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Opinion

Cancer initiation: breaching developmental barriers

Steven A. Frank [1,*]

Cancer is commonly understood to arise from oncogenic mutations that stimulate proliferation or tumor-suppressor mutations that remove constraints on cell division or survival. However, I show that ten of the most frequently mutated cancer genes (TP53, PIK3CA, KRAS, APC, KMT2C, KMT2D, BRAF, ARID1A, PTEN, and CDKN2A), in their normal function, either maintain cellular lineage identity or enforce terminal differentiation. I argue that the primary mechanism of cancer initiation arises when perturbations of these genes breach developmental barriers, releasing the plasticity characteristic of development. Proliferation follows from the less differentiated state rather than acting as the initiating event. This perspective reframes oncogene and tumor suppressor classifications by placing loss of developmental constraint at the center of tumor initiation.

Significance

Cancer is thought to begin with mutations that accelerate cell division or disable cell death. But ten of the most commonly mutated cancer genes normally hold cells either in a settled lineage identity or at the end of a developmental path. This article proposes that cancer starts when mutation breaks that hold, releasing the developmental plasticity that builds tissues in early life. Developmental flexibility creates a new proliferating tissue—a tumor.

How do tumors start?

In the conventional genetic model of cancer, tumors begin when **oncogenic mutations** (see Glossary) increase cell proliferation, **tumor-suppressor mutations** remove restraints on cell division or disable cell death pathways, and **chromatin-regulator** mutations disrupt **epigenetic control** [1,2]. These effects are central to cancer, but they may explain how tumors grow after **initiation** rather than what first starts tumor formation. In earlier articles, I argued that the release of **developmental plasticity** is a primary cause of tumor initiation [3–5]. Accumulating evidence supports the role of **cellular plasticity** in the origin of tumors [1,6–8].

To extend this argument, I suggest that early mutations in cancer may breach the **barriers** that constrain developmental plasticity by disrupting mechanisms that maintain **cell lineage identity** or enforce **terminal differentiation**. To analyze this argument, I first identified ten of the most commonly mutated cancer **driver genes** [9] (Table 1), conventionally classified as oncogenes (KRAS, PIK3CA, and BRAF), tumor suppressors (TP53, APC, PTEN, and CDKN2A), and chromatin regulators (KMT2C, KMT2D, and ARID1A). Table 1 describes the methods used to choose these particular genes. In this opinion article, I summarize evidence showing that each of these genes normally helps maintain cell lineage identity or enforce terminal differentiation.

Mutations in many of these genes arise early in tumor formation and may breach the barriers that constrain developmental plasticity. That release of plasticity can drive the earliest steps of initiation. In some cases, increased proliferation and survival may follow directly as consequences of the less differentiated, more plastic state. Additionally, the proliferative and survival effects conventionally attributed to these genes may contribute importantly to subsequent tumor growth and progression. The question here is not whether those subsequent effects matter, but whether they are the primary events by which tumors begin.

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Table 1. Ten commonly mutated cancer drivers and their developmental identity functions

Gene	Frequency (%)	Normal developmental function	Cancer initiation mechanism	Refs
TP53	35	Enforces asymmetric stem cell division; drives progenitor-to-differentiated transitions	Loss traps cells in undifferentiated transitional states with elevated growth signaling	[10,11]
PIK3CA	13	Regulates lineage commitment; required for exit from pluripotency	Mutational alteration blocks differentiation; restores stemness markers	[12]
KRAS	11	Regulates progenitor identity in lung, pancreas, and other epithelia	Locks cells in plastic progenitor states prior to hyperproliferation	[13,14]
APC	10	Enables exit from Wnt-maintained intestinal stem cell compartment	Loss constitutively maintains stem cell state; developmental arrest	[15,16]
KMT2C	9	Deposits histone marks at lineage-specific enhancers during commitment	Loss destabilizes epigenetic programs that maintain committed identity	[17,18]
KMT2D	9	Required for activation of differentiation enhancers	Loss destabilizes committed identity; licenses progenitor programs	[17,18]
BRAF	8	Regulates thyroid differentiation	Drives thyroid dedifferentiation	[19,20]
ARID1A	7	Opens chromatin at differentiation genes via SWI/SNF complex	Loss maintains progenitor state; accelerates tumorigenesis with KRAS	[21]
PTEN	6	Promotes progenitor-to-differentiated transition in blood	Loss causes developmental arrest with concurrent hyperproliferation	[22]
CDKN2A	See [a]	Locks terminal differentiation via p16/RB axis; makes cell cycle exit irreversible	Loss makes differentiated state unstable and reversible	[23]

