

Lineage dependency and lineage-survival oncogenes in human cancer

Levi A. Garraway^{*†§||¶} and William R. Sellers^{*#}

Abstract | Although cell-lineage and differentiation models dominate tumour classification and treatment, the recognition that cancer is also a genomic disease has prompted a reconfiguration of cancer taxonomies according to molecular criteria. Recent evidence indicates that a synthesis of lineage-based and genetic paradigms might offer new insights into crucial and therapeutically pliable tumour dependencies. For example, *MITF* (microphthalmia-associated transcription factor), which is a master regulator of the melanocyte lineage, might become a melanoma oncogene when deregulated in certain genetic contexts. *MITF* and other lineage-survival genes therefore implicate lineage dependency (or lineage addiction) as a newly recognized mechanism that is affected by tumour genetic alterations.

In recent years there has been tremendous progress towards a detailed characterization of genetic alterations that underlie many human tumour types. The effect of array-based technologies that profile global gene expression and chromosomal variations raises the possibility that a widespread reclassification of human cancers according to genetic criteria might emerge within the next few decades. If so, the main challenge will be to discern essential cellular dependencies that are perturbed by tumour genetic lesions, and to link these to rational therapeutic intervention¹.

Progress might benefit from looking again at hallmark processes that operate in normal cellular counterparts during development and differentiation. The emergence of tumour cells from non-transformed precursors is the output of a complex interplay between genetics, epigenetics and cell lineage. Towards this end, recent evidence indicates that overlaying lineage development and survival information with knowledge of cancer genetic perturbations might reveal new insights into tumour biology. In particular, cellular dependencies that are imprinted during lineage development might both shape the range of tumour genetic alterations and reveal a distinct class of lineage-associated cancer genes.

Cell-lineage models for human carcinogenesis

Frameworks for cancer pathophysiology and treatment incorporate multiple paradigms that are based on distinct types of scientific evidence. Accordingly, several overlapping but contrasting hypotheses that have been developed over the past few decades purport

to explain the range of human carcinogenesis (TABLE 1). Implicit in each of these models is the notion that cancer biology is linked to and influenced by the lineage and differentiation states of tumour precursor (stem) cells (BOX 1). Although they overlap to a certain extent, each hypothesis that is shown in TABLE 1 highlights a distinct explanatory model of cancer biology with important treatment implications. For example, the efficacy of all-trans retinoic acid (ATRA) in acute promyelocytic leukaemia (APL) relates in part to the differentiation and maturation hypothesis that is commonly applied to haematological malignancies². APL consists of neoplastic cells that are aberrantly blocked in the promyelocytic stage of myeloid differentiation. Treatment with ATRA restores a normal myeloid differentiation programme by displacing the *PML* (promyelocytic leukaemia)–*RARA* (retinoic acid receptor α) fusion oncoprotein that drives APL carcinogenesis³.

Lineage models also constitute the *de facto* clinical approach to many solid tumours, in part because of the organ-specific developmental history that is associated with these cancer types. From a treatment standpoint, a lung adenocarcinoma represents an entirely separate disease entity from an adenocarcinoma of another tissue type, such as colon adenocarcinoma or breast adenocarcinoma. Lineage-specific endocrine dependencies guide therapeutic approaches in breast cancer and prostate cancer, which frequently require hormonal blockade to effect tumour regression. Biological differences that segregate with lineage might also define selective (though poorly understood) vulnerabilities to

^{*}Department of Medical Oncology, [†]Melanoma Program in Medical Oncology and [§]Center for Cancer Genome Discovery, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, USA.

^{||}Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.

[¶]The Broad Institute of Harvard and MIT, Cambridge, Massachusetts 02141, USA.

[#]Novartis Institutes for Biomedical Research Inc., Cambridge, Massachusetts 02139, USA.

Correspondence to L.A.G. e-mail: levi_garraway@dfci.harvard.edu
doi:10.1038/nrc1947

At a glance

- The close association between cell lineage and cancer phenotype has long been recognized. This link raises the possibility that cellular mechanisms that govern lineage proliferation and survival during development might also underlie tumorigenic mechanisms.
- Many somatic genetic alterations show lineage-restricted patterns across human tumours, which indicates that genetic changes in cancer might be conditioned by the lineage programmes that are embedded in tumour precursor cells.
- A convergence of lineage-based and genetic observations gives rise to a lineage-dependency (or lineage-addiction) model of human cancer, wherein tumour cells depend crucially on survival mechanisms that are programmed into lineage precursor cells during development, which might be affected by acquired genetic alterations. Unlike oncogene addiction, which invokes a dependency on a tumour-specific gain-of-function event, lineage addiction involves the persistence and/or deregulation of crucial lineage-survival mechanisms during carcinogenesis or tumour progression.
- Presumably, lineage-dependency mechanisms that promote tumour progression involve master regulatory genes that also exert key developmental survival roles. Such genes can be termed lineage-survival oncogenes.
- MITF (microphthalmia-associated transcription factor) and the androgen receptor are prototype lineage-survival oncogenes in melanoma and prostate cancer, respectively. A review of the scientific literature readily identifies several more genes with presumptive or predicted lineage-survival functions in different cancers.
- Recognition of the lineage-dependency model might expand existing paradigms for tumour biology by emphasizing the importance of lineage in shaping key oncogenic mechanisms, thereby offering an explanatory framework for the distribution of genetic alterations in cancer. Targeting lineage dependencies as well as classical gain-of-function events might require combinatorial or synthetic-lethal therapeutic approaches to cancer.

conventional cytotoxic agents. Primitive neuroectodermal tumours and germ-cell tumours exemplify this point; these cancers tend to be much more chemoresponsive than those of many other lineages, so chemotherapy figures prominently in the treatment approaches that are applied.

