential memory recall phenomenon).

Cancer precursor cells also retain malignant phenotypes in epigenetic memory after they were programmed by the tissue environment. Inflammation triggers an adaptive memory through epigenetic and transcriptional changes in pancreatic acinar cells which predisposes these cells to subsequent acinar-to-ductal metaplasia and tumor formation long after the initial inflammation has resolved [12]. Interestingly, the transcription factor Egr1, a crucial memory regulator in the brain [13], has a central role in this process. Similarly, inflammation has been reported to induce an epigenetic memory in pancreatic acinar cells that predisposes them to oncogenic transformation upon KRAS mutation [14]. Importantly, this memory can be antagonized by MAPK inhibition which increases the threshold for transformation. Cancer cells can also retain a prometastatic memory after being exposed to the nutritional compound palmitic acid and this phenotype persists after removal of the stimulus [15]. Yet another memory process in cancer is the establishment of mechanical memory driving subsequent metastasis efficiency [16]. In this process, interaction of cancer cells with the primary tumor’s microenvironment induces a stimulus-dependent mechanical memory which drives malignancy during metastasis [16].

Epithelial–mesenchymal transition (EMT), a central process in many cancers [17], involves the acquisition and storage of stable changes in cell and tissue characteristics and is thus a memory process. Previous work has referred to an “EMT memory” [18] and the activity of CREB, a memory regulator in the brain [19] and immune system [20], is involved in this transition process [21], thereby establishing an interesting link between these two mechanisms. Similarly, Netrin1, a gene that is involved in synaptic plasticity and memory in the brain [22], is crucial in EMT [23].

Cancers use mechanisms associated with physiological learning and memory

A central mechanism for learning and remembering complex information in animals is the stimulus-dependent induction of stable single-cell state changes and the translation of these cellular state changes into higher order cell-to-cell network alterations. In the brain and immune system these include, at the cellular level, stimulus-dependent induction of adaptive transcription programs, epigenetic remodeling via DNA methylation and histone modifications, the induction of distinct metabolic programs and bioelectrical changes.

Molecular learning mediators in cancer

Cancers use several molecules to promote malignancy that are central positive regulators of memory formation in the brain and immune system, i.e. many memory genes are oncogenes and, vice versa, many memory suppressor genes are tumor suppressor genes. The protein Fos (Fos proto-oncogene), a prototypical neuronal activation marker [24] which is involved in neuronal memory [25] and immune memory [26], was early on characterized as an oncogene [27]. CREB is an adaptive transcription factor with functions in several forms of cellular plasticity [28] and is crucially involved in learning and memory in the brain [19], adaptive immune function [20] and cancer progression [29-31] with increased CREB function mediating resistance to chemotherapy [32] and radiotherapy [33]. Similarly, MEF2, which is involved in learning in the brain [34] and adaptive immune plasticity [35], positively regulates cancer progression [36-39]. Conversely, protein phosphatase 1 (PP1) negatively regulates memory formation in the brain [40] and acts as a growth suppressor in cancer cells [41]. Several other adaptive transcription mediators are implicated in neuronal memory formation and cancer [28]. NMDA receptors (NMDARs) are prime regulators of synaptic plasticity and memory formation in the brain [42] as well as neuronal survival [43] and are involved in adaptive immune system regulation [44,45]. They are implicated in the positive regulation of progression in breast cancer [46], pancreatic cancer [47] and melanoma [48]. At the epigenetic level, DNA methylation patterns are substrates for cellular memory [49] and DNA methyltransferases (DNMTs) which control these methylation patterns are central regulators of neuronal memory in the brain [50,51] and immune memory [52]. DNMTs are implicated in oncogenesis [53]. Warburg-like metabolic programs, which are a central feature of many cancers [54], are induced in neurons after synaptic stimulation [55] and in immune cells undergoing plasticity [56]. Instead of cells undergoing physiological plasticity using a cancer metabolic program, cancers most likely use this metabolic program that is associated with cellular adaptation and learning under physiological conditions.

