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This is the final version of the accepted manuscript. The original article has been published in final edited form in:

Cancer Discovery  
2024 APR 04 ; 14(4): 610-614  
doi: [10.1158/2159-8290.CD-23-1510](https://doi.org/10.1158/2159-8290.CD-23-1510)

Publisher: [American Association for Cancer Research](#)

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## *Cell States in Cancer: Drivers, Passengers, and Trailers*

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**Keywords:** cancer cell states, intratumor heterogeneity, non-genetic tumor evolution.

## Summary

*Cancer is traditionally perceived through a genetic lens, with therapeutic strategies targeting oncogenic driver mutations. We advocate an overarching framework recognizing tumors as comprising driver, passenger, and trailer cell states: tailoring therapies to simultaneously target driver genetics and cell states may enhance effectiveness and durability.*

## Main text

Cancer arises from convergent evolution of genetic and nongenetic factors (1). The pivotal role of genetic mechanisms in cancer, including mutations and structural aberrations, is well established in driving tumor initiation, progression, and therapy resistance. Oncogenic 'driver' aberrations primarily shape the cancer cell phenotypes, along with 'passenger' ones, contributing to intratumoral genetic heterogeneity(2). However, despite significant advances in precision targeting of oncogenic drivers, the intrinsic resistance of primary cancers like brain tumors and the transient nature of responses in metastatic diseases like melanoma underscore the limitations of this approach.

Here, we propose to repurpose the cancer genetic classification of driver and passenger mutations into functional phenotypic cell entities as a blueprint for conceptualizing the contribution of various tumor cell states to disease evolution (**Figure 1**). Emerging evidence that a complex spectrum of cancer cell states is recurrently identified across cancer types supports a scenario in which "driver cancer cell states", like their genetic counterparts, are the primary propellants of tumor initiation, progression, metastasis, and therapy resistance. Their influence supersedes that of genetic and epigenetic aberrations. To account for the distinct contribution of phenotypes, we classify non-driver states as 'passengers'—neutral and lacking an additive contribution to tumor evolution— or as 'trailers', which impact tumor evolution and therapeutic responsiveness in context-dependent manner. The latter still affects tumor cell fitness and tumor tissue homeostasis beyond (epi)genetics but imparts both driver-like advantage and vulnerabilities to the tumor akin to deleterious passengers in cancer genetics.

Importantly, the driver cell states in tumors extend beyond cancer cells themselves. Cancer cell identity is shaped by the dynamic interplay with the tumor microenvironment (TME). Conversely, cancer cells profoundly influence the non-transformed TME cells, orchestrating a reciprocal relationship where distinct cell states from the TME ultimately become pro-tumoral entities. Among these, the immunosuppressive M2-like myeloid (M2L) cell states and T-reg known to support tumor growth and therapy recurrence.

## **Driver tumor cell phenotypes**

The paradigm of driver cancer cell states is best exemplified by the Cancer Stem Cell (CSC) and the Mesenchymal-like cell states. The original CSC hypothesis posited tumor initiation and maintenance are restricted to CSCs, with limited numbers, indefinite self-renewal, slow/asymmetric replication, and differentiation ability(3). Brain tumors served as one prototypical solid tumor in which the CSC hypothesis was confirmed, systematically tested, and reassessed from an entity- and hierarchy-driven cancer to later incorporate the concept of cell plasticity(4), likely as a function of tumor subtype and grade. The early view of CSCs as strictly hierarchical across all cancers and tumor grades was oversimplified. The evolved CSC hypothesis(3,4) posits that cancer cell plasticity may offer a much more diverse source of driver states, with an extreme scenario in which virtually all cancer cells could potentially transit to a driver state when, for instance, exposed to specific extrinsic/niche signals. While lineage-tracing in mouse models supports the functional

restriction of self-renewal to a limited number of cells at any given moment, within human tumors, such property may not be restricted to specific cell entities. For each cancer type, multiple progenitors could serve as redundant sources for cancer renewal and heterogeneity, within the context of similar driver aberrations. In this case, the tumor grade, size and temporal evolution might dictate the finite number of distinct CSC states so that aggressive solid tumors have parallel sources of renewal if compared to some blood and low-grade solid tumors or cancers in autochthonous mouse models.