Lineage specification in development and cancer

The intimate association between cell lineage and tumorigenesis has guided cancer classification for well over a century. Histopathologists have long noted the phenotypic resemblance in growth and migratory properties between many tumour cells and embryonal cells; indeed, cancer classification schemas in current use derive heavily from this recognition^{4,5}. Embedded in development-oriented cancer taxonomies is a molecular assumption that tumours must (aberrantly) elaborate various cellular mechanisms that function in their ancestral precursor cells. A related notion underlies the epithelial-to-mesenchymal transition (EMT), which invokes a commonality between migratory mechanisms that operate in development and those that operate in the tumour metastatic process^{6,7}. According to the EMT model, tumours acquire metastatic potential in part through ectopic expression of mesenchymal

components that function during embryogenesis. By extension, tumour cells might co-opt many further normal developmental pathways for functions that are linked to tumour progression^{8,9}.

Even a cursory survey of embryological mechanisms reveals a rich potential for convergence between cell lineage and tumour survival. In particular, two deeply interwoven molecular phenomena guide vertebrate development: genome-wide chromatin remodelling¹⁰ and temporal, coordinated actions of transcription factors that direct lineage-associated gene-expression programmes^{11–13} (FIG. 1). Regarding the former, histone modifications, DNA methylation and ATP-dependent nucleosomal repositioning constitute well-known epigenetic remodelling mechanisms^{14–18}. Together, these processes conduct sequential gene activation patterns that are characteristic of axis formation, body segmentation and subsequent lineage differentiation. The gene-expression reprogramming that is associated with chromatin remodelling is governed initially by factors such as Polycomb- or Trithorax-group proteins¹⁹ and Hox transcriptional regulators, which control pattern formation during development²⁰. Subsequently, other transcription-factor subtypes predominate, depending on the progenitor cell types. On establishment of relevant progenitor lineages, the ensuing processes of tissue formation and cell maturation require environmentally induced as well as cell-autonomous migration, proliferation and survival processes. Apoptosis has a key role in defining the morphology of tissues and in cell-lineage formation at various points in development.

The above observations indicate that a detailed examination of lineage-associated tumour-survival properties might reveal novel and clinically pertinent tumour mechanisms. Indeed, several lines of evidence support a lineage-dependency model for tumorigenesis. First, lineage-restricted genetic or epigenetic alterations in chromatin-remodelling proteins such as *SNF5* (also known as integrase interactor 1 and SWI/SNF-related,

Table 1 | **Lineage-based models for human carcinogenesis**

Model	Definition	Example
Differentiation hypothesis	Cancer as a maturation or differentiation abnormality	Acute leukaemias
Tissue-lineage hypothesis	Malignant transformation of characteristic cells from distinct tissue types	Lung versus breast adenocarcinoma
Embryological hypothesis	Malignant transformation of embryologically distinct cell types	Carcinoma versus sarcoma
Cell-lineage hypothesis	Malignant transformation of histologically distinct cell types	Squamous-cell carcinoma versus adenocarcinoma

Box 1 | Tumour stem cells

Tumour stem cells are a proposed subpopulation of cells within a given tumour that have: an unlimited replicative potential; the capacity to regenerate the complete range of malignant cells that are present in an individual tumour when explanted; and a high degree of resistance to conventional chemotherapy^{87,100,101}. Tumour stem cells could in principle be transformed adult stem cells (or related lineage precursor cells), as by definition these cells also possess self-renewal and differentiation abilities. On the other hand, immortalization and resistance to apoptosis might also occur *de novo* as a result of genetic and epigenetic alterations that direct carcinogenesis; therefore, many tumour precursor cells might be predicted to harbour a stem-cell phenotype regardless of the cell of origin.

matrix-associated, actin-dependent regulator of chromatin B1) and the **BMI1** oncoprotein occur either causally or in strong association with tumour progression and metastasis^{21–26}. Second, deregulated expression of many transcription factors that govern pattern formation and lineage development also occurs in association with tumorigenesis^{27,28}. Moreover, a recent comparison of tumour-derived gene-expression patterns with those from corresponding normal developmental lineage precursors indicated that recapitulation of lineage developmental programmes might comprise a general molecular property that is characteristic of many diverse solid tumour types²⁹. Collectively, these observations imply that a defined molecular repertoire that is established through developmental programming might comprise the ‘universe’ of putative effectors that are available to a given tumour stem cell. If so, we might expect to observe a primarily lineage-restricted pattern of cancer mechanisms across human tumours. Moreover, lineage-survival factors that operate in the normal setting might

be exploited as key oncogenic dependencies during carcinogenesis and tumour progression.

Conditioning of somatic genetics by lineage

Lineage-oriented views of cancer biology stand in contrast to mechanistic models in current use^{4,30}. Much evidence from the past three decades has firmly established that tumour-cell evolution involves an accumulation of genetic alterations that activate oncogenes and inactivate tumour-suppressor genes. Accordingly, recent genome-era advances have precipitated the widespread application of high-throughput methods to characterize human cancer on a global scale^{31,32}. Therefore, the notion of cancer as a fundamentally genetic disease might eclipse the lineage paradigms articulated above.