Intercellular communication

In the brain, synaptic communication between cells gives rise to neuronal engrams which are hypothesized to store memories [57] and adaptive immune responses require the coordination between multiple cell types [58]. Adaptive responses and the expression of memories are hence to a large extent implemented by multicellular networks. Malignant tumors display heterogeneous tissue architectures with distinct functional compartments [59] and intercellular coordination [59-

61]. Glioblastoma cells can form electrically connected networks [62-66] and this property of cellular network formation correlates positively with therapy resistance [62,67,68]. In astrocytomas, tumor cells form long-range projections via microtubes and connect to each other via Connexin-43-positive gap junctions [62]. These cell connections implement a functional network with synchronized network-wide calcium spikes. Interestingly, these networks are highly adaptive, can repair themselves after laser-induced injury and promote resistance to radiotherapy. Subsequent work demonstrated that, in glioblastoma, tumor cells form functional networks with a heterogeneous architecture containing driver cells that drive rhythmic calcium transients in the network, which in turn activates cellular MAPK cascades [63].

Dynamic membrane depolarization patterns

Bioelectricity is an important factor in memory formation in the brain, the immune system and in oncogenesis. In the brain, dynamic membrane voltage changes are one of the primary ways to encode information, for instance in the form of postsynaptic potentials and action potentials, and neuronal excitability is correlated to memory engram formation [69]. Adaptive immune functions involve ion channel signaling [70] and dynamic membrane potential changes [71]. Bioelectrical alterations have been reported in various cancer types [72] (e.g. depolarization in breast cancer cells [73]) and optogenetically mediated membrane voltage alterations can reduce tumor formation *in vivo* [74]. Dynamic membrane depolarization patterns of a subset of glioblastoma cells in an electrically connected tumor cell network can activate the MAPK pathway and determine tumor viability and growth [63]. Cancer cells even display membrane potential spiking patterns similar to neurons [75]. Thus, cancers, the brain and the immune system share a crucial similarity in that impacting cellular excitability influences adaptive function.

The cancer memory hypothesis

We thus have two interesting lines of experimental findings: 1) Cancer cells and their precursors hold complex functional phenotypes in epigenetic memory, 2) Cancer cells use learning and memory mechanisms during progression that are physiologically used in the brain and immune system and the use of these mechanisms correlates positively with malignancy.

This invites the hypothesis that cancers encode and retrieve memory similar to the brain and immune system (Fig. 1). Cancer memory can be divided into *basal cancer memory* and *complex cancer memory*. In *basal cancer memory*, which several recent studies discussed above have demonstrated, malignant phenotypes can be encoded at the cellular level. Epigenetic memory encoded in histone modifications and DNA methylation is one of the major mechanisms of holding cell states in memory [76,77] and cancers can make use of these mechanisms to encode malignant phenotypes after different types of environmental stimulation.

Additionally, just like in the brain where certain cognitive representations cannot be completely reduced to the single cell level (e.g. through genomic sequencing), cancer might harbor information at higher levels in *complex cancer memory*. The fact that cancers can form electrically coupled cell networks with heterogeneous functional architectures is well-suited to support this

phenomenon. Perhaps then, cancers encode phenotypes in multi-cellular ensembles giving rise to “cancer memory engrams”.

By using physiological multi-scale learning mechanisms, cancers might be figuring out how to survive and spread through the host organism and recent work has indeed delineated cancer progression as a learning process [78]. In the cancer memory model proposed here, cancer acquires an independent agency by uncoupling itself from the rest of the organism and encodes “cancer memories” to support its survival. By forming and recalling its own memories at the expense of the whole organism cancer emerges as an individual within the organism in a process we might term *oncogenic individuation*. A central problem is then how constituent cells know that they are part of this novel individual. Perhaps certain stably inherited marks including DNA mutations and epigenetic modifications have the function of marking and meditating a cell’s belonging to the cancer individual as opposed to the rest of the host body. A few selected cancer identity marks might establish a fundamental programming error, reverting cancers to a selfish mode of action. Previous work has shown that gene expression patterns in different clones of the same mammalian cell type can be stably inherited [79], providing evidence that epigenetic memory can be transmitted across cell generations. Cells connected in identity via these defined marks could start leveraging learning and memory mechanisms to store useful information that helps them to adapt to the many challenges of oncogenic progression. As memory formation is a central process in binding individual agents together [80], the formation of cancer memories could be the basis for the sub-organism individuation process that is oncogenesis.