Cancer Epithelial-to-Mesenchymal transition (EMT) is a cellular program observed across many solid tumors and represents the convergent malignant evolution of developmental programs, adult tissue regeneration and repair, cell-intrinsic metabolic adaptation and stress responses(5). As such, cancer EMT assumes a driver's seat for key processes across various solid tumors and their metastases. It is now evident that the cancer EMT spectrum is the sum of individual cell states that play critical and distinct contributions to tumor homeostasis. For instance, an epithelial-like state is found in both primary and metastatic lesions, suggesting that EPI-like states dictate symmetric/asymmetric proliferative potential. Instead, a mesenchymal-like state is hardwired in infiltration and therapy-resistance potential. Finally, the simultaneous presence of quasi-epithelial/mesenchymal (or partial/hybrid) EMT states confers the tumor tissues with the plasticity required to execute both primary renewal and metastasis-initiating ability(6). This plasticity is also a cancer cell intrinsic feature as the mesenchymal phenotype builds onto the pre-existing identity and is reversible(7).

The immunosuppressive M2-like myeloid (M2L) state emerges upon myeloid immune cells' activation. Similar to the EMT program, myeloid cells undergo a broad set of cell state transitions with the original M1-M2 binary classification now incorporating hybrid, transient or context-specific intermediates(8). Whereas the specification of M1-like and M2-like extremes is regulated by a variety of factors revolving around the JAK/STAT pathway and IRF transcription factors intersection with the activity of transcription factors downstream the NF- $\kappa$ B or TGFB signaling, respectively, its full spectrum is influenced by a multitude of factors and signaling pathways beyond just these. In normal homeostasis, macrophages adopt an M2-like state in response to wounds, allergic reactions, and parasitic infection. Instead, tumor-associated macrophages (TAM) more often respond to acidic and hypoxic microenvironments. M2L TAM facilitates cancer cell invasion, promotes neoangiogenesis and immune suppression in experimental models, and impairs responses to immunotherapy in patients(9). Targeting M2L states will likely involve their reprogramming to interfere with immunosuppression.

The Treg is a CD4 T cell state that suppresses adaptive immune responses, establishing and maintaining self-antigen tolerance in homeostasis and disease(8). CD4 T cells acquire the Treg state via the cooperativity between the transcription factor forkhead box P3 and TGFB and JAK/STAT signaling to exert their suppressive function via secretion of inhibitory cytokines (e.g., IL-10, TGF- $\beta$ ), expression of checkpoint inhibitors (e.g. CTLA-4) and metabolic reprogramming (e.g. aerobic glycolysis). Whereas Treg cells play a crucial role in preventing autoimmunity and limiting collateral tissue damage during acute responses, tumors hijack this state to dampen antitumor immunity, at least in part via immune checkpoint inhibition(10). Despite its context-dependent nature, this state features a non-autonomous tumor driver categorization.

### ***Of passengers and trailer phenotypes***

Passenger states as bystanders replicate the landscape of somatic aberrations that, while widespread, may not contribute to tumor aggression, treatment resistance, or

metastasis. The cancer cell states that retain the signature of host tissue cell types are likely candidates for a “passenger” role. Their signatures may reflect the memory of the cell of origin, their intrinsic differentiation states due to transient lack of proliferation, or result from adaptation/connectivity to the surrounding cell types. Whereas demonstrating the pure neutral role of passengers presents experimental challenges (see below) and recurrent biological entities are unlikely entirely neutral, the key traits of a driver state defines the remaining ones.