At the same time, it has long been apparent that lineage exerts a substantial effect on the distribution of genetic alterations in tumours. A survey of several well-known oncogenes illustrates this point, as shown in FIG. 2. Activating point mutations in Ras family, **BRAF**, **EGFR** (which encodes epidermal growth factor receptor 1) and **PIK3CA** (which encodes phosphatidylinositol 3-kinase catalytic subunit- α) oncogenes tend to occur at high frequencies in a few discrete lineages, such that their overall prevalence is attributable to a relatively small number of tumour types. Even the location of the activating base mutations within a given oncogene might vary markedly according to tumour lineage, as exemplified by Ras family mutations³³. Lineage-restricted somatic mutation patterns therefore constitute a prominent feature of genetic changes in cancer. By contrast, the tumour-suppressor genes **CDKN2A** (which encodes cyclin-dependent-kinase inhibitor 2A) and **TP53** seem to exemplify lineage-independent mutation patterns, consistent with the universal cell-cycle gatekeeper functions of the proteins that they encode (FIG. 2b). However, even in these cases, mechanisms of inactivation might vary by lineage. For example, loss-of-function mutations that directly affect **TP53** occur infrequently in melanomas compared with other lineages; instead, deletion that involves the **INK4a/ARF** locus might serve the same purpose in these tumours^{34,35}. These observations support the general premise that many essential tumour dependencies reflect an interplay between genetic alterations and the lineage specification that is wired into the relevant progenitor cells (FIG. 1).

Like the point mutations in oncogenes that are described above, ‘macro-genomic’ alterations (such as large DNA amplifications, deletions or translocations) also might show lineage-restricted alterations in human cancer. Haematological malignancies contain the clearest examples of this phenomenon; balanced translocations that define distinct molecular subtypes of leukaemia and lymphoma segregate exquisitely according to tumour cell lineage. Amplifications in **CCND1** (which encodes cyclin D1), **ERBB2** (also known as **HER2**) and **EGFR** also show lineage-restricted alterations^{36–40} (FIG. 2). Our group has used high-density single-nucleotide polymorphism (SNP) arrays (BOX 2) to map genomic copy-number and loss of heterozygosity (LOH) changes at high resolution for a large collection of human tumours and cancer cell

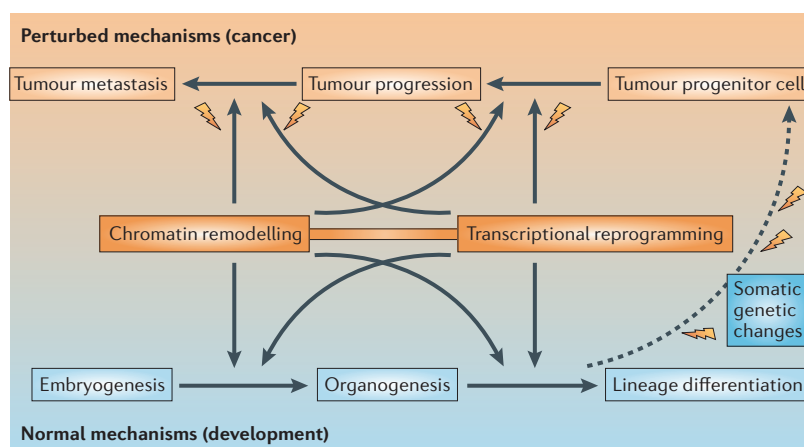


Figure 1 | Aberrant lineage ontogeny and somatic genetics in human tumour formation. Cardinal developmental processes such as chromatin remodelling and specific transcriptional programmes embed lineage-restricted proliferation and survival mechanisms that direct tumour formation in the relevant precursor cells. Somatic genetic alterations that lead to cancer (indicated schematically by lightning) might therefore be influenced (or ‘conditioned’) by the cell or tissue lineage.

lines^{41,42}. When hierarchical clustering algorithms were applied to the chromosomal copy-number data that was generated by SNP array hybridization, many cancer cell

lines and tumour samples clustered according to tissue of origin, which is consistent with lineage-driven genetic perturbations^{41,43}. Collectively, these observations indicate that somatic cancer genetics is commonly 'conditioned' by tumour lineage. Therefore, global surveys of chromosomal alterations that are present in both tumour samples and appropriate model systems (such as cell lines, short-term cultures and xenografts) might provide a means to characterize lineage-associated cancer genes that are affected by genetic lesions.

Lineage addiction as a tumour dependency

A synthesis of the lineage-dependency hypothesis and the genome-centred view of cancer suggests that lineage-survival pathways might operate aberrantly during carcinogenesis and tumour progression, often as a result of genomic alterations. In this view, many tumours might rely crucially on (or be addicted to) hallmark proliferation or survival programmes that are embedded through development within normal lineage precursor cells. The lineage-dependency model (FIG. 1) therefore offers a counterpoint to oncogene addiction⁴⁴, in which cellular signals that are activated in tumour cells but absent in corresponding normal tissue elicit aberrant proliferative and/or anti-apoptotic effects on which tumour cells become excessively dependent. The biological and therapeutic relevance of oncogene addiction has been shown in studies of the *BCR-ABL* fusion oncoprotein in chronic myelogenous leukaemia, activating mutations in the *KIT* oncogene in **gastrointestinal stromal tumours**, and *EGFR* mutations in non-small-cell lung cancer subsets⁴⁵⁻⁴⁸. By contrast, the lineage-addiction theory does not require the gain of a new and tumour-specific cellular function, but instead posits the persistence and deregulation of survival mechanisms that operate during normal lineage development. Therefore, although both models invoke an unusual tumour reliance on key cellular dependencies, the origin of and basis for such dependencies differs significantly between the two models.

