REVIEW

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Cells of origin in cancer

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Both solid tumours and leukaemias show considerable histological and functional heterogeneity. It is widely accepted that genetic lesions have a major role in determining tumour phenotype, but evidence is also accumulating that cancers of distinct subtypes within an organ may derive from different 'cells of origin'. These cells acquire the first genetic hit or hits that culminate in the initiation of cancer. The identification of these crucial target cell populations may allow earlier detection of malignancies and better prediction of tumour behaviour, and ultimately may lead to preventive therapies for individuals at high risk of developing cancer.

Remarkably, the oldest description and surgical treatment of cancer dates back to 1600 BC in Egypt, where the papyrus described eight cases of tumours occurring on the breast and their treatment by cauterization. Today, cancer is a leading cause of death worldwide, with the number of deaths from cancer projected to increase markedly, owing partly to an ageing global population. This immense cancer burden demands strategies that permit earlier detection, better stratification of tumours to guide therapy and the development of effective preventive therapies. Targeted therapeutic strategies that suppress the progression of preneoplastic cells towards the malignant state hold great promise for circumventing the huge challenges associated with the treatment of late-stage disease.

Tumours show marked heterogeneity in their cellular morphology, proliferative index, genetic lesions and therapeutic response. The molecular and cellular mechanisms underpinning tumour heterogeneity remain central questions in the cancer biology field. Key issues include whether the different subtypes of cancer reflect a distinct 'cell of origin', the extent to which the genetic mutational profile contributes to tumour phenotype and the nature of the relationship between the cell of origin and the cancer stem cell. This Review focuses on the strategies used to identify cells of origin, the impact of these cells on cancer cell fate and behaviour, and the implications for the development of improved prognostic markers and preventive therapies.

Cell-of-origin and cancer stem-cell concepts are distinct

It is important to note that the cell of origin, the normal cell that acquires the first cancer-promoting mutation(s), is not necessarily related to the cancer stem cell (CSC), the cellular subset within the tumour that uniquely sustains malignant growth. That is, the cell-of-origin and CSC concepts refer to cancer-initiating cells and cancer-propagating cells, respectively (Fig. 1). Although the tumour-initiating cell and the CSC have been used interchangeably, the tumour-initiating cell more aptly denotes the cell of origin. There is considerable evidence that several diverse cancers, both leukaemias and solid tumours, are hierarchically organized and sustained by a subpopulation of self-renewing cells that can generate the full repertoire of tumour cells (both tumorigenic and non-tumorigenic cells)[1]. The cell of origin, the nature of the mutations acquired, and/or the differentiation potential of the cancer cells are likely to determine whether a cancer follows a CSC model. In most instances, the phenotype of the cell of origin may differ substantially from that of the CSC.

Tumour heterogeneity

Phenotypic and functional heterogeneity are hallmarks of cancers arising in several organs. Variability can occur between tumours arising in the same organ (intertumoral heterogeneity), leading to the classification of discrete tumour subtypes. These subtypes are typically characterized by their molecular profile, together with their morphology and expression of specific markers (such as hormone and growth-factor receptors). Variation also occurs within individual tumours (intratumoral heterogeneity), in which the tumour cells often have a range of functional properties and a diverse expression of markers. For example, the proportion of cells that express the oestrogen receptor within a patient's breast tumour can vary extensively, from 1% to 100%. The CSC and clonal-evolution models have been put forward to account for intratumoral heterogeneity and intrinsic differences in tumour-regenerating capacity (reviewed in refs 1 and 2). Interestingly, despite the heterogeneous nature of tumours, the histopathology and gene-expression profiles of tumours arising in patients often remain relatively stable during progression from localized disease to metastatic and even end-stage disease[3,4].

Two main mechanisms have been conceptualized to explain intertumoral heterogeneity: different genetic or epigenetic mutations occurring within the same target cell result in different tumour phenotypes (Fig. 2a), and different tumour subtypes arise from distinct cells within the tissue that serve as the cell of origin (Fig. 2b). It is important to note that these cellular and molecular mechanisms are not mutually exclusive, but can act together to determine tumour histopathology and behaviour. In addition, extrinsic mechanisms may be involved in generating tumour heterogeneity, because interactions between tumour cells and the stromal micro-environment are a crucial determinant of malignant growth[5]. Several studies on human cancers and mouse models have highlighted the importance of specific genetic aberrations in contributing to tumour behaviour. Many oncogenes and tumour-suppressor proteins, most prominently phosphatidylinositol-3-OH kinase (PI(3)K), MYC, RAS, p53, PTEN, $p16^{Ink4a}$ and retinoblastoma protein (RB), are frequent culprits in diverse cancers, although the overall mutational profiles of different cancer types can vary considerably. Tumour maintenance undoubtedly depends on the continued expression of certain oncogenes — a phenomenon known as oncogene addiction[6]. Lineage-dependency oncogenes that have key survival roles, in which genetic changes may be predetermined by the lineage programs inherent in the tumour precursor cell[7], are also likely to contribute. There is mounting evidence, however, that the nature of the cellular target has an important influence on tumour cell fate and

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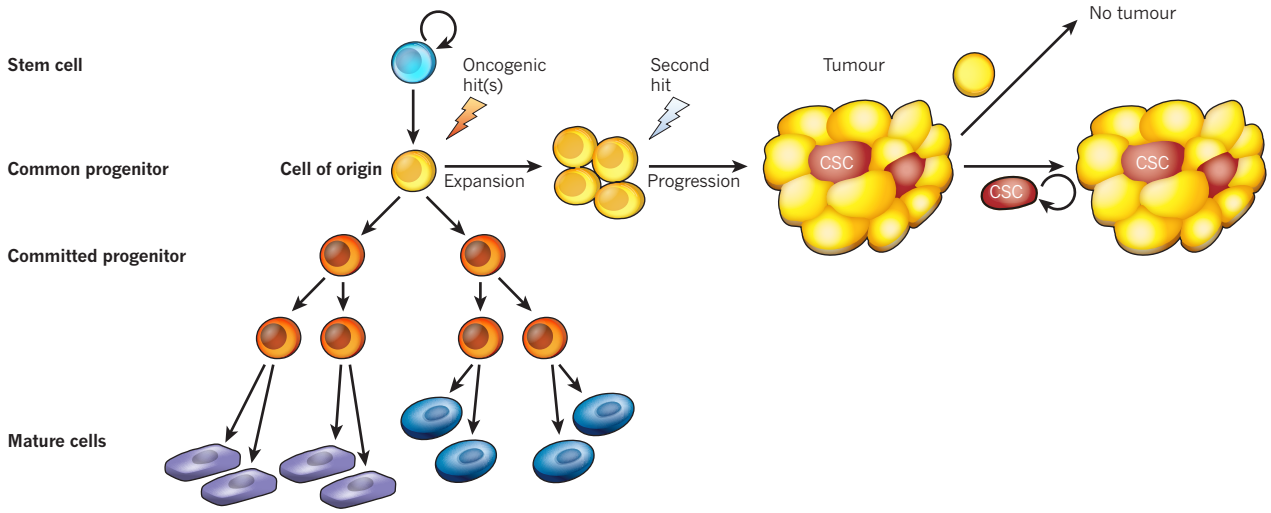

Figure 1 | The cell of origin and evolution of a cancer stem cell. Normal cellular hierarchy comprising stem cells that progressively generate common and more restricted progenitor cells, yielding all the mature cell types that constitute a particular tissue. Although the cell of origin for a particular tumour could be an early precursor cell such as a common progenitor, the accumulation of further epigenetic mutations by a cell within the aberrant population (in this case expanded) during neoplastic progression may result in the emergence of a CSC. In this model, only the CSCs (and not other tumour cells) are capable of sustaining tumorigenesis. Thus, the cell of origin, in which tumorigenesis is initiated, may be distinct from the CSC, which propagates the tumour.

pathology. Indeed, activation of the same oncogenic pathway in different cellular compartments or contexts may profoundly influence malignant potential[8]. For example, transgenic mouse models have shown that mutant *Hras* targeted to the hair follicle region highly predisposed mice to squamous carcinomas, whereas its targeting to more differentiated interfollicular or suprabasal cells resulted in papillomas with low malignant potential[9,10]. Moreover, transformation of distinct breast epithelial cells *in vitro* has indicated that the target cell is an important determinant of tumour phenotype[11].