Therefore, a “trailer” state is one that has functional traits that supersede the (epi)genetic makeup of the tumor but holds both pro-tumor (e.g. driver-like) and anti-tumor functions in a context-dependent manner. The archetype of a “trailer” cell state is cellular senescence, a natural cellular state trajectory observed in embryos and during organismal aging, which acts as a barrier to tumorigenesis in premalignant lesions and is amplified by anticancer therapy(11). Senescent cells exhibit both antitumorigenic properties such as exit from the cell cycle and deep differentiation, and paradoxical pro-tumorigenic ones such as senescence-associated secretory phenotypes. Non-neoplastic cells engage the senescence state in response to genotoxic stress and oncogenic activity, involving the temporal activity of NF-kB and AP-1 transcription factors. Failure to enter senescence is causal to tumorigenesis in certain types of cancers, such as melanoma. In frank tumors, escape from senescence or failure to enter senescence lead to therapy resistance. Hence, senescence may come with fitness cost to a limited set of cells in a tumor that is offset and potentially selected for if promotes non-autonomous advantage to non-senescent ones. Modulating senescent cells, rather than depleting them, may prove superior to limiting cancer progression in the short-term while avoiding long-term organismal adverse events, including tumor recurrence. Targeting the SASP would be critical to enhance the “bulky” anti-tumor aspect of this state and restore its tumor suppressive role.

Among the non-cancer cell states, CD8 T cell exhaustion might be considered as a trailer state. Originally described as the outcome of persistent antigen and hypertonic T cell receptor stimulation during chronic infections, the T cell exhaustion observed in cancer is an umbrella definition covering parallel programs building onto ‘normal’ T effector cell differentiation. As in the case of EMT and macrophage polarization, there may be a continuum of T cell dysfunctional or divergent states, driven by transcriptional regulators such as NFAT, NR4A and TOX in cooperation with hypertonic signaling, myeloid cell activity and tumor metabolism(12). Whereas its role in promoting tumor evolution by inactivating CD8 effector function would feature a driver function, the potential reversibility of this phenotype, as well as the observation of precursor exhausted CD8 T cells with anti-tumor potential, collectively support a trailer categorization. Understanding these mechanisms will be key to attaining phenotypic reversal, if not preventing its specification.

### ***Of States, Pathways and genes***

The definition as “drivers” or “trailers” tumor cell states encompasses their recurrence across tumor types and is corroborated by perturbation experiments substantiating their functional relevance. This trait connects genotype, cell identity, and microenvironmental settings.

Among other ways, driver/trailer states supersede genetics, through the modulation of cell-cell communications and intracellular pathways. Cancer EMT delineates the framework incorporating the interplay between driver states and genetics. In fact, loss of “prototypic” tumor suppressors such as TP53, CDKN2A/B, or epigenome regulators like ARID1A and

EED, confers plasticity to cancer cells in adopting specific states among the EMT spectrum, but are insufficient to that end and do not restrict the final fate of the cancer cells.

The case of brain tumor CSCs indicates that driver states are dictated or enabled by the cancer genome (oncogenes and tumor suppressors) but fully emerge from the cooperation between transcription factor modules (e.g. SOX2, OLIG2, FOSL1, etc.) and signaling pathways (e.g. NF- $\kappa$ B, TGFB, MAPK, Wnt, Notch PI3K/Akt/mTOR, etc.), which impart additional advantageous traits(4). The modulation of such pathways is both cell intrinsic and non-autonomous and shared by nearly all other tissue CSCs(3,4). For example, cancer EMT is largely tissue agnostic owing to the activity of broad pathways such as TGF $\beta$ , RAS–MAPK, glycolysis, and a core transcriptional module (e.g. SNAI1-2, ZEB1-2 Twist1-2, etc.). The key EMT transcription factors act by repressing cell identity programs and chromatin acts as a barrier to EMT(13), thereby featuring a pivotal role for transcriptional repression in the EMT.