Oncogenesis could be a process that bears functional similarity to seemingly unrelated disorders in other learning systems including post-traumatic stress disorder (PTSD) and addiction in the brain. In both of these latter diseases, environmental stimulation leads to a malignant reprogramming of a learning system (i.e. memory circuits in the brain) with a subsequent uncoupling from regulatory signals, a hyperoptimization of local system goals and progressive deterioration at the cost of the whole organism. Not only are there functional similarities but oncogenesis and psychiatric disorder development share many molecular mechanisms such as adaptive transcription [28].

With regard to DNA aberrations it is interesting to note that there are strong similarities in that neurons and cancer cells display genomic heterogeneity (e.g. physiological variation in neuronal karyotypes [81] and genomic sequence [82], cancer cell aberrations in karyotype [83] and genomic sequence [84]. Perhaps genomic mutations are leveraged by both learning systems, the brain and cancer, to enhance response diversity and hence adaptability. In this sense, cancers as agents use lower-level mutation rate increases to enhance their survival as higher-level individuals. Perhaps then genomic changes are just one of the many ways in which cancer, as a higher-level individual, creates functional variety among its parts to enhance overall capacity for adaptation and memory encoding.

Implications of cancer memory for oncology and therapeutic development

There are several important implications of cancer memory for oncology and therapeutic research.

Malignancy determinants could be hidden in higher organization levels and more complex and subtle cellular changes and hence not be accessible to commonplace detection methods including protein overexpression assays (e.g. immunohistochemistry) and genomic sequencing (Fig. 2). The amounts of plasticity proteins could be at physiological levels and there could be no genomic sequence alterations. Malignancy phenotypes could instead be encoded in the constellation of epigenetic marks within single cells, influencing dynamic response patterns upon stimulation, in bioelectrical patterns of single cells or spread out over cellular ensembles where each cell encodes partial information via these changes. Trying to sequence in the genome a certain type of immune system evasion mechanism would be like trying to sequence an object location memory in the brain.

As a consequence of the flexible encoding of malignancy via epigenetic mechanisms, cancers might be programmed and “trained” through electrical stimulation patterns and complex interventions including mechanical tissue stress (Fig. 3). For instance, cancer cells can harbor a mechanical memory which predisposes them towards more malignant phenotypes in metastasis [16]. Surprisingly, in mice, breast cancer can be counteracted by subjecting the mice to a simple stretching protocol in which the mice hold on to an object and the experimenter stretches the animal longitudinally [85]. Thus, perhaps the mechanical cancer memory is overwritten or extinguished by complex tissue stimulation to lessen malignancy.

It would be helpful to find adequate ways to influence cancer memory physiology and “talk” to tumors, i.e. to understand the code with which cancers interact with the rest of the organism (e.g. constellations and dynamics of growth factors and cytokines, as well as innervation patterns in the whole organism) (Fig. 3). Optogenetic methods are used to manipulate memory storage and retrieval in the brain [86] and these methods would be useful to influence information encoded in tumor cell networks. It might be possible to suppress or extinguish cancer memories and thereby create more effective chemo- or radiotherapy concepts. A relevant concept from neurobiology is that memories can become fragile during recall [87,88], which might be leveraged in cancer therapy in that cancers could become more susceptible to cancer memory extinction therapies if they are acutely challenged by a treatment effort. Since memory formation in the brain and immune system is dependent on combinations of various signaling factors (e.g. neuromodulators, interleukins, growth factors), it might also be possible to influence cancer memory via combinations of signaling molecules.

Cancers hijack other organ systems to further their own growth, including the nervous system [89], endocrine system [90] and adipocytes [91]. Via cancer memory, cancer cells could progressively learn to interact with and program these systems to further their own goals. A more speculative proposition is that cancers could extract from and incept into the nervous system higher-level information such as regulatory patterns (e.g. circadian rhythms in hormone secretion), behavioral patterns or emotional states. If we combine the insights that depolarization patterns can regulate cell cycle progression and proliferation [92-94] with the fact that several cancers functionally interface with the nervous system [64,95-98], perhaps it becomes possible to influence cancer with distinct neural activation patterns (e.g. thoughts), thus potentially making cognitive therapy a fundamental way to influence cancer memory and treatment (Fig. 3).