Understanding the normal cellular hierarchy within a given tissue is an important prerequisite to identifying the cells of origin of cancers. Organ development proceeds in a hierarchical manner from stem cells to committed progenitor cells, which in turn yield differentiated cells that constitute the bulk of the tissue or organ (Fig. 1). The most primitive cells, stem cells, have been favoured candidates for targets of transformation because of their inherent capacity for self-renewal and their longevity, which would allow the sequential accumulation of genetic or epigenetic mutations required for oncogenesis. Nevertheless, any cell in the hierarchy with proliferative capacity could serve as a cell of origin in cancer, if it acquires mutations that re-instigate self-renewal capacity and prevent differentiation to a post-mitotic state.

The normal lineage hierarchy can serve as a framework to probe potential targets of carcinogenesis by comparison of lineage markers expressed on the surface of normal and neoplastic cell subsets. More accurate correlations, however, depend on comparisons of the expression signatures of normal cell populations with those of the different tumour subtypes arising within that organ. Notably, histologically indistinguishable glial-cell tumours from different parts of the central nervous system have distinct molecular gene signatures and chromosomal abnormalities, suggesting that they originated in different subpopulations of site-restricted progenitor cells[12,13]. In a recent integrated genomics approach to studying tumour heterogeneity, the transcriptomes of human brain tumours were matched to those of mouse neural stem cells (NSCs) from different cellular compartments within the central nervous system. Embryonic cerebral NSCs and adult spinal NSCs were revealed as the potential cells of origin for supratentorial and spinal ependymomas, respectively[14]. In breast cancer, the different molecular subtypes[15,16] have also been linked to normal epithelial subpopulations by the interrogation of specific gene-expression signatures[17]. Such observations remain correlative, however, until the tumorigenic potential of specific cells is proven *in vivo* by clonality or lineage-tracing studies. Although the hierarchy provides an important framework for understanding cells of origin in cancer, if tumour cells show phenotypic plasticity or dedifferentiate during neoplastic progression, then lineage markers and molecular signatures of tumour cells may not precisely reflect the true cell of origin in normal tissue.

Strategies to investigate the cellular origins of cancers

Genetically engineered mouse models have proven indispensable in addressing the cellular origin of cancers (Fig. 3). Two primary approaches have been used to tackle this question: one, transgenic or conditionally targeted gene technologies to explore the effects of oncogenes and tumour suppressors in different cellular contexts; and, two, genetic alteration of cells *ex vivo* before evaluating their tumorigenic capacity in mice. The first approach requires cell-specific promoters that direct expression of an oncogene, or Cre-mediated deletion of a tumour-suppressor gene, in a specific subset of cells *in vivo* (Fig. 3a). Ideally, such studies should use at least two promoters with different cell-type specificity to reveal the tumorigenic susceptibility of distinct cell subpopulations within that tissue. In this model, targeting of only one cell subpopulation is expected to reveal tumours that recapitulate the phenotype of the human cancer being modelled. Although this approach has been increasingly used to study cells of origin, particularly in brain tumours, it is often hampered by a lack of established cell-lineage-specific promoters, given that unique markers of stem and progenitor cells do not exist for the overwhelming majority of organs and tissues.

A further refinement of this *in vivo* targeting approach involves lineage tracing of cells as they undergo transformation. In this system, the main oncogenic event is activated conditionally in a limited number of cells rather than simultaneously in all cells that express the promoter. For example, a tamoxifen-inducible Cre recombinase–oestrogen receptor fusion protein (CreER)[18,19] driven by a cell-type-specific promoter allows inducible gene expression, in which the dose and number of pulses can be fine-tuned to ensure single-cell tracking. Lineage tracing at the clonal level is the current 'gold standard' for delineating the target cell of transformation in mouse models (Table 1).

In the second approach, defined cell subpopulations are genetically manipulated *ex vivo* and subsequently transplanted orthotopically into mice to assess their predisposition to tumour initiation (Fig. 3b). The strategy is applicable to cells from both human and mouse tissues, and

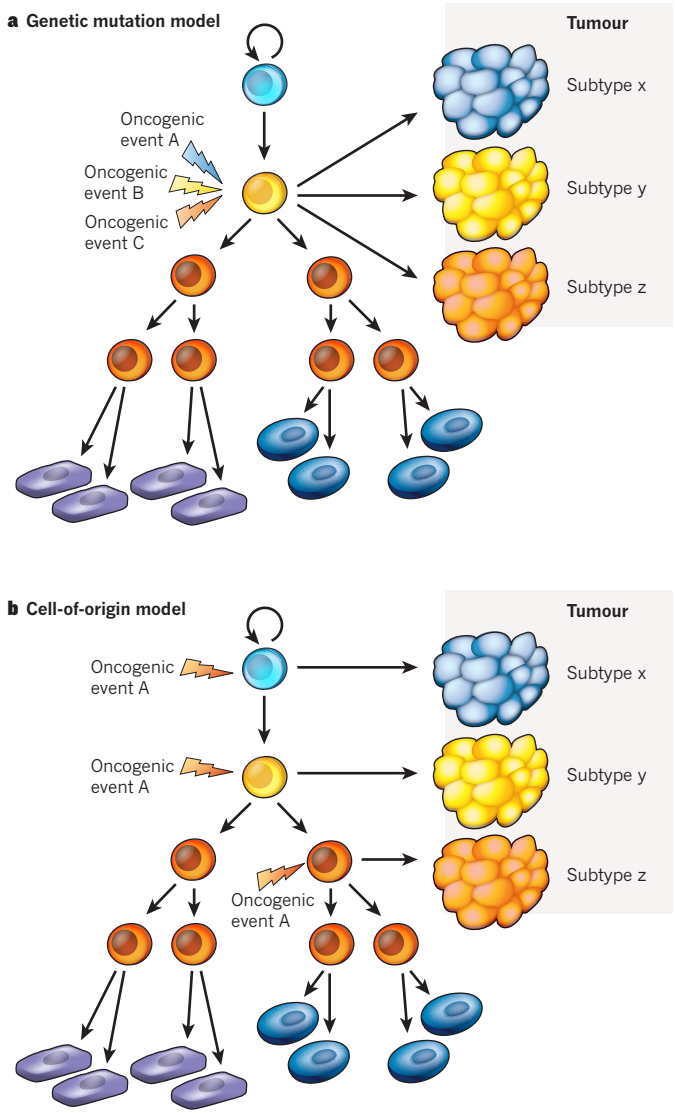

Figure 2 | Two models of intertumoral heterogeneity. **a**, In the genetic (and epigenetic) mutation model, mutations primarily determine the phenotype of the tumour, such that different mutations result in different tumour morphology. **b**, In the cell-of-origin model, different cell populations in the lineage hierarchy serve as cells of origin for the different cancer subtypes arising within that organ or tissue.

relies on the reproducible sorting of functionally defined populations that can serve as targets for the introduction of relevant oncogenic lesions. This approach has been widely exploited to identify potential cells of origin in human leukaemias, many of which contain characteristic chromosomal translocations.