The activation of broad pathways alone is insufficient to define a driver or trailer state. For instance, the NF- $\kappa$ B pathway is an unquestionable driving force of tumor initiation, progression, resistance to therapy, and metastasis. Whereas the engagement of pro-survival programs is a underlying feature of the sterile inflammation executed by cancer cells, tumor-associated immune cells and stroma, to execute context-specific, and temporally controlled gene expression programs, NF- $\kappa$ B cooperates with the driver oncogene, the cell-of-origin, and microenvironmental signaling. Consequently, high NF- $\kappa$ B activity is required for but does not specifically define a driver or trailer state. In fact, this pathway is paradoxically central to the specification of the driver pre-EMT, the trailer senescence, and cancer cell apoptosis. JAK/STAT and TGFB/SMAD activation features a similar role in context-dependent state specification. For example, activation of the BMP pathway *in vitro* leads to deep astrocytic differentiation of brain tumor CSCs and abrogation of their self-renewal(4), but BMP pathway activation in absence of deep differentiation does not feature per se a “trailer” function.

The adoption of a glycolytic/plurimetabolic state (GPM) is another trait overlapping between several functional cancer cell states with driver and trailer functions(3,4) but insufficient to define them. A GPM can be driven by or respond to acidic and hypoxic microenvironments and often correlates with the progressive acquisition of malignant/dysfunctional states. In fact, hypoxia and EMT signatures may be erroneously connected because of the converging evolution between hypoxia with GPM and GPM with EMT. This trait is associated with the peculiar cancer aerobic glycolysis and it is hard to disentangle a GPM state from its manifestation on cell states such as quasi-mesenchymal or senescent. A driver state is, therefore, most likely to adopt a GPM state, albeit under specific circumstances, regression to OXPHOS was associated with driving metabolic adaptation and nongenetic resistance(14).

### ***From observation to intervention***

Effectively deploying combinatorial treatments will require us to functionally characterize all cancer and stromal/immune cell states within the tumor ecosystem. Single-cell OMICs in patient samples charted an atlas of cell states, linking phenotypic manifestations in tumors with clinical covariates “retrospectively”. Identifying some states as drivers or trailers based on causal evidence is possible(6)(7), while categorizing passengers due to their lack of discernible functions poses a more significant challenge. Phenotypic states tied to tissue identity or stress responses may lack a dominant role over the (epi)genome (i.e. passengers), or a driver/trailer function may not have been discovered for lack of suitable context. The use of genetic barcoding in preclinical models

offers the opportunity to dissect the interplay between genetic and non-genetic drivers. Addressing which cancer states are truly functional and which rather encode the memory of past identities and microenvironmental editing, will require dedicated testing, similar to how causality was established for drivers of tumor initiation and progression. To this end, combining advanced cell identity reporters(7) and single-cell barcoding(15) can serve to functionally rank the contributions of individual states within a tumor. Massive parallel understanding of the roles played by different cell states will pave the way for innovative therapeutic strategies that target the true drivers while considering the contextual relevance of each state in cancer progression and therapy resistance.

The experimental categorization of cancer cell identities based on driver, passenger, and trailer states is offered as a framework to plan “prospective” experimental testing in accurate preclinical contexts. In turn, this will enable to introduce selective pressures and measure metastability or heritability of cell phenotypes. However, for these efforts to be relevant, it is essential that preclinical models aim at mirroring tumor phenotypes with the highest possible fidelity.

### ***Integrative Evolutionary Model of Tumor homeostates***

Whereas the terminology “tumor heterogeneity” suggests an entropic distribution of cell states within the individual tumor ecosystem and across patients, long-standing evidence in animal models and emerging spatial omics in patients’ tissues are consistently showing that tumor and tumor-associated cells might adopt distinct cell states as a function of tissue macro-areas. In particular, their proximity to vessels and nutrient/oxygen availability, or lack thereof in necrotic areas, likely shape metabolisms and cell identity. Hence, to reflect a tissue-driven organization of clusters of tumor cells adopting similar states (**Figure 1**), we refer to those as “tumor homeostates”.