The commonly mutated genes based on frequency estimates from epidemiologically weighted pan-cancer point mutation analyses [9]. I exclude LRP1B and FAT4, which rank high in mutation frequency but encode very large proteins whose mutation rates are inflated by coding region size [24]. FAT4 has well-characterized roles in developmental morphogenesis and planar cell polarity [25]. LRP1B influences development, but the mechanism is unclear [26].
[a]CDKN2A is one of the most commonly inactivated tumor suppressors across human cancers but is predominantly inactivated by homozygous deletion and promoter methylation rather than point mutation [27,28], excluding it from point mutation frequency rankings. This article focuses primarily on point mutations to provide methodological consistency in estimating the frequency of gene perturbations. But of course other types of mutations and epigenetic perturbations are also important, as illustrated by CDKN2A.

Mechanisms of developmental identity control

Commonly mutated cancer drivers influence normal development in three ways: transcriptional programs lock terminal fate, signaling pathways regulate **stemness** versus commitment, and epigenetic mechanisms stabilize committed identity. Cancer mutations often release cells from their developmental identity rather than directly accelerating proliferation.

Transcriptional enforcement of terminal fate: TP53 and CDKN2A

TP53 is often described as the guardian of the genome, but its role in enforcing terminal differentiation may be equally important. In mammary tissue, **p53** regulates the asymmetric division of stem cells: wild type p53 biases cell division so that one daughter cell differentiates, while the other remains a stem cell [10].

Loss of p53 shifts this division asymmetry toward symmetric renewal, in which both daughters remain stem cells. Mutant cells show reduced production of differentiated progeny. Mechanistically, p53 enforces these fate decisions directly as a transcription factor by activating differentiation gene programs.

Glossary

Barriers: mechanism that stabilizes lineage identity or terminal differentiation and limits access to other states.
Cell lineage identity: stable pattern of gene activity that defines a cell type and limits what it can become.
Cellular plasticity: cell's ability to adopt different traits or identities without requiring an additional DNA mutation for each change.
Chromatin regulator: protein that changes DNA packaging or epigenetic tags, making genes easier or harder to use.
Dedifferentiation: shift from a mature cell toward a less specialized, more plastic, or progenitor-like state.
Developmental plasticity: flexibility characteristic of development that allows diverse cell states, identities, and tissue traits to form.
Driver genes: a gene that when mutated contributes causally to cancer by giving a cell a selective advantage.
Enhancer: DNA segment that increases the activity of a target gene, often from a distance.
Epigenetic control: control of gene activity through DNA packaging or chemical tags without changing the DNA sequence.
Epithelial–mesenchymal transition (EMT): developmental and repair program in which epithelial cells lose some of their adhesion and gain mobility and plasticity; tumors can reactivate parts of it.
H3K4me1: chemical mark commonly found at enhancers; it is added to the histone H3 protein around which DNA is wrapped.
Initiation: earliest changes that allow cells to begin forming a tumor, as distinct from later expansion and progression.
Metaplasia: conversion or replacement of one mature cell type by another, often after injury and sometimes preceding cancer.
Oncogenic mutations: mutations in genes that create or increase activity promoting cancer.
p53: tumor-suppressor protein encoded by the TP53 gene. It controls gene activity in response to cellular stress, influencing DNA repair, cell-cycle arrest, and cell death; it also influences differentiation.
PI3K/AKT/mTOR pathway: signaling network that regulates metabolism,

In the lung, p53 drives relatively undifferentiated stem-like alveolar type 2 cells to differentiate into the mature type 1 cells that line the lung surface. Loss of p53 traps cells in an undifferentiated transitional state with elevated growth signaling. This developmentally plastic transitional state appears to permit tumor development [11]. In this case, the tumor-suppressive role of p53 arises from enforcing cell-fate commitment rather than from controlling apoptosis.