An alternative way of exploring early cellular changes that occur before the onset of overt disease is to dissect the cellular components of preneoplastic tissue from individuals in families at high risk of cancer. These include carriers of germline mutations in the adenomatous polyposis coli (*APC*) gene, hereditary non-polyposis colorectal cancer (HNPCC) genes (such as *MSH2* and *MLH1*), and *BRCA1* or *BRCA2* genes. Carriers of mutated *APC* and HNPCC genes are predisposed to developing colorectal cancer[20]; female *BRCA1*- or *BRCA2*-mutation carriers are prone to breast and ovarian cancer[21]; and male *BRCA2*-mutation carriers often develop prostate cancer. This strategy has proven insightful in the case of *BRCA1*-mutation carriers (see 'Histopathology does not necessarily reflect cell of origin'). Combined with transplantation and clonality studies, **cell subsets predisposed to neoplastic progression can thus be identified.**

Cells of origin in haematopoietic malignancies

In different leukaemias, both normal stem and committed progenitor cells have been implicated as cellular targets of transformation. In chronic myeloid leukaemia (CML) — one of the first disorders to be defined by a dominant genetic mutation — the long-term haematopoietic stem cell (HSC) containing the *BCR–ABL* mutation has been established as the cell of origin by *in vivo* clonality studies in humans[22]. Although the HSC maintains the chronic phase of the disease, analysis of samples from patients in blast crisis — the acute and advanced stage of disease — has indicated that subsequent genetic events occurring in downstream progenitor cells give rise to leukaemia stem cells, highlighting the dynamic state of the tumorigenesis process[23]. The cells of origin for acute leukaemias, including myeloid, lymphoid and mixed-lineage, have not been definitively established. Human acute myeloid leukaemia (AML) may originate within the primitive haematopoietic cell compartment, on the basis of the similar cell-surface phenotypes of the leukaemia-initiating cell and the HSC, as well as lentivirus-mediated clonal-tracking studies[24]. A primitive human haematopoietic cell may also be the primary target of *MLL* fusion genes[25,26]. Moreover, *in vivo* evidence has implicated a human HSC-like cell as the initiating cell in a case of childhood leukaemia arising *in utero*[27].

Several studies have addressed potential cells of origin in mouse leukaemia models by transducing primary haematopoietic cell populations with oncogenes before transplantation, but these have yielded variable results. For mouse models of CML, only *BCR–ABL* targeted to HSCs, but not to committed progenitor cells, induced myeloproliferative disease[28], consistent with findings for human CML. Interestingly, the MLL–GAS7 fusion protein produced mixed lymphoid leukaemia when transduced into HSCs or multipotential progenitor cells but not when introduced into lineage-restricted progenitors. However, the MOZ–TIF2 (ref. 28), MLL–AF9 (ref. 29) and MLL–ENL[30,31] fusion proteins all initiated AML irrespective of the cell subtype transduced. Although HSCs generally appeared more susceptible to transformation than committed progenitors, a self-renewal program seemed to be reactivated in the latter cells during leukaemogenesis. In a 'knock-in' mouse model of *MLL–AF9*, only HSCs that expressed high levels of the fusion product and not the granulocyte–macrophage progenitors were transformed, but the latter could be efficiently transformed by a higher dose of *MLL–AF9* after retroviral transduction[32]. Thus, oncogene dosage affects transformation susceptibility, emphasizing the importance of using models that permit oncogene expression at levels relevant to human disease.

Further evidence that cancer can be initiated in cells other than stem cells has emerged from cell-fate mapping studies in transgenic mice overexpressing *Lmo2*: preleukaemic T-cell progenitors that had acquired self-renewal potential were identified as the cell of origin for T-cell acute lymphoblastic leukaemia (T-ALL) in this model[33]. Pertinently, mice lacking three pathways commonly repressed in cancer (p53, $p16^{Ink4a}$ and $p19^{Arf}$) contain cells that phenotypically resemble haematopoietic multipotential progenitor cells but have long-term reconstituting ability, indicating that they have acquired self-renewal capacity[34].

Cells of origin in solid tumours

Evidence is increasing that either stem or progenitor cells can act as targets for tumour initiation in a range of solid tumours (Table 1). Lineage-tracing studies (shown schematically in Fig. 4a) have identified probable cells of origin of intestinal, prostate and basal cell carcinomas, as well as pancreatic ductal adenocarcinoma, in mouse genetic models. Several other reports have used cell-specific promoters to drive Cre-mediated expression of the oncogenic event(s) in different cellular compartments of the mouse, whereas genetic manipulation of discrete cellular subsets has provided valuable insight into cell types prone to the initiation of carcinogenesis. It is crucial to note that although many studies have clearly identified the lineage in which the cancer originates, the precise cell type in the hierarchy (the cell of origin) in which transformation occurs remains elusive in most cases. Nevertheless, **in mouse models of intestinal and prostate tumours, it seems clear that the cancers**

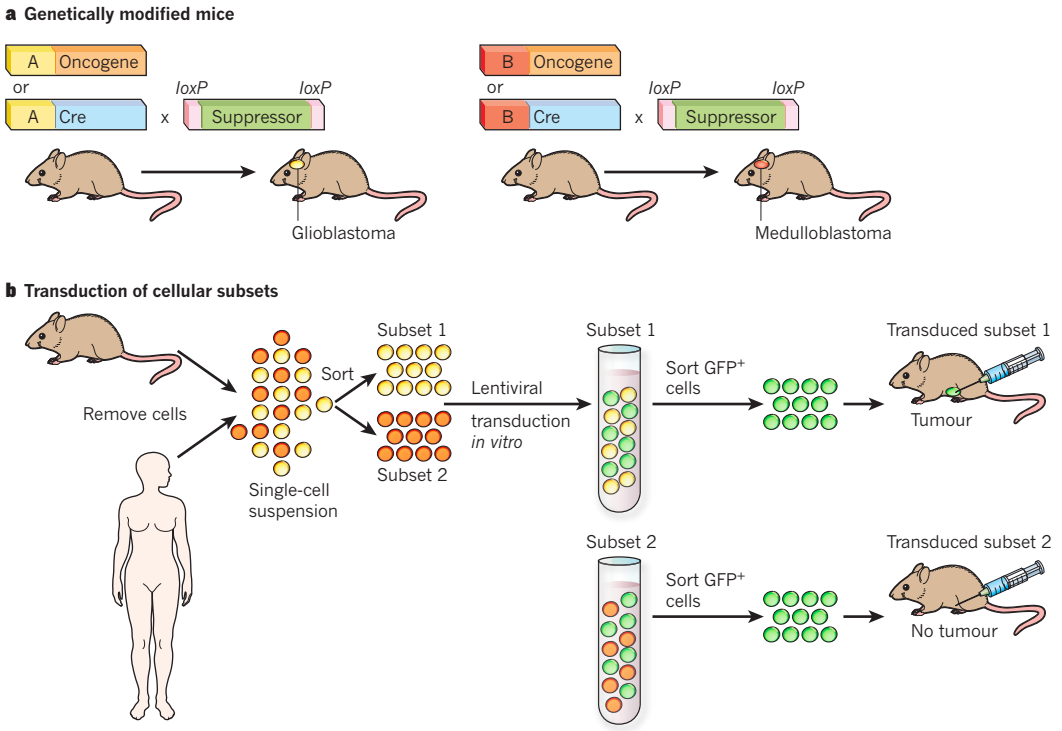

Figure 3 | Strategies used to identify cells of origin in cancer. a, Genetic mouse models can be used to either activate an oncogene or inactivate a tumour-suppressor gene in a discrete subpopulation of cells using cell-type-specific promoters. Comparative mouse models in which different promoters (A or B) drive expression of the same oncogenic lesion (either oncogene activation or tumour-suppressor inactivation) in the brain. Initiation of a glioblastoma is observed in the case of promoter A and a medulloblastoma in the case of promoter B, where promoters A and B are active in different cell subpopulations within the brain. **b**, Potential cells of origin in cancer can be addressed through the sorting of defined subpopulations from human or mouse tissue and their genetic manipulation *ex vivo*. Cell subpopulations are first transduced with genes encoding the oncogenic lesion(s), together with a fluorescent marker, then transplanted orthotopically into immunocompromised mice to evaluate the tumorigenic potency of the different subpopulations. GFP, green fluorescent protein.

originate in a bona fide stem cell that is capable of self-renewal and multilineage differentiation. Although the lineage in which the cancer originates has been revealed for skin, pancreatic, brain and breast tumours, the precise cells of origin have yet to be defined.