Moreover, different drugs that are known to induce amnesia in patients or help with memory extinction could be studied as adjuvants in cancer therapy with the caveat that they might also

interfere with immune memory. Support for the idea of cancer memory interference by breaking down multicellular communication comes from experimental observations in which disturbance of tumor cell networks through gap junction blockers increases susceptibility to chemotherapy [67]. Recent efforts in targeting epigenetic processes in cancer [99] could be refined to interfere with cancer memory establishment and recall.

A potential problem that could arise with the targeting of general memory mechanisms in cancer therapy would be interference with immune memory formation. During oncogenesis, two learning systems antagonize each other, i.e. cancer and the immune system. As outlined above, both use very similar mechanisms for learning and memory and it could thus be important to find selective ways to influence only cancer memory and not target memory in other organ systems.

In general, cancer memory is an expression of the adaptation-maladaptation dilemma [6,7] which states that an adaptation mechanism can harm the system if misdirected. Informally stated in the context of oncogenesis, it says: “Everything that makes an organism smarter, also makes its cancer smarter”. The adaptation mechanisms that allow learning and memory in the brain and immune system can be hijacked by cancer to form cancer memory. There is interestingly an inverse correlation between cancer and neurodegenerative disorders, especially those that interfere with memory formation (i.e. Alzheimer’s [100]).

Conclusions

Cancers can be seen as primordial biological learning agents in that they unleash the power of complex learning mechanisms for their own survival without integrating themselves into the higher functional logic of metazoan body-wide physiology. Cancers can hold malignancy phenotypes in epigenetic memory and use several mechanisms during progression that implement learning and memory in the brain and immune system. Cancers might hence create, store and retrieve complex memories to survive and spread more efficiently. Oncogenesis would emerge as an individuation process within the organism in which cancer constituents are bound by formation of cancer memories. The search for novel mechanisms in cancer progression could be inspired by how the brain and immune system leverage molecular and cellular mechanisms to encode high-level concepts in memories. Understanding the cancer memory code could enable the creation of novel treatment modalities such as cancer memory extinction protocols and novel pharmacological therapies that destabilize cancer memory engrams.

Contributions

TL conceived and wrote the manuscript.

Conflicts of interest

The author declares no conflict of interest.

Acknowledgments

The figures were produced with Biorender.

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Figures

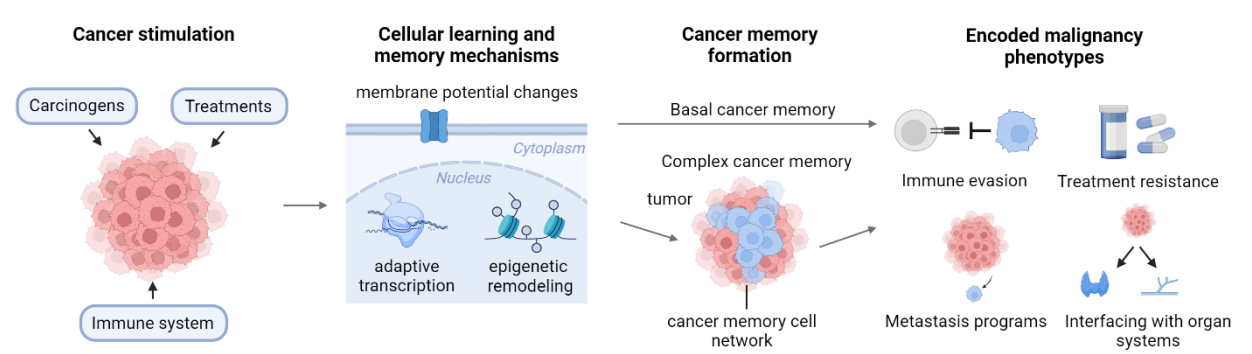

Figure 1. The cancer memory hypothesis. Stimulation of cancers or their precursor entities via carcinogens, therapeutic treatments or the immune system leads to the engagement of cellular learning and memory mechanisms, including membrane potential changes, adaptive transcription and epigenetic modifications. These adaptation mechanisms coordinate to form cancer memories. In basal cancer memory, information is encoded in these changes at the single cell level. In complex cancer memory, multiple cells employ basal cancer memory mechanisms to encode a phenotype in cell network states (“cancer memory engrams”), similarly to memory formation in the brain. Both basal and complex cancer memories encode malignant phenotypes including immune evasion, metastasis programs, treatment resistance and interfacing patterns with other organ systems. During cancer progression, a learning loop emerges to continuously modify cancer memories and resulting phenotypes in response to environmental stimulation to optimize survival and invasiveness.