CDKN2A encodes p16INK4a and p14ARF, which enforce cell-cycle arrest through **retinoblastoma (RB)** and p53, respectively. The conventional interpretation treats these functions as brakes on the cell cycle. However, CDKN2A can also promote irreversible exit from the cell cycle as part of terminal differentiation.

For example, RB cooperates with lineage-specific transcription factors to silence proliferation genes while helping to establish the differentiation programs that determine lineage identity [29–31]. Without the RB lock controlled by CDKN2A, the differentiated state can become unstable and reversible [23]. This enhanced developmental plasticity may be a key driver of tumor initiation.

Signaling control of stem cell state: KRAS, PIK3CA, APC, PTEN, and BRAF

These five genes act through distinct signaling pathways that influence whether a cell remains in a plastic **progenitor** state or commits to a differentiated identity.

In the pancreas, **transdifferentiation** of mature acinar cells into progenitor-like ductal cells is an early step in tumorigenesis. This acinar-to-ductal **metaplasia** is normally a transient injury response, but mutant KRAS makes it irreversible [13]. The identity change precedes hyperproliferation. Increased proliferation and tumorigenesis follow when additional triggers occur, such as inflammation, epigenetic remodeling, or altered cell–cell interactions in the microenvironment [32].

In the lung, KRAS-mutant cells enter a high-plasticity state with open chromatin at developmental genes [14]. Disrupting this state in early tumors prevents malignant progression [33]. In this case, the primary effect of KRAS mutation appears to be developmental deregulation.

PIK3CA encodes the catalytic subunit of PI3K in the **PI3K/AKT/mTOR pathway,** which is essential for embryonic development. PIK3CA knockout mice die by embryonic day 10.5 [34]. Homozygous PIK3CA mutations in human pluripotent stem cells cause widespread transcriptional remodeling and loss of the ability to exit the stem cell state, with cells upregulating stemness markers and failing to differentiate into any of germ layer [12].

In the breast epithelium, PIK3CA mutations transform lineage-restricted cells into multipotent ones. Mutated basal cells can give rise to luminal-like tumors, and mutated luminal cells can generate basal-like tumors. This bidirectional lineage conversion suggests that the primary effect is the release of developmental restriction rather than simply increased proliferation [35].

PIK3CA is traditionally classified as an oncogene that accelerates cell division. Yet in estrogen receptor-positive breast cancer, PIK3CA mutations are enriched in the low-proliferation luminal A subtype and are associated with relatively low proliferative signaling [36]. This contradiction between oncogene classification and relatively low proliferation disappears if the primary effect of PIK3CA mutations is to relieve developmental restrictions rather than to accelerate proliferation.

growth, survival, and cell state; PIK3CA encodes one of its core enzymes.
Progenitor cell: partially specialized cell that can multiply and produce a limited range of mature cell types.
Retinoblastoma (RB) pathway: pathway centered on the RB protein, which restrains cell division and helps stabilize differentiated identity; the p16 protein encoded by CDKN2A helps keep RB active.
Stemness: stem-cell traits, especially self-renewal and the ability to produce specialized descendants.
SWI/SNF complex: SWItch/Sucrose Non-Fermentable complex rearranges DNA packaging, changing how easily selected genes, including lineage and differentiation genes, can be used.
Terminal differentiation: final stage of specialization, usually characterized by a stable identity and little capacity to divide or change fate.
Transdifferentiation: direct conversion from one specialized cell type to another without fully returning to a progenitor-like state.
Tumor-suppressor mutations: mutations in genes whose normal activity helps prevent tumors; loss or reduction of that activity through mutation or epigenetic change favors cancer.
Wnt: protein in a developmental pathway controlling stem cell maintenance, cell identity, proliferation, and tissue organization; APC normally restrains it.

APC normally enables intestinal cells to exit the **Wnt**-maintained stem cell state and terminally differentiate as they migrate up the villus [15]. An APC knockout prevents the normal developmental cascade and constitutively maintains the stem cell state. Restoration of functional APC in colorectal cancer cells causes rapid differentiation and cessation of growth, demonstrating that the cells were developmentally trapped and not simply dividing uncontrollably [16].