Contrasting the oncogene and lineage addiction models also allows predictions about the types of oncogene that are expected to provide the relevant cellular effects. Each of the best-known examples of oncogene addiction that are mentioned above involves so-called classical oncogenes — growth-promoting genes (often tyrosine kinases) that have undergone activating somatic mutations that confer a transformed phenotype in well-established experimental assays (such as loss of contact inhibition, induction of anchorage independence in NIH 3T3 cells and tumour formation in nude mice). Where present, lineage addiction might instead involve deregulated expression of master genes that mediate normal (and essential) developmental lineage functions. Although such effectors might include some classical oncogenes, in most cases lineage addiction will probably use a distinct class of cancer genes that have the biological properties that are outlined in BOX 3. We call such genes lineage-survival oncogenes, and speculate that many transcription factors and signalling proteins

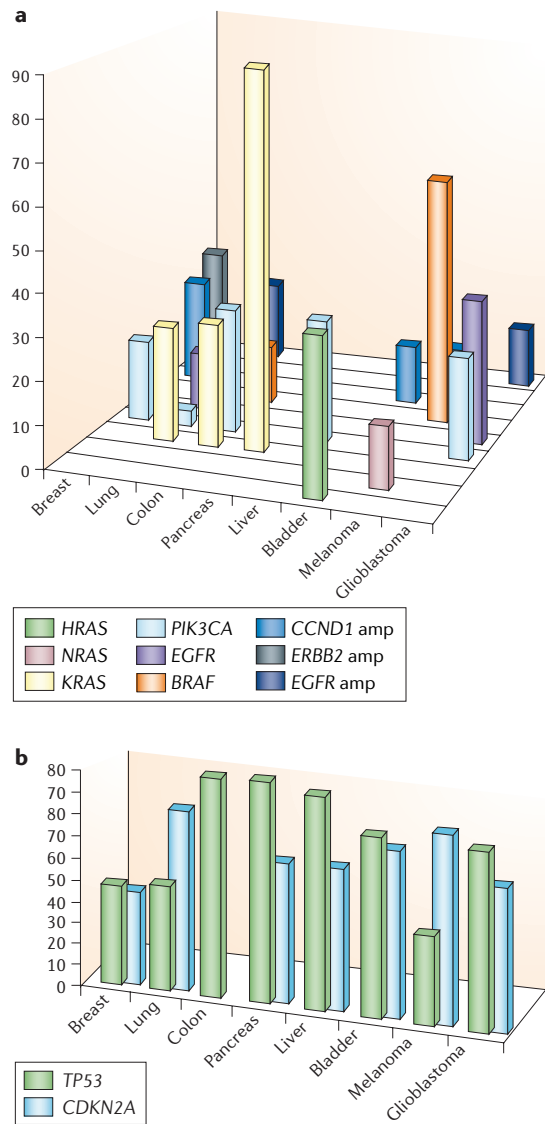


Figure 2 | Lineage-restricted patterns of activating oncogene mutations in human solid tumours.
a | An analysis of activating oncogene mutations across selected solid tumour lineages shows that the cell or tissue lineage has a dominant influence on mutation frequency (Y axis), even within a gene family (as shown for Ras genes). 'Amp' denotes high-level gene amplification; all other mutations indicated are point mutations. **b** | By contrast, some gatekeeper tumour-suppressor genes tend mainly to have lineage-independent patterns of somatic inactivation, though the mechanism of inactivation varies according to lineage. Frequency estimates were derived from the literature and the COSMIC database. *CCND1*, the gene that encodes cyclin D1; *CDKN2A*, the gene that encodes cyclin-dependent-kinase inhibitor 2A; *EGFR*, the gene that encodes epidermal-growth-factor receptor; *ERBB2*, also known as *HER2*; *PIK3CA*, the gene that encodes phosphatidylinositol 3-kinase catalytic subunit- α ; *TP53*, the gene that encodes tumour suppressor p53.

Box 2 | Single-nucleotide polymorphism (SNP) microarrays

SNP microarrays are oligonucleotide microarray tools for genome characterization. They contain DNA oligonucleotide probes that can determine the allele status (for example, homozygosity or heterozygosity) at hundreds of thousands of SNP loci in parallel, following hybridization of patient-derived genomic DNA. Although originally developed for large-scale genetic association studies, SNP arrays also provide a robust tool for cancer-genome mapping^{102,103}. The high SNP marker density (combined with SNP-specific minor-allele frequencies) enables the inference of genomic regions that have undergone loss of heterozygosity even when data from matched normal samples are unavailable¹⁰⁴. In addition, the signal intensities that result from tumour DNA hybridization provide a measurement of the chromosomal copy number at these same SNP loci when referenced to data from a collection of normal diploid controls¹⁰⁵ (similar to array-based comparative genomic hybridization technologies). The current generation of **Affymetrix** SNP array sets can genotype >500,000 SNP alleles in parallel.

p16–CDK4–RB pathway

A vital cell-cycle checkpoint that operates in mammalian cells. The p16 protein (encoded by *CDKN2A*) is a well-characterized cell-cycle inhibitor, and the RB (Retinoblastoma) protein was one of the first tumour suppressors to be described.

that operate during development might underlie the associated cellular dependencies in tumours from a wide range of lineages.