Two distinct crypt stem cells have been identified as the cells of origin for intestinal cancers. The vast majority of colorectal cancer is caused by mutations in the WNT signalling pathway, including loss of the negative regulator APC and activating mutations in β-catenin, both of which result in constitutive WNT activation[35]. *Apc* deletion in long-lived stem cells ($LGR5^+$) but not in short-lived transit-amplifying cells (using AhCre) revealed stem cells as a cell of origin for intestinal cancer in mice (Fig. 4b)[36]. This target cell is also marked by CD133 (also known as PROM1 or prominin 1)[37]. A novel intestinal stem cell located in the +4 or +5 position from the base of the crypt and therefore distinct from the $LGR5^+$ stem cell was also shown to be susceptible to tumorigenesis by deregulated WNT signalling using a BMI1–CreER knock-in model[38]. $LGR5^+$ stem cells are likely to be the target population for WNT-driven tumorigenesis in the stomach, where these cells seeded small adenomas[39]. The intestinal tumour load, however, precluded further lineage tracing of stem cells during the development of stomach cancer.

The cell of origin for brain cancers has been investigated using several mouse genetic models that have differed in design and the nature of the initiating oncogenic lesions. The models have predominantly included conditionally targeted mice, the RCAS–TVA system — in which gene transfer is mediated by an oncogene-carrying RCAS retrovirus to somatic cells in *TVA* transgenic mice[40] — and cell-culture-based analyses. Stereotactic injection of viruses into different areas of the brain[41,42] has also been used for the introduction of oncogenes or Cre recombinase to mimic focal tumorigenesis, but this approach cannot be used to identify cells of origin of cancer unequivocally as the transduced cell types are unknown. Although the available evidence argues for stem or multipotential neural progenitors in the subventricular zone (SVZ) as the primary cellular target for glioblastoma development, the cell of origin remains elusive owing to the complexity of this zone[43]. Many studies on brain tumorigenesis have used the nestin (*Nes*) or *Gfap* promoter regions to direct expression or inactivation: it is important to note that although both promoters drive expression in neural precursor cells, the *Gfap* promoter is also active in mature astrocytes[41]. Nonetheless, nestin-positive precursors were more susceptible to transformation by RAS and AKT than the GFAP-positive population, and produced high-grade glioblastomas, consistent with tumours originating in the stem/progenitor population[40]. Moreover, neural precursor cells in the SVZ of the adult brain efficiently initiated glioblastomas after conditional inactivation of *p53* (also known as *Trp53*), *Pten* and/or *Nf1* tumour-suppressor genes[41], and presymptomatic mice exhibited a premalignant cell population. By contrast, the more differentiated cell types in non-neurogenic areas of the adult brain proved less susceptible to malignant transformation[41,42]. Similarly, mice deficient in varying combinations of *p53*, *Pten* and/or *Rb* (also known as *pRb* and *Rb1*) developed tumours only in the SVZ and not from mature peripheral astrocytes[44]. Interestingly, the same stem/progenitor population seemed to initiate either gliomas or medulloblastomas, depending on the nature of the genetic lesions. More restricted progenitor cells may also initiate glioma development. Single-cell tracking studies of cells expressing mutant p53 implicate transit-amplifying cells in the SVZ[45]. Although oligodendrocyte progenitors and cells within the astrocyte compartment may also have the potential to seed glioblastomas[46,47], culturing cells before manipulation may not accurately reflect the *in vivo* situation, and the presence of more primitive cells within the cell cultures cannot be excluded. Thus, definitive evidence that mature astrocytes can serve as cells of origin for brain tumours awaits further experimentation.

Table 1 | Cells of origin (proven and candidate) identified in solid tumours by targeting distinct cellular subsets

Tumour type	Genetic model	Promoter–Cre construct	Lineage tracing	Cell of origin
Mouse models				
Brain: Glioblastoma	RAS, AKT activation (RCAS–TVA system: nestin, *Gfap* promoters)	NA	–	Neural progenitor cell[40]
	$p16^{Ink4a}$/$p19^{Arf}$, BMI1 inactivation; mutant EGFR	NA	–	Neural progenitor and astrocyte[46,47]
	p53, NF1 and/or PTEN inactivation	Nestin–CreERT2, Adeno–Cre	–	Multipotent progenitor[41]
	PDGFB activation (RCAS–TVA system)	NA	–	Oligodendrocyte progenitor[85]
	RAS, AKT activation; p53 inactivation	GFAP–Cre	–	Multipotent progenitor[42]
	Mutant p53 expression	GFAP–Cre	–	Neural progenitor or transit-amplifying cell[45]
	PTEN, p53 inactivation	GFAP–Cre	–	Multipotent progenitor[44]
Medulloblastoma	Patched inactivation	MATH1–Cre, GFAP–Cre	–	Multipotent progenitor and granule neuron progenitor[49]
	Smoothened activation	GFAP–Cre, MATH1–Cre, OLIG2–TVA–Cre	–	Multipotent progenitor and granule neuron progenitor[48]
	RB, p53, PTEN inactivation	GFAP–Cre	–	Multipotent progenitor[44]
	RB, p53 inactivation	Adeno–Cre	–	Neural progenitor cell[50]
	β-catenin mutant, p53 inactivation	BLBP–Cre, ATOH1–Cre	–	Dorsal brainstem progenitor[51]
Ependymoma (supratentorial)	$p16^{Ink4a}$/$p19^{Arf}$ inactivation; EPHB2 activation	NA	–	Embryonic cerebral stem/progenitor cell[14]
Intestine	APC inactivation	AhCre, LGR5–CreERT2	+	Stem cell[36]
	Mutant β-catenin	CD133–CreERT2	+	Stem cell[37]
	Mutant β-catenin	BMI1–CreER	+	Stem cell[38]
Lung	Kras activation	Adeno–Cre	–	Bronchioalveolar stem cell[77]
Mammary	NOTCH1 activation in cell subsets	NA	–	Luminal progenitor[65]
	BRCA1, p53 inactivation	BLG–Cre, K14–Cre	–	Luminal progenitor[63]
Pancreas	Kras activation, inflammation	RIP–CreER	+	Endocrine cell[69]
Prostate	PTEN inactivation	NKX3.1–CreERT2	+	Luminal stem cell[54]
	ERG1, PI(3)K and/or AR expression	NA	–	Basal progenitor[59]
	PTEN inactivation	PB–Cre	–	Basal progenitor[58]
	PTEN inactivation	PSA–Cre	–	Luminal cell[56,57]
Skin/basal cell carcinoma	Smoothened activation	K14–CreER	+	Interfollicular epidermal progenitor[72]
Stomach	APC inactivation	LGR5–CreERT2	+	Stem cell[39]
Human tissue				
Breast (basal-like subtype)*	Preneoplastic *BRCA1*$^{+/-}$ cell subsets	NA	–	Luminal progenitor[17]
Prostate	PI(3)K, ERG, AR into cell subsets	NA	–	Basal progenitor[60]

Adeno, adenoviral; Ah, cytochrome P450 1A1 gene (also known as *Cyp1a1*); AR, androgen receptor; BLG, β-lactoglobulin; K14, cytokeratin 14; NA, not applicable; PB, probasin (prostate-specific); PSA, prostate-specific antigen; RIP, rat insulin promoter.
*Refers to analysis of specific subsets from normal versus premalignant human breast tissue, leading to identification of a candidate cell of origin.

Unipotent cells within the mouse brain have been identified as the cell of origin for medulloblastoma. Constitutive hedgehog signalling (due to loss of *Ptc* or activation of *Smo*) in either the stem-cell compartment or granule neuron progenitor cells could initiate medulloblastomas but not astrocytomas or oligodendrogliomas[48,49]. Targeted deletion of a different set of genes (*p53* and *Rb*) also supports the notion that cerebellar stem cells or lineage-restricted granule progenitor cells can give rise to medulloblastomas[50]. Extending these observations further, it was shown that the cells must transition to the granule progenitor stage for the initiation of medulloblastomas, indicating that the true cell of origin for medulloblastomas that exhibit hedgehog pathway activation[48] is a unipotent progenitor cell[48]. A distinct cell type within the dorsal brainstem has recently emerged as the cell of origin for medulloblastomas that harbour activating mutations in the WNT pathway[51], indicating that different subtypes of medulloblastoma have distinct cellular origins. In mouse models of malignant peripheral nerve sheath tumours, tumours may initiate from differentiated glial cells in the adult brain[52,53].