In the hematopoietic system, PTEN normally promotes the developmental shift from proliferating precursor cells to the mature and mostly nondividing terminally differentiated state. PTEN deletion blocks stem cell differentiation into mature blood cells and also triggers stem cell hyperproliferation, a combination of developmental arrest and proliferation that resembles leukemia [22]. Similarly, PTEN deletion in prostate basal cells releases the multipotency of normal development and drives cellular reprogramming to initiate invasive tumors, with plasticity dependent on innate immune signaling [37].

During normal development, BRAF/mitogen-activated protein kinase (MAPK) signaling regulates the progression of differentiation [19]. A BRAF mutation in the thyroid epithelium drives papillary carcinomas that progressively lose their differentiated thyroid identity, including the capacity for iodine uptake and for thyroid-specific gene expression [20,38].

Epigenetic stabilization of committed identity: KMT2C, KMT2D, and ARID1A

Three genes that regulate chromatin and development are among the most commonly mutated driver genes. The prevalence of these chromatin regulators is more readily explained by disruption of developmental identity than by direct effects on cellular proliferation, as emphasized in the classic oncogene–tumor suppressor framework.

KMT2C and KMT2D are histone methyltransferases that regulate **enhancer** function and tissue-specific gene expression, for example, by depositing **H3K4me1** at enhancer regions [17]. These epigenetic marks support lineage-specific enhancer activity during development. Loss of these marks destabilizes the regulatory programs that maintain committed identity. For example, KMT2D loss in neural crest cells impairs differentiation and causes craniofacial defects during development [39]. In cancer, KMT2C and KMT2D loss reshapes chromatin organization in ways that can reactivate progenitor programs [18].

ARID1A is a component of the **SWI/SNF** chromatin remodeling complex, which opens chromatin at differentiation genes. In the pancreas, following KRAS mutation, ARID1A loss locks cells in a progenitor-like state and dramatically accelerates tumorigenesis [21]. Once again, we see the destabilization of committed epigenetic identity as the primary early event.

Overall, my argument is that the release of developmental identity is the primary mechanism of cancer initiation, allowing target cells to take on a wider range of cell states. Cases in which mutations primarily enhance proliferation or do not strongly block differentiation add important depth but do not significantly contradict the main argument. For example, in some tissues, PTEN mutations increase stem cell proliferation without fully blocking differentiation [40,41]. The important question for future studies is whether the mutated stem cells give rise to a wider range of cell states.

Relation to prior ideas

The idea that developmental disruption drives cancer has a long history. However, the oncogene and tumor suppressor gene framework for increased proliferation remains the dominant

explanation of cancer initiation. The evidence in the earlier section suggests that disruption of normal development deserves greater consideration. This section places the developmental framing in the context of prior literature.

A study in the 1960s showed that malignant cells retained the capacity to differentiate into more benign cell types, suggesting that directed differentiation might provide an alternative to cytotoxic therapy [42]. Another study around the same time described cancer as a disease of cell differentiation [43]. In 1994, this idea was extended to propose that many cancers arise when stem cells or early progenitors fail to complete normal differentiation, leading to expansion of proliferating, incompletely differentiated cells [44].

These ideas were prescient but had limited influence. The subsequent identification of oncogenes and tumor suppressors, the discovery of growth factor signaling cascades, and the popularity of the hallmarks of cancer framework organized the field around a different set of questions [2]. What signals drive cell division? How do cancers disable the checkpoints that restrain growth? Cellular plasticity was recognized as a possible initiating process but was never emphasized as the primary driver [1].

These hallmarks questions frame cancer as the progressive acquisition of sustained proliferative signaling, evasion of growth suppressors, activation of invasive traits, and, ultimately, metastatic spread. Cellular plasticity and **epithelial–mesenchymal transition (EMT)** appear in this framework as capabilities that enable invasion and metastasis—acquired properties of established tumors rather than initiating events. The question of whether plasticity is causal at tumor initiation has received far less attention [1,6–8].

Driver genes have been classified into three core functions [45]. Two are the standard cancer-related pathways: cell survival and genome maintenance. The third is cell fate, recognizing that developmental lineage identity is a major target of driver mutations. Yet this insight has not been incorporated into any widely discussed theory of initiation, and the field's attention remains focused primarily on proliferation and survival.