MITF as a prototype lineage-survival oncogene

Further insights into lineage addiction and associated oncogenes might derive from a closer inspection of particular cell lineages. Maturation and survival of the melanocyte lineage is an informative process in this regard. Neural-crest cells, which are the archetypal melanocyte precursors, are controlled by coordinated transcription-factor programmes that involve **SOX9** (SRY-box 9), **SOX10**, **FOXD3** (forkhead box D3), **Id** (inhibitor of DNA binding) proteins and **SNAI2** (also known as SLUG), among others^{9,49}. Crucially, the master transcriptional regulator **MITF** (microphthalmia-associated transcription factor) has a decisive role in both differentiation and survival of the melanocyte lineage^{50–52}. Therefore, the success of this lineage depends crucially on proliferative and survival signals that converge on and are mediated by MITF function. Recently, integrated genetic studies revealed that **MITF** undergoes amplification in 15–20% of metastatic melanomas³⁴. Functional assays demonstrated that MITF cooperates with activated **BRAF^{V600E}** to transform immortalized human melanocytes. Importantly, this transforming capacity of MITF was only manifest in the context of aberrant mitogen-activated protein kinase (MAPK) pathway activation (set up through **BRAF^{V600E}** co-expression) and cell-cycle deregulation, which is mediated in part through p16–CDK4 (cyclin-dependent kinase 4)–RB pathway inactivation. By directing melanocyte lineage survival during development and promoting tumorigenesis in a subset of melanomas as a result of genetic alterations, MITF therefore seems to function as a lineage-survival oncogene⁵³.

Further elucidation of the MITF contribution to melanoma genesis might also show how a tumour lineage dependency might condition the range of associated genetic alterations, as described above. Towards this end, MITF is known to have two fundamental roles in melanocyte development: regulation of the melanocyte differentiation programme, which is associated with growth arrest; and melanocyte lineage survival, which might involve both proliferative (through **CDK2**)⁵⁴ and anti-apoptotic (through **BCL2** (B-cell lymphoma 2))⁵⁵ mechanisms. In the subset of melanomas in which MITF has an oncogenic lineage-survival function, its melanocyte differentiation function is presumably dispensable and possibly even detrimental because of the growth arrest that follows. Therefore, it seems that MITF-dependent melanomas must undergo further genetic or epigenetic alterations to inactivate key growth-inhibitory mechanisms that function in fully differentiated melanocytes.

In this regard, MITF-induced growth arrest in melanocytes seems to involve the p16 (encoded by *CDKN2A*) and/or **RB** (Retinoblastoma) proteins^{56,57}, and melanocytes that escape this MITF-mediated arrest show loss of p16 expression⁵⁶. Deletion or silencing of *CDKN2A* also occurs commonly in melanoma (FIG. 2b), leading to RB inactivation and therefore a substantial lesion to a crucial cell-cycle checkpoint⁵⁸. MITF-dependent melanomas should also require constitutive MAPK pathway activation as an **ERK** (extracellular signal-regulated kinase)-dependent phosphorylation event is necessary for MITF transactivation⁵⁹. To this end, it is now well-recognized that most cutaneous melanomas contain activating somatic mutations in **NRAS** or **BRAF**, which encode two key MAPK signalling proteins^{32,60,61}. Arguably, genetic alterations that lead to both p16 loss and constitutive MAPK activation provide a favourable context for an melanoma MITF dependency to emerge. The lineage-dependency model might therefore help to explain why these specific genetic alterations occur so much more frequently in melanoma than in other tumour types.

Lineage-survival oncogenes in other cancers

A review of the literature with the above principles in mind identifies several more genes that probably have oncogenic lineage-survival roles in human tumours. Selected examples of putative lineage-survival oncogenes are listed in TABLE 2. The androgen receptor (**AR**) is an informative example: like MITF in the melanocyte lineage, this transcription factor is required for the development and survival of the prostate epithelial lineage⁶². Prostate luminal differentiation requires AR and leads to cell growth arrest after a defined period of epithelial proliferation⁶³. However, ectopic AR expression in prostate epithelial cells that have been engineered to have inactivated RB and p53 cell-cycle checkpoints makes these cells able to form tumours following orthotopic injection and androgen stimulation in nude mice⁶⁴. So, both MITF and AR function as master transcriptional regulators of development and/or survival in their respective lineages, but might also have oncogenic roles

Box 3 | Predicted properties of lineage survival oncogenes

- Crucial role(s) in normal lineage proliferation and/or survival during development
- Persistent or deregulated expression in cancers of the associated lineage
- Affected by somatic genetic alterations in tumour subsets
- Required for tumour survival and/or progression
- Are more likely to be lineage-associated transcription factors than signalling proteins

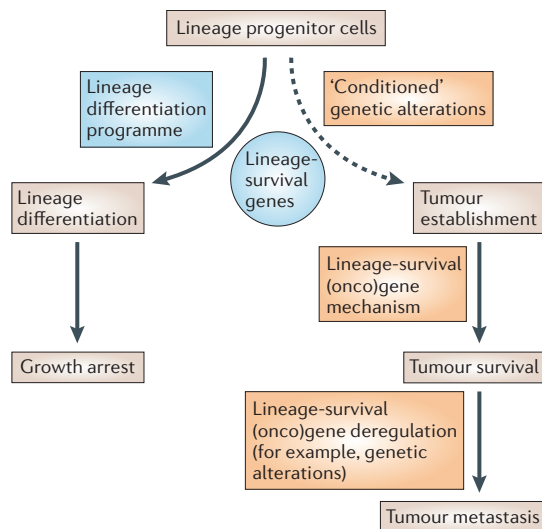


Figure 3 | A lineage-dependency model for human cancer. During development, master regulatory genes can have crucial roles within the tissue or organ progenitor cells to mediate lineage survival and subsequent cell differentiation (left). Lineage-survival mechanisms that are elicited by these genes can influence (or ‘condition’) the range of tumour genetic alterations that are observed in particular tumour types while also exerting their own oncogenic functions in certain genetic contexts (right). During tumour progression, these lineage-survival oncogenes can become deregulated through genetic or epigenetic alterations.

in certain genetic contexts. Moreover, both of these factors can be affected by genetic alterations in association with advancing malignancy, which supports the notion that certain tumours maintain their lineage dependence on these factors throughout disease progression.