Prostate cancer can originate from distinct cell lineages

Prostate cancers have been widely presumed to originate from mature luminal cells as these cancers are characterized by an expansion of luminal cells and the absence of basal cells. Recent findings, however, implicate distinct stem cells in the basal and the luminal cellular compartments, each of which can be targeted for oncogenesis by the loss of PTEN or PI(3)K activation. Rare luminal epithelial stem cells that express NKX3.1 and are castration resistant were identified[54], and these cells could initiate high-grade prostate intraepithelial neoplasia (PIN) and carcinomas. It is not yet clear whether these cells, termed CARNs, exist within 'normal' mouse or human prostate (that is, the

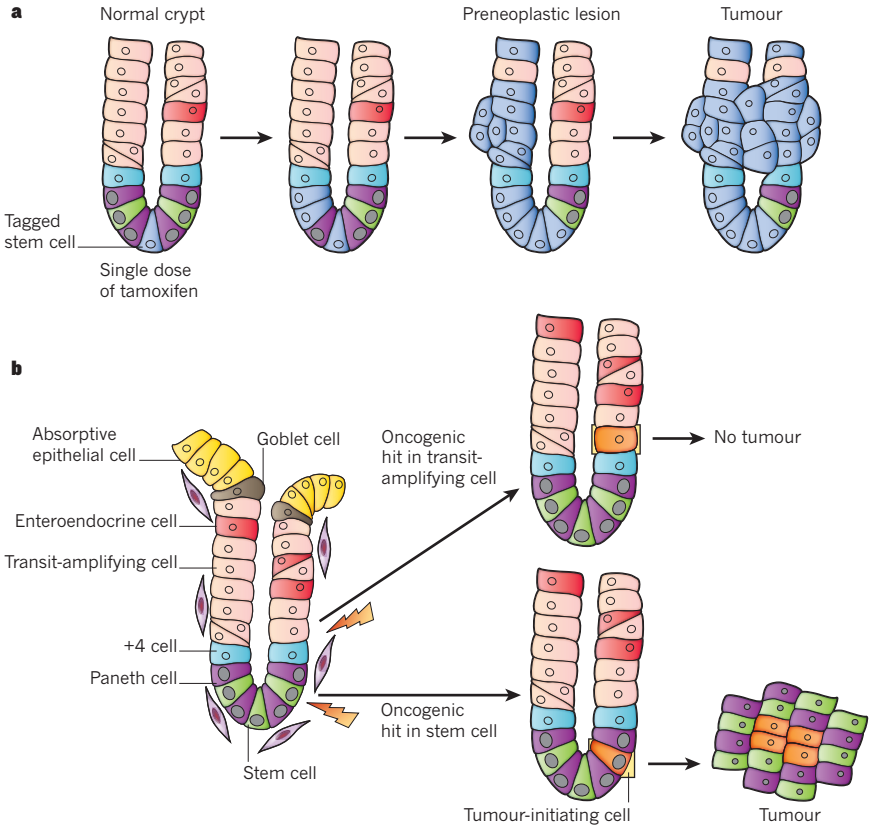

Figure 4 | Identification of crypt stem cells as the cell of origin in intestinal cancer by lineage tracing. **a**, Schematic depiction of lineage tracing in a colonic crypt, in which a single dose of tamoxifen can be used to activate CreER specifically in a stem cell to drive expression of a given oncogenic lesion in this cell population. The promoter that drives CreER expression will determine the cells in which this occurs. In the case of a stem cell, the incorporated reporter gene, such as *lacZ*, will mark all progeny of the stem cell. **b**, Schematic representation summarizing the data from ref. 36, in which lineage tracing of either stem or transit-amplifying cells deficient in *Apc* shows the initiation of intestinal tumours from stem cells only.

non-castrated state), but these bipotent, self-renewing cells may be mobilized as facultative stem cells during prostate regeneration after androgen withdrawal. Indeed, only the basal population isolated from normal mouse prostate has been demonstrated to contain stem cells with prostate-regenerative potential[55]. The question of whether CARNs exist in patients with prostate cancer is difficult to address as castration is implemented only after the development of advanced disease. The identification of a luminal cancer-initiating cell is consistent with findings that deletion of *Pten* in luminal cells of the mouse prostate leads to prostatic hyperplasia[56,57].

Conversely, basal cells have been demonstrated as an efficient target of tumorigenesis in a *Pten*-deficient mouse model[58] or when genetically manipulated *ex vivo* to overexpress *Erg*, androgen receptor (*Ar*) and/or PI(3)K, resulting in PIN lesions and carcinomas[59]. The tumorigenic susceptibility of purified basal and luminal subpopulations from human prostate tissue was recently evaluated [60]. When the cells were transduced with relevant oncogenic lesions, together with a fluorescent marker, and transplanted into immunocompromised mice, only the basal cells could initiate the development of prostate cancer reminiscent of the luminal-like cancers that arise in humans.

Histopathology does not necessarily reflect cell of origin

Tumours have largely been classified on the basis of their histological appearance and expression of markers (such as ER and HER2 in breast cancer) that predict the response of the tumour to a given treatment. However, the histological and cell-surface marker profiles of tumours do not necessarily predict the cell of origin, as illustrated above for prostate cancer. Other examples that underscore this point include breast, pancreatic and basal cell carcinomas, as discussed below.

Individuals that harbour mutations in the *BRCA1* tumour-suppressor gene develop breast cancers that usually resemble the basal-like subtype, typically associated with poor clinical prognosis[61,62]. The basal stem cell has therefore been presumed to be the transformation target for this tumour subtype, but the luminal progenitor has instead emerged as the likely cell of origin. Analysis of cellular subsets in precancerous breast tissue from *BRCA1*-mutation carriers demonstrated expansion of luminal progenitor cells that showed altered growth properties and aberrantly produced nodules when transplanted into mice (ref. 17 and F. Vaillant and J.E.V., unpublished data). Moreover, there are significant similarities between the gene-expression profiles of normal breast luminal progenitors, preneoplastic tissue from *BRCA1*-mutation carriers and basal-like breast cancers[17]. Indeed, inactivation of *Brca1* (and *p53*) in either luminal or basal cells of the mouse mammary gland showed that only the luminal cell population initiated basal-like cancers reminiscent of those arising in *BRCA1*-mutation carriers[63]. The presence of $ALDH1^+$ lobules in pathologically normal tissue from *BRCA1*-mutation carriers[64] is compatible with a luminal cell of origin, because luminal progenitors exhibit ALDH activity (F. Vaillant and J.E.V., unpublished data). NOTCH1 activation also targets luminal progenitor cells, generating an aberrant, self-renewing progenitor cell that yields mammary hyperplasia and, eventually, tumours[65]. Accordingly, high *NOTCH1* levels occur in basal-like breast cancers and predict poor prognosis[66]. The cells of origin for most other breast cancers have yet to be defined. In particular, the role of the mammary stem cell in breast oncogenesis is unclear, although WNT pathway activation primarily targets this population[67], and the 'claudin-low' subtype of breast cancer, which is characterized by low expression of genes involved in tight junctions and cell–cell adhesion, shares a similar molecular profile to that of the stem-cell subset[17,68].

Pancreatic ductal adenocarcinoma (PDAC) and premalignant ductal lesions (termed pancreatic intraepithelial neoplasia) have a ductal morphology, suggesting that they develop from pancreatic duct cells[69]. Unexpectedly, however, premalignant lesions were shown to derive from differentiated acinar cells that were reprogrammed to a duct-like phenotype[69–71]. Moreover, targeting a *Kras* oncogenic signal to insulin-positive endocrine cells induced PDAC. Notably, the ductal reprogramming of acinar cells required inflammatory tissue damage, highlighting a role for non-genetic factors in contributing to tumour phenotype. Ductal adenocarcinoma can also arise from other pancreatic cell lineages in the absence of tissue injury, for example PDX1-expressing cells[69].