Recent studies have shown that specific oncogenic mutations can induce **dedifferentiation** and transdifferentiation at tumor initiation, and that differentiated cells can become tumor-initiating cells through this plasticity [8,35]. Other work has documented diverse plasticity programs linking driver mutations to altered differentiation programs [46]. A related theory proposes that tumors arise when stress converts somatic cells into polyploid giant cancer cells that dedifferentiate to a blastomere-like state [47–49]. Mutations are one stressor among many [47].

In previous work with colleagues, we proposed that nonheritable phenotypic plasticity drives early cancer evolution, with later genetic changes stabilizing the initially nonheritable phenotypic variants [4]. Furthermore, we argued that early cancer-initiating mutations in genes such as KRAS and TP53 function primarily to release developmental plasticity rather than to act as direct stimulators of cell division or disruptors of apoptosis [5]. I later synthesized these ideas into a general framework in which genetics releases plasticity, plasticity creates novel cellular traits, and subsequent genetic changes stabilize those novelties [3].

Concluding remarks

The evidence suggests that ten commonly mutated cancer driver genes enforce developmental identity in normal tissue, and mutations in those genes initiate tumors

Outstanding questions

Does cancer start with increased cell division and abrogation of normal cell death? Or are the first steps a release from terminal differentiation, triggering the greater cellular plasticity that creates the novel tissue functions that make a tumor?

Why do normal tissue cells often carry driver mutations without forming tumors? Which subsequent steps are needed to transform normal cells into a tumor? Does release of developmental plasticity facilitate that transformation?

Why do specific driver mutations dominate in specific tissues? Can the normal developmental role of each gene in each tissue predict which cancers it initiates and the phenotype of the resulting tumor?

Beyond the ten commonly mutated drivers, do less frequently mutated driver genes sometimes also function as developmental identity regulators?

Do oncogenic and tumor-suppressor mutations associate with clonal expansion because mechanistically the mutations release the tissue identity state that locks cells into terminal differentiation? Are links to cell cycle control and apoptosis consequences of the underlying developmental and identity state mechanisms?

Does the association between wounding, inflammation, tissue healing, and cancer arise because they share the release of developmental plasticity? What role do commonly mutated cancer driver genes play in normal wound healing?

Can experimental perturbation of developmental identity, without any mutation, initiate early steps in tumor formation?

Does aging affect the stability of committed cell identity? Does age-related epigenetic drift contribute to cancer risk independent of somatic mutation?

Which cancers in their early stages retain developmental and epigenetic reversibility? Does reversing the release of developmental plasticity halt progression?

by releasing developmental constraints. The ten genes regulate development by three distinct mechanisms: transcriptional enforcement, signaling control of stem cell state, and epigenetic stabilization. Several predictions follow from this theory of developmental perturbation as the primary initiating event in cancer (see Outstanding questions).

The tumorigenic potential of mutations in a particular gene should be tissue-specific in ways that reflect the normal developmental role of that gene. Mutations in APC dominate colorectal cancer because APC-controlled Wnt signaling maintains the intestinal stem cell compartment [15,16]. The same mutation has little oncogenic effect in tissues in which different regulators hold cells in their committed state. The developmental framework predicts such tissue specificity more precisely than the proliferation framework does.

Driver mutations should frequently persist in normal tissues without causing cancer. If mutations primarily release developmental plasticity rather than directly triggering uncontrolled division, additional steps such as inflammation, injury, cooperating mutations, or stromal remodeling should be required to convert a plastic cell into a growing tumor. Widely observed clonal mosaicism is consistent with this prediction. TP53 mutations accumulate extensively in sun-exposed skin, KRAS mutations persist in normal pancreatic tissue, and APC mutations are common in normal colonic epithelium, all without invariably producing cancer [50,51]. Mutations in these genes may release developmental constraints. However, forming a novel growing tissue requires more.

Therapeutic restoration of differentiated identity should reverse early cancer. Acute promyelocytic leukemia, cured by restoring differentiation with retinoic acid and arsenic trioxide, is an example [52]. The developmental framework predicts that similar approaches should work wherever the identity block remains epigenetically reversible. Such reversibility would most likely occur early in tumor progression, before subsequent genetic or epigenetic changes stabilize cancerous states.

The data on the most mutated cancer driver genes call into question the dominance of the oncogene and tumor suppressor classification. The early mutations driving cancer may act primarily by abrogating the normal developmental control of cell identity. Cancer is normal development spun out of control [3].