Our proposed framework for categorizing tumor homeostates incorporates aspects of both Darwinian- and Lamarckian-like evolution theories(14). Darwinian selection emphasizes the role of random mutations and natural selection as the driving forces of adaptation, whereas Lamarckian evolution theorizes that acquired traits can be directly inherited. In most evolutionary processes, these theories are seen as alternative and the Darwinian model appears dominant, not least because selected traits often become heritable. However, the n-of-1 short lived tumors might equally represent those models. Driver states that propel tumor initiation and progression could be viewed as undergoing selection and outcompeting other states over successive generations, in a Darwinian sense. However, phenotypic plasticity and the ability of states to change in response to microenvironmental cues also invokes Lamarckian ideas. Likewise, trailer states, fueled by unfavorable (epi)genetic aberrations align more closely with a context-dependent selection of "Darwinian" perspective, while incorporating "Lamarckian" elements when non-autonomously influencing driver cell behavior and shaping tumor evolution via microenvironmental conditioning.

If passenger states are proven to exist, they would be neutral or contingent results of the cancer evolutionary process. On one hand, the persistence of passenger state cells during evolution or after therapy may depend on their sheer quantity, following statistical principles like the law of large numbers, rather than being selected traits. On the other hand, these states help explain phenotypic plasticity. For instance, a transition from a passenger to a driver state, transiently sustained by environmental pressures, would explain the alternating dominance of genetically similar clones.

Our framework for integration of functional states allows for a nuanced understanding of cancer cell heterogeneity, recognizing both the inherited drivers of disease and the

interplay of tissue structure and function, chance, and the evolving microenvironment in shaping tumor evolution.

### ***Therapeutic targeting of driver states***

Targeting driver states is becoming clinically attainable(3). Tumor homeostates classification will enable shifting the focus from traditional target-based strategies to those that consider the driver “oncogenes” or the synthetic lethality associated with loss of tumor suppressors to those as important as functional cancer states that drive evolution and transcend genetic and epigenetic variations. Target-based strategies overlook the complexity of cancer cell states as established when conventional chemotherapy was proven ineffective in the presence of quiescent CSCs(3,4). The case of acute promyelocytic leukaemia, nearly extinct owing to a therapeutic targeting of both its driver oncogene (PML-RARA) and driver state (i.e. undifferentiated promyelocytic) paves the way forward. Conversely, a therapy that successfully engage one molecular driver but fails at conditioning the tumor homeostates, submits itself to both intrinsic and non-genetic resistance (i.e. cancer plasticity). For instance, BRAF-driven melanoma is sensitive to BRAF-targeted inhibition, but its recurrence is almost inevitable, with genetics playing a critical but not exclusive role. By reinterpreting the evidence within the tumor homeostate framework, BRAF inhibition may deplete cancer cells in “passenger” but not (all) “driver” states(6), leading to persisters, and therapy may promote a switch from passenger to driver states owing to cell adaptation/plasticity. More broadly, the disjunction between genetic and non-genetic drivers may also explain why differentiation therapies did not yield success in more aggressive solid tumors.

The tumor microenvironment, including immune and stromal cells, significantly contributes to cancer progression and must be considered integral to the therapeutic targeting framework. Targeting a driver/trailer immune states may be effectively depleting both the state and the target cell type, since these cells are not transformed. However, targeting such states must remove the source of the acquisition of such states or else it will only hold transitory effects. Indeed, the organismal renewal leads to the inevitable replenishment of the target cells (e.g. resident macrophages replaced by blood-derived macrophages or neutrophils, CD4 Tregs cells replaced by conventional ones, CD8 Tex by newly exhausted CD8 T cells).