Though not exhaustive, TABLE 2 also highlights several more transcription factors and other effector proteins that might function as lineage-survival oncogenes

on the basis of the criteria that are outlined in BOX 3. The well-characterized cyclin D1 oncoprotein undergoes frequent gene amplification in subsets of breast cancers. Cyclin D1 promotes the cell cycle, but also controls the final stages of mammary gland maturation that occur during pregnancy^{65–67}, which indicates a concomitant mammary lineage dependency. The gene that encodes *FLT3* (FMS-related tyrosine kinase 3) also has several properties of lineage-survival oncogenes; *FLT3* is a receptor tyrosine kinase that directs myeloid lineage maturation, and the gene also harbours somatic point mutations in a significant fraction of acute myeloid leukaemias^{47,68,69,106}.

As large-scale efforts to characterize somatic genetic alterations in tumours continue, the list of lineage-survival oncogenes should continue to expand. Already, there are several other genes, the functions of which indicate a lineage-survival mechanism that could also promote carcinogenesis, although they have not yet been shown to be affected by somatic genetic alterations (TABLE 2). The oestrogen receptor (ER), which is encoded by *ESR1*, provides a provocative example: this transcription factor has key roles in breast development that are analogous to those of AR in prostate^{70,71}; however, *ESR1* has not been shown convincingly to undergo somatic genetic alterations in breast cancer. This gender discrepancy suggests that other cellular means might suffice to effect ER deregulation in the subset of breast tumours that have an oestrogen-sensitive dependency. In support of this, gene amplification of ER transcriptional cofactors has been observed in breast and ovarian cancer^{72,73}.

The thyroid transcription factor 1 homeodomain protein (*TITF1*)⁷⁴ (TABLE 2) is an appealing candidate lineage-survival oncogene in lung cancer. This DNA-binding protein is required for both thyroid and lung development, and is highly expressed in small-cell lung cancers and lung adenocarcinomas^{75,76}; indeed, *TITF1* is a useful histological marker in the differential diagnosis of primary pulmonary (versus non-pulmonary) neoplasms⁷⁷. The caudal-type homeobox transcription

Table 2 | Predicted lineage-survival oncogenes

Gene	Lineage	Function	Genetic alterations?	Existing or possible therapeutics
<i>MITF</i>	Melanocytic	Transcription factor	Yes	Antisense <i>BCL2</i>
<i>AR</i>	Prostate	Transcription factor	Yes	Hormone therapy
<i>CCND1</i>	Mammary	Cell-cycle regulator, transcription factor	Yes	CDK inhibitors
<i>FLT3</i>	Myeloid	Receptor tyrosine kinase	Yes	<i>FLT3</i> inhibitors
<i>ESR1</i>	Mammary	Transcription factor	Yes, in co-activators	Hormone therapy
<i>TITF1</i>	Lung	Transcription factor	No	?
<i>CDX1</i>	Intestine	Transcription factor	No	?
Ets oncogenes	Prostate, mammary, other	Transcription factors	Yes (prostate)	?

AR, the gene that encodes the androgen receptor; *BCL2*, B-cell lymphoma 2; *CCND1*, the gene that encodes cyclin D1; *CDX1*, the gene that encodes caudal-type homeobox transcription factor 1; *ESR1*, the gene that encodes oestrogen receptor 1; *FLT3*, the gene that encodes FMS-related tyrosine kinase 3; *MITF*, the gene that encodes microphthalmia-associated transcription factor; *TITF1*, the gene that encodes thyroid transcription factor 1 homeodomain protein.

factor 1 (*CDX1*) is another intriguing candidate⁷⁸; this protein controls intestinal development and differentiation, in which it has also been purported to exert an oncogenic effect⁷⁹. Ongoing cancer-genome mapping should soon establish whether either *TTF1* or *CDX1* is affected by genetic alterations in lung or gastrointestinal cancer subsets, as predicted by the lineage-dependency model.

Although this discussion has focused on oncogenes, several tumour-suppressor genes also have lineage-restricted tumour inactivation patterns. Prominent examples include *APC* (adenomatosis polyposis coli) in colon cancer⁸⁰, *RB* in retinoblastoma⁸¹ and *NFI* in neurofibromatosis⁸². In such cases, distinct cell lineages might either preferentially accumulate genetic hits to these loci or respond differently to loss of the remaining allele. In either scenario, the relevant tumour-suppressor gene might have a dominant inhibitory function within a key growth or survival pathway that is itself governed by the lineage-specific reprogramming mechanisms that are outlined above. Future studies that explore the link between cell lineage and tumour suppression might demonstrate new dependencies that operate in tissue-specific tumorigenesis and maintenance.

Lineage-independent paths to malignancy

The foregoing argument implies that lineage dependency provides a relatively common tumour-promoting mechanism. Theoretically, tumour precursor cells from any lineage, the development and survival of which use certain master regulatory genes, might deregulate such factors through genetic and epigenetic alterations along the path to cancer. At the same time, it is unlikely that lineage dependency provides a universal oncogenic process. For example, although most melanomas maintain *MITF* expression throughout disease progression, many melanomas show *MITF* downregulation in association with advanced or aggressive disease⁸³, which indicates that *MITF* function is dispensable in these cases. Similarly, about 1% of prostate cancers are negative for *PSA* (prostate-specific antigen)⁸⁴. As *PSA* expression is androgen-regulated, this indicates that at least some of these variants might have AR-independent biology. In such cases, carcinogenesis or tumour progression (or both) might have happened in a lineage-independent fashion. Therefore, although the lineage-addiction model might be applicable to many tumour types, it will probably involve only a subset of tumours from each lineage.