Author contributions

S.A.F. developed the conceptualization for this opinion article and wrote the original draft.

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Declaration of interests

The author declares no competing interests.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author used Claude, ChatGPT, and Elicit (https://elicit.com) in order to search the literature for references, check the accuracy of particular statements, and suggest alternative phrasing for specific sentences. After using these tools, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Key references

1. Mendiratta, G. *et al.* (2021) Cancer gene mutation frequencies for the U. S. population. *Nat. Commun.* 12, 5961. 10.1038/s41467-021-26213-y

This article provides the epidemiologically weighted ranking of driver mutation frequencies across US cancers used by this article (Table 1). The link between development and common cancer drivers depends on this list.

2. Hanahan, D. (2022) Hallmarks of cancer: new dimensions. *Cancer Discov.* 12, 31–46. 10.1158/2159-8290.CD-21-1059

This statement reflects the field's currently dominant framework: it includes phenotypic plasticity as an emerging hallmark but describes it as an acquired capability that facilitates tumorigenesis and progression rather than as the initiating event. By contrast, the argument here makes developmental plasticity the primary initiating event, with the classic effects on cell division and cell death following.

3. Burdziak, C. *et al.* (2023) Epigenetic plasticity cooperates with cell-cell interactions to direct pancreatic tumorigenesis. *Science* 380, eadd5327. 10.1126/science.add5327.

KRAS-driven epigenetic plasticity in the pancreas occurs before tumor initiation. Such plasticity explores a variety of cell–cell interactions and eventually becomes tumorigenic when it establishes specific, novel tissue interactions. The release of developmental identity, by itself, is insufficient. Subsequent microenvironmental changes are required for a growing tumor to form.

4. Jiang, C. *et al.* (2025) Innate immunity and the NF-κB pathway control prostate stem cell plasticity, reprogramming and tumor initiation. *Nat. Cancer* 6, 1537–1558. 10.1038/s43018-025-00994-3

PTEN deletion in prostate basal cells releases the multipotency of normal development and drives cellular reprogramming to initiate invasive tumors, with the released plasticity dependent on innate

Author biographies

Steven A. Frank is the Donald Bren Professor and UCI Distinguished Professor of Biological Sciences at the University of California, Irvine. He is an evolutionary biologist who uses mathematical and computational models to study how natural selection shapes biological design and how failures of that design contribute to disease. His research spans cancer evolution, infectious disease, social evolution, genome evolution, regulatory control, and the theoretical foundations of natural selection. His current cancer research examines how developmental control and cellular plasticity shape tumor initiation and evolution. Frank has published more than 190 scientific articles and five books, including *Dynamics of Cancer: Incidence, Inheritance, and Evolution* (Princeton, 2007). He is a Fellow of the American Academy of Arts and Sciences.

immune signaling. This work identifies inflammation as a trigger that cooperates with the release of early developmental identity.

5. Frank, S.A. (2025) How cancer arises: genetics releases, plasticity creates, genetics stabilizes. *Proc. Natl. Acad. Sci. USA* 122, e2505377122. 10.1073/pnas.2505377122

This work synthesizes the idea that the release of developmental plasticity is the primary driver of tumor initiation. Early genetic changes release developmental plasticity, this plasticity creates the novel traits that make a tumor, and subsequent genetic changes stabilize those traits. The present manuscript enhances this framework by showing that ten commonly mutated driver genes play important roles in normal development.