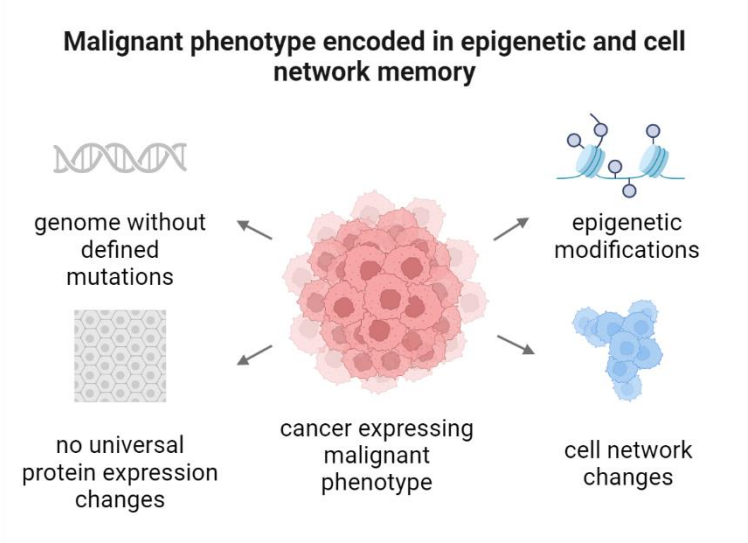

Figure 2. Encoding of a malignant phenotype in epigenetic cancer memory. A malignant phenotype (e.g. drug resistance, metastasis program, immune evasion ability) can be encoded in cancer memory without defined genetic mutations and without universal protein expression changes. Instead, it could be mediated by more subtle epigenetic modifications, even without changes in the levels of overall epigenetic proteins, and in higher-level changes in cell networks (e.g. electrical coupling strengths). Accordingly, many commonly employed diagnostic methods including genomic sequencing and immunohistochemistry might miss important determinants of malignancy.

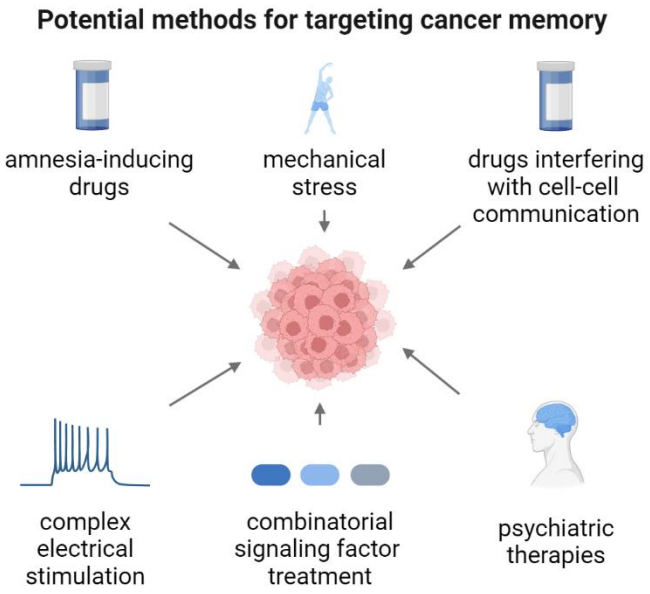

Figure 3. Potential methods for targeting cancer memory. Cancer memory could be targeted pharmacologically, for instance by drugs that cause amnesia or those that interfere with cell-cell communication (e.g. ion channel blockers). Combinations of signaling factors (e.g. growth factors, immune modulators, neuromodulators) could be used to influence cancer memory formation and recall. Cancer memory could perhaps also be influenced by complex stimulation patterns that engage cancer at higher organizational levels including electrical tissue stimulation, mechanical stress or psychiatric therapies.