Selective targeting of tumor homeostates will involve modulating biochemical pathways active in cancer and tumor-associated cells via multiple orthogonal and possibly unrelated pathways. This could be achieved by repurposing small molecules affecting the maintenance of driver/trailer states. In turn, this may lead to synergistic anti-tumor tissue function without such combination therapies synergizing “biochemically”. Rather, additively targeting different tumor homeostates will lead to a high-order synthetic lethality at the diseased tissue level. Also in these cases, to gain “prospective” evidence that selected therapeutic combinations reach the intended synthetic lethality, thereby limiting the emergence of resistance, combining phenotypic reporters with therapeutic responses and single-cell readouts in predictive preclinical models will be key.

Alternatively, the targeting of cell states within the tumor ecosystem may be exploited in a sequential fashion with treatments conditioning tumor evolution towards a less aggressive phenotype (e.g. a driver-to-trailer transition), followed by immunotherapy clearance of residual cancer cells via microenvironmental reprogramming (e.g. immune-checkpoint therapies). We refer to this as the “lock-in/wipe-out” strategy. For the latter, we speculate that exploiting tissue-resident innate immunity will offer a specific opportunity

to deal with the most pressing issues associated with tumor progression, like drug persister cells/minimal residual disease levels, dormancy, and metastasis.

Here, we draw on classic cancer genetics to incorporate cellular and evolutionary perspectives into a novel framework for describing, targeting and eradicating cancer. Under these premises, the driver and trailer diseased cells of the tumor tissues become priority targets of intervention and the future goal of a successful combination therapies is to develop therapeutics that selectively target these functional states, in both cancer and tumor-associated cells, disrupting tumor evolution at its core or forcing tumor evolution towards extinction.

### **Acknowledgments**

This opinion piece respects words and references limits of the journals' format. As a result, we only minimally included the primary research work that shaped our thinking and that is largely covered by the cited review articles, which provide a broader perspective about the individual topics covered herein. We thank Mark Dawson and Colinda Scheele for input on the passenger and lock-in/wipe-out concepts, Ernesto Guccione and Anton Henssen for comments. G. Gargiulo acknowledges funding from MDC, Helmholtz (VH-NG-1153), ERC (StG:714922 and PoC:101069235), Deutsche Krebshilfe (7011508) and DFG (GA3203/3-1), M. Serresi from DFG (SE2847/2-1 and SE2847/2-2) and JC. Marine from FWO (G0C530N and G070622N), Stichting Tegen Kanker (FAF-F/2018/1265), Flanders excellence grant (IBOF) and the Belgian Excellence of Science (EOS) program.

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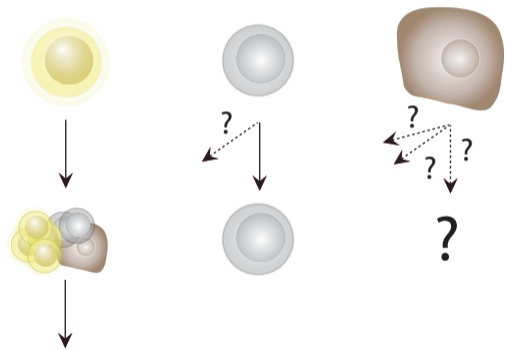
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**Figure 1 | A framework for tumor cell state-driven cancer progression.** Left, shows three primary functional cell states in tumors. The driver state, key for tumor progression, generates all progeny states. Multiple driver states may coexist in a tumor, influenced by its stage and the supportive non-transformed microenvironment. Passenger states contribute minimally beyond the inherent cancer (epi)genome. In contrast, trailer states, sensitive to context, affect tumor fitness positively and negatively, depending on the biological environment. Right, in yellow, depicts four distinct driver state niches (tumor homeostates) organized by macro-areas or cell-cell interactions. The brownish trailer states are influenced by necrosis and hyper-mesenchymal transdifferentiation or cell-cell interactions. Grey cells represent cancer and tumor-associated cells in passenger states. Abbreviations: CSC=cancer stem cell, M2L=M2-like, SEN=senescence, MES=mesenchymal.

# Functional tumor cell states

Driver - Passenger - Trailer



Progression, resistance, metastasis

# Spatial distribution of drivers/trailers