References

1. Hanahan, D. (2022) Hallmarks of cancer: new dimensions. *Cancer Discov.* 12, 31–46
2. Hanahan, D. and Weinberg, R.A. (2011) Hallmarks of cancer: the next generation. *Cell* 144, 646–674
3. Frank, S.A. (2025) How cancer arises: genetics releases, plasticity creates, genetics stabilizes. *Proc. Natl. Acad. Sci. U. S. A.* 122, e2505377122
4. Frank, S.A. and Rosner, M.R. (2012) Nonheritable cellular variability accelerates the evolutionary processes of cancer. *PLoS Biol.* 10, e1001296
5. Frank, S.A. and Yanai, I. (2024) The origin of novel traits in cancer. *Trends Cancer* 10, 880–892
6. Puisieux, A. *et al.* (2018) Cellular pliancy and the multistep process of tumorigenesis. *Cancer Cell* 33, 164–172
7. Gupta, P.B. *et al.* (2019) Phenotypic plasticity: driver of cancer initiation, progression, and therapy resistance. *Cell Stem Cell* 24, 65–78
8. Pérez-González, A. *et al.* (2023) Cancer cell plasticity during tumor progression, metastasis and response to therapy. *Nat. Cancer* 4, 1063–1082
9. Mendiratta, G. *et al.* (2021) Cancer gene mutation frequencies for the U.S. population. *Nat. Commun.* 12, 5961
10. Cicalese, A. *et al.* (2009) The tumor suppressor p53 regulates polarity of self-renewing divisions in mammary stem cells. *Cell* 138, 1083–1095
11. Kaiser, A.M. *et al.* (2023) p53 governs an AT1 differentiation programme in lung cancer suppression. *Nature* 619, 851–859
12. Madsen, R.R. *et al.* (2019) Oncogenic *PIK3CA* promotes cellular stemness in an allele dose-dependent manner. *Proc. Natl. Acad. Sci. U. S. A.* 116, 8380–8389
13. Storz, P. (2017) Acinar cell plasticity and development of pancreatic ductal adenocarcinoma. *Nat. Rev. Gastroenterol. Hepatol.* 14, 296–304
14. Marjanovic, N.D. *et al.* (2020) Emergence of a high-plasticity cell state during lung cancer evolution. *Cancer Cell* 38, 229–246.e13
15. Sansom, O.J. *et al.* (2004) Loss of *Apc* in vivo immediately perturbs Wnt signaling, differentiation, and migration. *Genes Dev.* 18, 1385–1390
16. Dow, L.E. *et al.* (2015) *Apc* restoration promotes cellular differentiation and reestablishes crypt homeostasis in colorectal cancer. *Cell* 161, 1539–1552
17. Van, H.T. *et al.* (2024) KMT2 family of H3K4 methyltransferases: enzymatic activity-dependent and -independent functions. *J. Mol. Biol.* 436, 168453
18. Wang, N.T. *et al.* (2025) Loss of *Kmt2c* or *Kmt2d* primes urothelium for tumorigenesis and redistributes KMT2A-menin to bivalent promoters. *Nat. Genet.* 57, 165–179
19. Zhang, Z. *et al.* (2024) Proteostatic reactivation of the developmental transcription factor TBX3 drives BRAF/MAPK-mediated tumorigenesis. *Nat. Commun.* 15, 4108
20. Knauf, J.A. *et al.* (2005) Targeted expression of BRAF-V600E in thyroid cells of transgenic mice results in papillary thyroid cancers that undergo dedifferentiation. *Cancer Res.* 65, 4238–4245
21. Livshits, G. *et al.* (2018) *Arid1a* restrains *Kras*-dependent changes in acinar cell identity. *Elife* 7, e35216
22. Yilmaz, Ö.H. *et al.* (2006) *Pten* dependence distinguishes haematopoietic stem cells from leukaemia-initiating cells. *Nature* 441, 475–482
23. Hatzistergos, K.E. *et al.* (2019) Tumor suppressors RB1 and CDKN2a cooperatively regulate cell-cycle progression and differentiation during cardiomyocyte development and repair: implications for stimulating neomyogenesis with cell-based therapy. *Circ. Res.* 124, 1184–1197
24. Lawrence, M.S. *et al.* (2013) Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature* 499, 214–218
25. Saburi, S. *et al.* (2008) Loss of Fat4 disrupts PCP signaling and oriented cell division and leads to cystic kidney disease. *Nat. Genet.* 40, 1010–1015
26. Dietrich, M.F. *et al.* (2010) Ectodomains of the LDL receptor-related proteins LRP1b and LRP4 have anchorage independent functions *in vivo*. *PLoS One* 5, e9960
27. Herman, J.G. *et al.* (1995) Inactivation of the *CDKN2/p16/MTS1* gene is frequently associated with aberrant DNA methylation in all common human cancers. *Cancer Res.* 55, 4525–4530
28. Beroukhim, R. *et al.* (2010) The landscape of somatic copy-number alteration across human cancers. *Nature* 463, 899–905
29. Skapek, S.X. *et al.* (2006) Regulation of cell lineage specification by the retinoblastoma tumor suppressor. *Oncogene* 25, 5268–5276
30. Calo, E. *et al.* (2010) *Rb* regulates fate choice and lineage commitment *in vivo*. *Nature* 466, 1110–1114