Lineage-tracing studies have shown that basal cell carcinomas originate in progenitor cells resident in the interfollicular epidermis of the skin rather than from stem cells as originally postulated[72]. Conditional activation of hedgehog signalling in different cellular compartments, combined with cell-fate mapping, showed that long-lived progenitors in the interfollicular epithelium, but not the hair follicle bulge stem cell or the transit-amplifying cells, produced tumours. The block in differentiation evident in interfollicular epidermal cell clones with constitutive hedgehog signalling correlated with the expression of basal lineage markers (such as P-cadherin and keratins 7 and 15) and may have led to the notion that basal cell carcinomas arise from hair follicle bulge stem cells[8,73].

Potential relationships between cells of origin and CSCs

Although a stem cell may sustain the first oncogenic hit, subsequent alterations required for the genesis of a CSC can occur in descendent cells (Fig. 1). This is exemplified by CML, in which the HSC is the cell of origin in the more indolent phase of the disease but in patients with CML blast crisis, granulocyte–macrophage progenitors acquire self-renewal capacity through a β-catenin mutation and emerge as the probable CSC[23].

In some instances, particularly in early-stage cancers, the CSC may closely resemble the cell of origin, although this remains to be proven. For example, the leukaemia-initiating cell in AML[74] may prove to be the same as the leukaemia stem cell that propagates the disease. In a mouse model of intestinal cancer, despite all neoplastic cells arising from $CD133^+$ stem cells, only a small fraction of the tumour cells retained CD133 expression. It is tempting to speculate a hierarchical model of tumour progression in which this small subset of $CD133^+$ cells might generate the full repertoire of tumour cells and thereby correspond to CSCs. This notion is compatible with the observation that CD133 marks CSCs in certain human colorectal tumours[75,76]. Nevertheless, it remains to be determined whether these $CD133^+$ or $LGR5^+$ cells have tumour-propagating ability. Bronchioalveolar stem cells (BASCs) have been implicated as the cell of origin for lung adenocarcinomas induced by mutant *Kras*[77] in mice and may be closely related to the CSC, because the BASC marker Sca1 was recently shown to identify CSCs in certain mouse models of non-small-cell lung cancer[78]. In prostate cancer, if the oncogenic transformation of CARNs leads to the formation of CSCs in prostate cancer, then this might explain how early events occurring in the cell of origin can contribute to the emergence of hormone-refractory disease[54]. Although the relationships between tumour cells of origin and CSCs are not well understood, comprehensive cellular analyses of the preneoplastic and neoplastic states of different tumour subtypes should eventually shed light on this issue.

Therapeutic and diagnostic implications

Identification of the cell of origin has important implications for new preventive therapeutic approaches to suppress or reverse the initial phase of disease. Cancer chemoprevention will be most applicable to individuals within families at high risk of cancer such as *BRCA1/2*-mutation carriers. Cell-surface markers or proto-oncogenic kinases such as c-KIT[17] that show altered expression in cell subsets in preneoplastic tissue can be evaluated as prognostic markers, and for their ability to eradicate or modulate aberrant cells in either preneoplastic or established disease.

In principle, individuals that carry a defect in the *APC* gene, and are thus highly susceptible to colorectal cancer, could benefit from prophylactic treatment that targets APC-deficient cells for apoptosis. Tumour-necrosis-factor-related apoptosis-inducing ligand (TRAIL) in combination with all-*trans* retinoic acid selectively induced apoptosis in APC-deficient premalignant cells and intestinal polyps, thus inhibiting tumour growth[79]. Furthermore, treatment of biopsy samples of human colonic polyps from patients with familial adenomatous polyposis showed selective apoptosis of polyps, whereas normal tissue was unaffected, providing a potentially effective method of chemoprevention in these patients. In other families at high risk of colorectal cancer, with mutations in the *MLH1* or *MSH2* mismatch repair genes, inhibition (short-term and intermittent) of selective DNA polymerases may be a potential chemopreventive strategy, as these agents have been shown to elicit tumour cell death in patients with HNPCC[80].

Tamoxifen and aromatase inhibitors (inhibitors of oestrogen action and biosynthesis, respectively) are the prototypes for chemopreventive agents in hormone-receptor-positive breast cancer, as they markedly reduce the rate of disease recurrence and more than halve the incidence of new cancers in patients[81]. Recent findings have clarified how ovarian hormone exposure enhances breast cancer risk by showing that mammary stem cells, despite lacking receptors for these hormones, are highly responsive to steroid hormone signalling *in vivo*[82]. As the paracrine signals relayed to these stem cells seem to involve the receptor activator of NF-κB (RANK) signalling pathway, an exciting corollary of these findings is that it should be possible to prevent some forms of breast cancer by driving stem cells into a dormant state — for example, by blockade of the RANK pathway — for which inhibitors are already in clinical trial for bone metastases. There may also be prophylactic benefit for *BRCA1/2*-mutation carriers in the use of poly(ADP-ribose) polymerase (PARP) inhibitors[83], which are being evaluated for the treatment of *BRCA1/2*-associated breast cancers[84], if the early lesions in these individuals prove to be defective in DNA repair.

Perspective

It seems intuitive that both the cell of origin and the pattern of acquired mutations determine tumour fate and phenotype. The close association between cell lineage and cancer phenotype suggests that lineage-restricted mechanisms that normally operate during development may contribute to tumorigenesis. The cell of origin may often correspond to the normal tissue stem cell, exploiting its intrinsic self-renewal ability. This may particularly apply to tissues with very high turnover, such as the gut, because progenitor cells may not live long enough to acquire the full set of mutations required for malignancy. The stem cell or an early progenitor cell has also emerged as a likely cell of origin in certain leukaemias, glioblastomas and prostate cancer. In other malignancies, however, the initiating cell can be a restricted progenitor, as in the case of medulloblastomas, basal cell carcinomas and *BRCA1*-associated breast cancer. Indeed, in cell types that retain high proliferative potential, such as some differentiated lymphoid cells, the cell of origin could even be a mature cell type. Notably, there are several examples indicating that tumour phenotype may not directly reflect tumour histology or lineage marker expression, thus highlighting the requirement for *in vivo* studies to assess the propensity of cell populations to act as cells of origin.

Mouse models of oncogenesis have been pivotal in uncovering the cellular origins of cancer and the impact of specific mutations on tumorigenesis. Arguably, the choice of the genetically modified mouse model and the promoter/enhancer to recapitulate the effects of the oncogenic lesion has a major influence on tumour phenotype and behaviour. More specific promoters to drive expression of an initiating event within a definitive cellular compartment are likely to evolve as the normal lineage hierarchies within tissues are further refined. For studies on the cell of origin in human tissues, genetic and cellular analyses of tumour cell populations, at the single-cell level, from patients at different stages of disease should provide substantial insight into the relationships among normal cells, cells of origin and CSCs.

Identification of the cell of origin may permit a more systematic analysis of the genetic lesions involved in tumour initiation and progression, and serve as a platform for the identification of early disease biomarkers. It may also have important implications for preventing relapse, particularly in cases in which relapse results from a 'premalignant' clone (perhaps the cell of origin itself) that persists in the patient before acquiring a mutation that renders it malignant. If so, even patients with cancer who have a profound regression may require

maintenance therapy to reduce the chance of relapse. Finally, the gene signature of the cell of origin may elucidate key molecular pathways and driver mutations that could lead to new therapeutic approaches to prevent or target early-stage disease. ■