It is also tempting to speculate that lineage-independent mechanisms drive the genesis and maintenance of many so-called poorly differentiated cancers⁸⁵. These aggressive malignancies frequently lack the gene-expression programmes that are characteristic of their more differentiated malignant counterparts and of the fully differentiated cell lineages from which they originate⁸⁶. So far, a systematic genomic study of poorly differentiated cancers has not been conducted; however, the lineage conditioning of genetic alterations that are observed in other tumour types might be mainly absent in these tumours if lineage-independent tumour-survival mechanisms predominate. Such data might also

help to resolve a longstanding question of the tumour stem-cell theory⁸⁷: whether tumour precursor cells derive from transformed stem cells themselves or from more differentiated progeny that then attain stem-cell-like properties during carcinogenesis (BOX 1). If poorly differentiated cancers from a given lineage show the same patterns of genetic alterations as their more differentiated counterparts, this might support the notion that they arose from progenitor cells in which a degree of lineage maturation had already occurred.

On the other hand, even highly aggressive and poorly differentiated tumour cells might preserve a lineage memory that reflects their developmental history. This phenomenon was recently demonstrated in an elegant series of experiments in which well or poorly differentiated melanoma cells were injected into chick embryos and observed for their patterns of migration during development⁸⁸. Unlike their more differentiated counterparts, poorly differentiated melanoma cells tracked with neural-crest cells, indicating that these cells remained configured to respond to the inductive signals that directed their developmental ancestors. Moreover, recent evidence from microRNA-profiling studies indicates that the developmental lineages of poorly differentiated tumours are manifest from microRNA-expression profiles even though they are often invisible in mRNA-expression analyses⁸⁹. Therefore, lineage-dependency mechanisms could still operate in some poorly differentiated cancers, though the specific effectors that are involved could reflect a shift 'backwards' in the developmental timeline of the tumour progenitor cells.

Biological and therapeutic implications

Recognition of the lineage-dependency model gives an additional dimension to comparative studies of tumour cells and their non-malignant counterparts. Such investigations often proceed according to an implicit assumption that hallmark cancer mechanisms must show tumour-specificity — for example, through gain-of-function or loss-of-function alterations that generate new cancer-promoting signals exclusively in the tumour progenitor cells. The lineage-dependency model expands the prevailing notion — in which oncogenic factors are typically absent in normal cells and present in tumour cells — to a framework that includes those that are present in normal cells and deregulated in tumour cells. By accommodating expanding evidence that the normal lineage programme might profoundly influence many aspects of tumour progression and metastasis⁹, the lineage-dependency theory emphasizes the continuum between normal processes and malignant tumour-survival processes and also provides a developmental context in which associated genetic and epigenetic changes can be considered.

In this regard, the lineage-dependency model might also deepen understanding of the patterns of somatic alterations that are observed across human cancers. Large-scale cancer-genome characterization efforts have already proved fruitful for cancer gene discovery; ultimately, these approaches should yield a comprehensive catalogue that provides predictive power about the

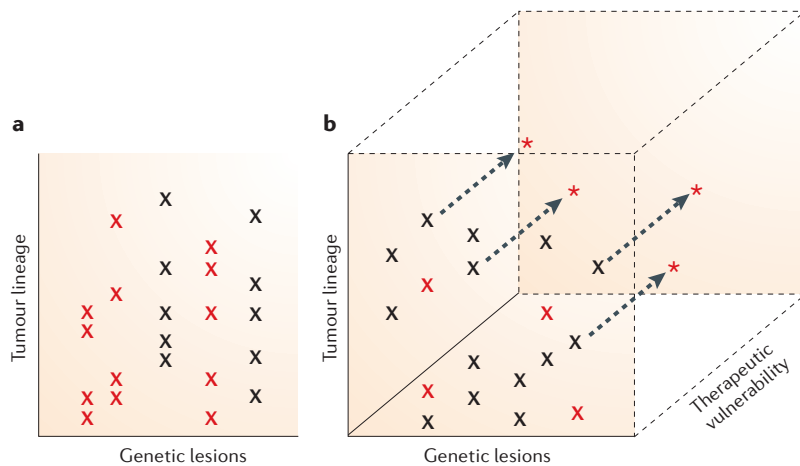


Figure 4 | Therapeutic implications of tumour lineage dependency. Schematic relationship between tumour lineage and genetic alterations in which oncogene addiction (a) or lineage addiction with conditioned genetic alterations (b) predominates. Genetic lesions are depicted across tumour lineages (Xs), including those that confer crucial dependencies (red Xs). In one model, additive gain-of-function oncogenic mutations might yield targetable tumour dependencies irrespective of lineage (a). Such dependencies might be targeted through direct inhibition of the mutated oncoprotein. Alternatively, tumour lineage dependencies might influence whether or not the associated genetic alterations will elicit addiction, and whether this addiction occurs in direct association with (red Xs) or orthogonally to (red asterisks) the relevant alterations (b). Targeting these dependencies might require a combined or 'synthetic lethal' therapeutic strategy.

frequencies of genetic alterations across different tumour types. In the future, knowledge of the underlying tumour lineage dependencies and how they might condition the genetics of individual tumours might also add explanatory power to the relationship between genetics and lineage in human cancer. Conversely, elucidating the cellular effects of tumour-promoting genetic alterations might clarify key mechanisms that operate in normal lineage counterparts during development.