31. Janostiak, R. *et al.* (2022) Understanding retinoblastoma post-translational regulation for the design of targeted cancer therapies. *Cancers* 14, 1265
32. Burdziak, C. *et al.* (2023) Epigenetic plasticity cooperates with cell-cell interactions to direct pancreatic tumorigenesis. *Science* 380, eadd5327
33. Chan, J.E. *et al.* (2026) Critical role for a high-plasticity cell state in lung cancer. *Nature* 651, 231–241
34. Bi, L. *et al.* (1999) Proliferative defect and embryonic lethality in mice homozygous for a deletion in the p110α subunit of phosphoinositide 3-kinase. *J. Biol. Chem.* 274, 10963–10968
35. Van Keymeulen, A. *et al.* (2015) Reactivation of multipotency by oncogenic *PIK3CA* induces breast tumour heterogeneity. *Nature* 525, 119–123
36. Loi, S. *et al.* (2010) *PIK3CA* mutations associated with gene signature of low mTORC1 signaling and better outcomes in estrogen receptor-positive breast cancer. *Proc. Natl. Acad. Sci. U. S. A.* 107, 10208–10213
37. Jiang, C. *et al.* (2025) Innate immunity and the NF-κB pathway control prostate stem cell plasticity, reprogramming and tumor initiation. *Nat. Cancer* 6, 1537–1558
38. Chakravarty, D. *et al.* (2011) Small-molecule MAPK inhibitors restore radioiodine incorporation in mouse thyroid cancers with conditional BRAF activation. *J. Clin. Invest.* 121, 4700–4711
39. Shpargel, K.B. *et al.* (2020) The KMT2D Kabuki syndrome histone methylase controls neural crest cell differentiation and facial morphology. *Development* 147, dev187997
40. Groszer, M. *et al.* (2001) Negative regulation of neural stem/progenitor cell proliferation by the *Pten* tumor suppressor gene in vivo. *Science* 294, 2186–2189
41. Wang, S.Y. *et al.* (2006) *Pten* deletion leads to the expansion of a prostatic stem/progenitor cell subpopulation and tumor initiation. *Proc. Natl. Acad. Sci. U. S. A.* 103, 1480–1485
42. Pierce, G.B. *et al.* (1960) Teratocarcinogenic and tissue-forming potentials of the cell types comprising neoplastic embryoid bodies. *Lab. Investig.* 9, 583–602
43. Markert, C.L. (1968) Neoplasia: a disease of cell differentiation. *Cancer Res.* 28, 1908–1914
44. Sell, S. and Pierce, G.B. (1994) Maturation arrest of stem cell differentiation is a common pathway for the cellular origin of teratocarcinomas and epithelial cancers. *Lab. Investig.* 70, 6–22
45. Vogelstein, B. *et al.* (2013) Cancer genome landscapes. *Science* 339, 1546–1558
46. Yuan, S. *et al.* (2019) Cellular plasticity in cancer. *Cancer Discov.* 9, 837–851
47. Liu, J. (2018) The dualistic origin of human tumors. *Semin. Cancer Biol.* 53, 1–16
48. Liu, J. (2020) The "life code": a theory that unifies the human life cycle and the origin of human tumors. *Semin. Cancer Biol.* 60, 380–397
49. Liu, J. (2022) Giant cells: linking McClintock's heredity to early embryogenesis and tumor origin throughout millennia of evolution on Earth. *Semin. Cancer Biol.* 81, 176–192
50. Martincorena, I. *et al.* (2015) High burden and pervasive positive selection of somatic mutations in normal human skin. *Science* 348, 880–886
51. Kakiuchi, N. and Ogawa, S. (2021) Clonal expansion in non-cancer tissues. *Nat. Rev. Cancer* 21, 239–256
52. de Thé, H. *et al.* (2017) Acute promyelocytic leukemia: a paradigm for oncoprotein-targeted cure. *Cancer Cell* 32, 552–560