1. Visvader, J. E. & Lindeman, G. J. Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. *Nature Rev. Cancer* **8,** 755–768 (2008).
2. Marusyk, A. & Polyak, K. Tumor heterogeneity: causes and consequences. *Biochim. Biophys. Acta* **1805,** 105–117 (2010).
3. Ma, X. J. *et al.* Gene expression profiles of human breast cancer progression. *Proc. Natl Acad. Sci. USA* **100,** 5974–5979 (2003).
4. Weigelt, B. *et al.* Gene expression profiles of primary breast tumors maintained in distant metastases. *Proc. Natl Acad. Sci. USA* **100,** 15901–15905 (2003).
5. Tlsty, T. D. & Coussens, L. M. Tumor stroma and regulation of cancer development. *Annu. Rev. Pathol.* **1,** 119–150 (2006).
6. Weinstein, I. B. Addiction to oncogenes—the Achilles heal of cancer. *Science* **297,** 63–64 (2002).
7. Garraway, L. A. & Sellers, W. R. Lineage dependency and lineage-survival oncogenes in human cancer. *Nature Rev. Cancer* **6,** 593–602 (2006).
8. Perez-Losada, J. & Balmain, A. Stem-cell hierarchy in skin cancer. *Nature Rev. Cancer* **3,** 434–443 (2003).
9. Bailleul, B. *et al.* Skin hyperkeratosis and papilloma formation in transgenic mice expressing a *ras* oncogene from a suprabasal keratin promoter. *Cell* **62,** 697–708 (1990).
10. Brown, K., Strathdee, D., Bryson, S., Lambie, W. & Balmain, A. The malignant capacity of skin tumours induced by expression of a mutant H-*ras* transgene depends on the cell type targeted. *Curr. Biol.* **8,** 516–524 (1998).
11. Ince, T. A. *et al.* Transformation of different human breast epithelial cell types leads to distinct tumor phenotypes. *Cancer Cell* **12,** 160–170 (2007).
12. Sharma, M. K. *et al.* Distinct genetic signatures among pilocytic astrocytomas relate to their brain region origin. *Cancer Res.* **67,** 890–900 (2007).
13. Taylor, M. D. *et al.* Radial glia cells are candidate stem cells of ependymoma. *Cancer Cell* **8,** 323–335 (2005).
14. Johnson, R. A. *et al.* Cross-species genomics matches driver mutations and cell compartments to model ependymoma. *Nature* **466,** 632–636 (2010).
This paper demonstrates integrated genomic and cell-based approaches to identify cells of origin in ependymomas.
15. Sorlie, T. *et al.* Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc. Natl Acad. Sci. USA* **98,** 10869–10874 (2001).
16. Sotiriou, C. *et al.* Breast cancer classification and prognosis based on gene expression profiles from a population-based study. *Proc. Natl Acad. Sci. USA* **100,** 10393–10398 (2003).
17. Lim, E. *et al.* Aberrant luminal progenitors as the candidate target population for basal tumor development in *BRCA1* mutation carriers. *Nature Med.* **15,** 907–913 (2009).
Identification of an aberrant cell population in preneoplastic tissue, and discovery that mutant-*BRCA1* tissue and basal cancers share a gene signature with normal luminal progenitors.
18. Hayashi, S. & McMahon, A. P. Efficient recombination in diverse tissues by a tamoxifen-inducible form of Cre: a tool for temporally regulated gene activation/inactivation in the mouse. *Dev. Biol.* **244,** 305–318 (2002).
19. Metzger, D. & Chambon, P. Site- and time-specific gene targeting in the mouse. *Methods* **24,** 71–80, (2001).
20. Hewish, M., Lord, C. J., Martin, S. A., Cunningham, D. & Ashworth, A. Mismatch repair deficient colorectal cancer in the era of personalized treatment. *Nature Rev. Clin. Oncol.* **7,** 197–208 (2010).
21. Narod, S. A. & Foulkes, W. D. *BRCA1* and *BRCA2*: 1994 and beyond. *Nature Rev. Cancer* **4,** 665–676 (2004).
22. Fialkow, P. J., Denman, A. M., Jacobson, R. J. & Lowenthal, M. N. Chronic myelocytic leukemia. Origin of some lymphocytes from leukemic stem cells. *J. Clin. Invest.* **62,** 815–823 (1978).
23. Jamieson, C. H. *et al.* Granulocyte–macrophage progenitors as candidate leukemic stem cells in blast-crisis CML. *N. Engl. J. Med.* **351,** 657–667 (2004).
The first functional evidence that cells of origin and cancer-propagating cells in a given malignancy are likely to be distinct.
24. Hope, K. J., Jin, L. & Dick, J. E. Acute myeloid leukemia originates from a hierarchy of leukemic stem cell classes that differ in self-renewal capacity. *Nature Immunol.* **5,** 738–743 (2004).
25. Barabe, F., Kennedy, J. A., Hope, K. J. & Dick, J. E. Modeling the initiation and progression of human acute leukemia in mice. *Science* **316,** 600–604 (2007).
26. Wei, J. *et al.* Microenvironment determines lineage fate in a human model of *MLL-AF9* leukemia. *Cancer Cell* **13,** 483–495 (2008).
27. Hong, D. *et al.* Initiating and cancer-propagating cells in *TEL-AML1*-associated childhood leukemia. *Science* **319,** 336–339 (2008).
28. Huntly, B. J. *et al.* MOZ-TIF2, but not BCR-ABL, confers properties of leukemic stem cells to committed murine hematopoietic progenitors. *Cancer Cell* **6,** 587–596 (2004).
29. Krivtsov, A. V. *et al.* Transformation from committed progenitor to leukaemia stem cell initiated by MLL–AF9. *Nature* **442,** 818–822 (2006).
30. Cozzio, A. *et al.* Similar MLL-associated leukemias arising from self-renewing stem cells and short-lived myeloid progenitors. *Genes Dev.* **17,** 3029–3035 (2003).
31. Drynan, L. F. *et al. Mll* fusions generated by Cre-*loxP*-mediated *de novo* translocations can induce lineage reassignment in tumorigenesis. *EMBO J.* **24,** 3136–3146 (2005).
32. Chen, W. *et al.* Malignant transformation initiated by *Mll-AF9*: gene dosage and critical target cells. *Cancer Cell* **13,** 432–440 (2008).
This study highlights the importance of gene dosage when assessing the effects of oncogene expression in candidate cells of origin.
33. McCormack, M. P. *et al.* The *Lmo2* oncogene initiates leukemia in mice by inducing thymocyte self-renewal. *Science* **327,** 879–883 (2010).
34. Akala, O. O. *et al.* Long-term haematopoietic reconstitution by $Trp53^{-/-}$ $p16^{Ink4a-/-}$ $p19^{Arf-/-}$ multipotent progenitors. *Nature* **453,** 228–232 (2008).
35. Clevers, H. Wnt/β-catenin signaling in development and disease. *Cell* **127,** 469–480 (2006).
36. Barker, N. *et al.* Crypt stem cells as the cells-of-origin of intestinal cancer. *Nature* **457,** 608–611 (2009).
Using lineage-tracing studies, this paper demonstrates that colonic stem cells can act as the cell of origin for colon cancer. See also references 37 and 38.
37. Zhu, L. *et al.* Prominin 1 marks intestinal stem cells that are susceptible to neoplastic transformation. *Nature* **457,** 603–607 (2009).
38. Sangiorgi, E. & Capecchi, M. R. *Bmi1* is expressed *in vivo* in intestinal stem cells. *Nature Genet.* **40,** 915–920 (2008).
39. Barker, N. *et al.* $Lgr5^{+ve}$ stem cells drive self-renewal in the stomach and build long-lived gastric units *in vitro*. *Cell Stem Cell* **6,** 25–36 (2010).
40. Holland, E. C. *et al.* Combined activation of Ras and Akt in neural progenitors induces glioblastoma formation in mice. *Nature Genet.* **25,** 55–57 (2000).
41. Alcantara Llaguno, S. *et al.* Malignant astrocytomas originate from neural stem/progenitor cells in a somatic tumor suppressor mouse model. *Cancer Cell* **15,** 45–56 (2009).
42. Marumoto, T. *et al.* Development of a novel mouse glioma model using lentiviral vectors. *Nature Med.* **15,** 110–116 (2009).
43. Merkle, F. T., Mirzadeh, Z. & Alvarez-Buylla, A. Mosaic organization of neural stem cells in the adult brain. *Science* **317,** 381–384 (2007).
44. Jacques, T. S. *et al.* Combinations of genetic mutations in the adult neural stem cell compartment determine brain tumour phenotypes. *EMBO J.* **29,** 222–235 (2010).
45. Wang, Y. *et al.* Expression of mutant p53 proteins implicates a lineage relationship between neural stem cells and malignant astrocytic glioma in a murine model. *Cancer Cell* **15,** 514–526 (2009).
46. Bachoo, R. M. *et al.* Epidermal growth factor receptor and *Ink4a/Arf*: convergent mechanisms governing terminal differentiation and transformation along the neural stem cell to astrocyte axis. *Cancer Cell* **1,** 269–277 (2002).
47. Bruggeman, S. W. *et al.* Bmi1 controls tumor development in an Ink4a/Arf-independent manner in a mouse model for glioma. *Cancer Cell* **12,** 328–341 (2007).
48. Schuller, U. *et al.* Acquisition of granule neuron precursor identity is a critical determinant of progenitor cell competence to form Shh-induced medulloblastoma. *Cancer Cell* **14,** 123–134 (2008).
This study demonstrates that descendants of stem cells can act as crucial cellular targets of transformation. See also reference 49.
49. Yang, Z. J. *et al.* Medulloblastoma can be initiated by deletion of *Patched* in lineage-restricted progenitors or stem cells. *Cancer Cell* **14,** 135–145 (2008).
50. Sutter, R. *et al.* Cerebellar stem cells act as medulloblastoma-initiating cells in a mouse model and a neural stem cell signature characterizes a subset of human medulloblastomas. *Oncogene* **29,** 1845–1856 (2010).
51. Gibson, P. *et al.* Subtypes of medulloblastoma have distinct developmental origins. *Nature* **468,** 1095–1098 (2010).
52. Joseph, N. M. *et al.* The loss of *Nf1* transiently promotes self-renewal but not tumorigenesis by neural crest stem cells. *Cancer Cell* **13,** 129–140 (2008).
53. Zheng, H. *et al.* Induction of abnormal proliferation by nonmyelinating Schwann cells triggers neurofibroma formation. *Cancer Cell* **13,** 117–128 (2008).
54. Wang, X. *et al.* A luminal epithelial stem cell that is a cell of origin for prostate cancer. *Nature* **461,** 495–500 (2009).
This report establishes a new luminal stem cell as a target of prostate carcinogenesis and indicates a hierarchy of stem cells in this tissue.
55. Leong, K. G., Wang, B. E., Johnson, L. & Gao, W. Q. Generation of a prostate from a single adult stem cell. *Nature* **456,** 804–808 (2008).
56. Ma, X. *et al.* Targeted biallelic inactivation of *Pten* in the mouse prostate leads to prostate cancer accompanied by increased epithelial cell proliferation but not by reduced apoptosis. *Cancer Res.* **65,** 5730–5739 (2005).
57. Korsten, H., Ziel-van der Made, A., Ma, X., van der Kwast, T. & Trapman, J. Accumulating progenitor cells in the luminal epithelial cell layer are candidate tumor initiating cells in a *Pten* knockout mouse prostate cancer model. *PLoS ONE* **4,** e5662 (2009).
58. Mulholland, D. J. *et al.* $Lin^{-}Sca\text{-}1^{+}CD49f^{high}$ stem/progenitors are tumor-initiating cells in the *Pten*-null prostate cancer model. *Cancer Res.* **69,** 8555–8562 (2009).
59. Lawson, D. A. *et al.* Basal epithelial stem cells are efficient targets for prostate cancer initiation. *Proc. Natl Acad. Sci. USA* **107,** 2610–2615 (2010).
60. Goldstein, A. S., Huang, J., Guo, C., Garraway, I. P. & Witte, O. N. Identification of a cell-of-origin for human prostate cancer. *Science* **329,** 568–571 (2010).
This study demonstrates through transduction of isolated cell subsets that basal stem/progenitor cells are an important target cell.
61. Foulkes, W. D. *BRCA1* functions as a breast stem cell regulator. *J. Med. Genet.* **41,** 1–5 (2004).
62. Turner, N., Tutt, A. & Ashworth, A. Hallmarks of 'BRCAness' in sporadic cancers. *Nature Rev. Cancer* **4,** 814–819 (2004).
63. Molyneux, G. *et al. BRCA1* basal-like breast cancers originate from luminal

epithelial progenitors not from basal stem cells. *Cell Stem Cell* **7,** 403–417 (2010).
This study provides *in vivo* functional evidence that luminal progenitors rather than basal cells are an important target in the genesis of *BRCA1*-associated breast tumours.
64. Liu, S. *et al.* BRCA1 regulates human mammary stem/progenitor cell fate. *Proc. Natl Acad. Sci. USA* **105,** 1680–1685 (2008).
65. Bouras, T. *et al.* Notch signaling regulates mammary stem cell function and luminal cell-fate commitment. *Cell Stem Cell* **3,** 429–441 (2008).
66. Lee, C. W. *et al.* A functional *Notch–survivin* gene signature in basal breast cancer. *Breast Cancer Res.* **10,** R97 (2008).
67. Vaillant, F. *et al.* The mammary progenitor marker CD61/β3 integrin identifies cancer stem cells in mouse models of mammary tumorigenesis. *Cancer Res.* **68,** 7711–7717 (2008).
68. Prat, A. *et al.* Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer. *Breast Cancer Res.* **12,** R68 (2010).
69. Gidekel Friedlander, S. Y. *et al.* Context-dependent transformation of adult pancreatic cells by oncogenic K-Ras. *Cancer Cell* **16,** 379–389 (2009).
70. De La, O. J. *et al.* Notch and Kras reprogram pancreatic acinar cells to ductal intraepithelial neoplasia. *Proc. Natl Acad. Sci. USA* **105,** 18907–18912 (2008).
71. Habbe, N. *et al.* Spontaneous induction of murine pancreatic intraepithelial neoplasia (mPanIN) by acinar cell targeting of oncogenic Kras in adult mice. *Proc. Natl Acad. Sci. USA* **105,** 18913–18918 (2008).
72. Youssef, K. K. *et al.* Identification of the cell lineage at the origin of basal cell carcinoma. *Nature Cell Biol.* **12,** 299–305 (2010).
73. Owens, D. M. & Watt, F. M. Contribution of stem cells and differentiated cells to epidermal tumours. *Nature Rev. Cancer* **3,** 444–451 (2003).
74. Bonnet, D. & Dick, J. E. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. *Nature Med.* **3,** 730–737 (1997).
The first report indicating that early stem/progenitor cells are targeted for transformation in AML.
75. Ricci-Vitiani, L. *et al.* Identification and expansion of human colon-cancer-initiating cells. *Nature* **445,** 111–115 (2007).
76. O'Brien, C. A., Pollett, A., Gallinger, S. & Dick, J. E. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. *Nature* **445,** 106–110 (2007).
77. Kim, C. F. *et al.* Identification of bronchioalveolar stem cells in normal lung and lung cancer. *Cell* **121,** 823–835 (2005).
78. Curtis, S. J. *et al.* Primary tumor genotype is an important determinant in identification of lung cancer propagating cells. *Cell Stem Cell* **7,** 127–133 (2010).
79. Zhang, L. *et al.* Chemoprevention of colorectal cancer by targeting APC-deficient cells for apoptosis. *Nature* **464,** 1058–1061 (2010).
80. Martin, S. A. *et al.* DNA polymerases as potential therapeutic targets for cancers deficient in the DNA mismatch repair proteins MSH2 or MLH1. *Cancer Cell* **17,** 235–248 (2010).
81. Forbes, J. F. *et al.* Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol.* **9,** 45–53 (2008).
82. Asselin-Labat, M. L. *et al.* Control of mammary stem cell function by steroid hormone signalling. *Nature* **465,** 798–802 (2010).
83. Ashworth, A. Drug resistance caused by reversion mutation. *Cancer Res.* **68,** 10021–10023 (2008).
84. Tutt, A. *et al.* Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial. *Lancet* **376,** 235–244 (2010).
85. Lindberg, N., Kastemar, M., Olofsson, T., Smits, A. & Uhrbom, L. Oligodendrocyte progenitor cells can act as cell of origin for experimental glioma. *Oncogene* **28,** 2266–2275 (2009).

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