Furthermore, the lineage-addiction model supports an emerging paradigm for targeted therapies that are directed against genetically defined tumours. An extreme interpretation of the oncogene-addiction viewpoint could imply that cancer genesis and maintenance mechanisms might depend on certain cardinal somatic genetic alterations regardless of the lineage in which they occur, as illustrated in FIG. 4. If so, the optimal targeted therapy should involve direct pharmacological inhibition of either the mutated oncoprotein itself or a drug-responsive component of its effector pathway. On the other hand, if a lineage dependency has conditioned the genetic alterations of the tumour, a combined therapeutic strategy might be needed to intercept both the lineage-survival mechanism and the effects of its associated genetic perturbations. Attempts to target lineage addiction must also account for the caveat that agents that target dependencies that are present in both tumours and normal cellular counterparts could have increased toxic side effects. In such cases, the optimal and tumour-specific targets might be outside the lineage-survival pathway itself (FIG. 4).

Synthetic dosage lethality

A genetic interaction in which overexpression or activation of one gene or pathway becomes lethal to the cell when a second (normally non-lethal) mutation is also present.

To this end, discovering robust drug targets in the setting of tumour lineage dependency might benefit substantially from the 'synthetic dosage lethality' concept^{90,91}. Two cellular factors have a synthetic lethal relationship if alteration of either factor alone preserves cell viability, whereas simultaneous perturbation of both factors results in cell death. In the lineage-dependency model, the combined effects of deregulated lineage survival and its enabling (or otherwise associated) tumour genetic events might create an altered cellular state A in which a distinct factor B now provides an essential buffering effect to accommodate these changes⁹². Systematic efforts to identify and inhibit crucial buffering factors that operate in lineage addiction might therefore be an elegant way to elucidate 'context-driven' therapeutic indices⁹³ for many tumour types. Unbiased chemical screens for novel therapeutics that show selective potency against tumour cells with lineage-dependent genetic alterations should prove fruitful in this regard.

Preliminary clinical evidence already supports the notion that unique vulnerabilities might ensue when the correct combination of genetic alterations occurs in cellular contexts that are specified by lineage and differentiation. Anaplastic oligodendrogliomas that harbour hemizygous deletions on chromosome 1p provide an instructive example — the presence of this genetic aberration predicts enhanced chemosensitivity in these adult brain tumours⁹⁴; however, the same chemosensitivity might not correlate with 1p loss in tumours from other lineages. It is also intriguing to note that several proteins that are encoded by the proposed lineage-survival oncogenes in TABLE 2 are targets of known drugs or novel therapeutics in clinical development. These include AR and ER, which are the focal points of hormonal therapies that have been used in prostate and breast cancers for many years, as well as FLT3, which is the target of several emerging small-molecule tyrosine kinase inhibitors⁹⁵. Although many transcription factors are difficult to intercept therapeutically, their target effector genes might prove vulnerable. For example, expression of *BCL2* is regulated by MITF in the melanocytic lineage⁵⁵ and *BCL2* is targeted by antisense therapeutics in development^{96–98}. Although this strategy yielded disappointing results in clinical trials of unselected patients with melanoma⁹⁹, patient subgroups whose tumours have a MITF lineage dependency might benefit from such agents in combination with MAPK inhibitors and/or CDK inhibitors⁵³. These observations provide grounds for optimism that many cancers might harbour therapeutically malleable vulnerabilities that are associated with the lineage–genetics interface.

Conclusions

Taken to its extreme, the recognition that cancer is a genomic disease might be expected to relegate many currently employed histological distinctions into mere footnotes that annotate the essential genetic perturbations that drive human cancers. However, the lineage-dependency model suggests an alternate outcome: aspects such as cell and tissue of origin and degree of differentiation will probably remain influential in

cancer diagnosis and treatment, and might gain additional importance when considered together with tumour genetic information. The oncogene-addiction theory has already affirmed the premise that excessive dependency of tumour cells on individual perturbed pathways can give rise to cellular vulnerabilities that manifest selectively in the dependent tumour types.

Our recent observations involving *MITF* in melanoma, together with an informed retrospection, offer the possibility that certain lineage-survival mechanisms might become similarly usurped during tumour progression. Together with rigorous genetic analyses, an expanded understanding of lineage dependencies might inform a new era of targeted cancer therapeutic approaches.

1. Strausberg, R. L., Simpson, A. J., Old, L. J. & Riggins, G. J. Oncogenomics and the development of new cancer therapies. *Nature* **429**, 469–474 (2004).
2. Fenaux, P. & Degos, L. Differentiation therapy for acute promyelocytic leukemia. *N. Engl. J. Med.* **337**, 1076–1077 (1997).
3. Tallman, M. S. *et al.* All-trans-retinoic acid in acute promyelocytic leukemia. *N. Engl. J. Med.* **337**, 1021–1028 (1997).
4. Berman, J. J. Tumor taxonomy for the developmental lineage classification of neoplasms. *BMC Cancer* **4**, 88 (2004).
5. Berman, J. Modern classification of neoplasms: reconciling differences between morphologic and molecular approaches. *BMC Cancer* **5**, 100 (2005).
6. Thiery, J. P. Epithelial–mesenchymal transitions in tumour progression. *Nature Rev. Cancer* **2**, 442–454 (2002).
7. Kang, Y. & Massague, J. Epithelial–mesenchymal transitions: twist in development and metastasis. *Cell* **118**, 277–279 (2004).
8. Johnston, R. N., Pai, S. B. & Pai, R. B. The origin of the cancer cell: oncogeny reverses phylogeny. *Biochem. Cell. Biol.* **70**, 831–834 (1992).
9. Gupta, P. B. *et al.* The melanocyte differentiation program predisposes to metastasis after neoplastic transformation. *Nature Genet.* **37**, 1047–1054 (2005).
This paper provides direct experimental evidence that lineage programming contributes to the metastatic phenotype in melanoma cells.
10. Muller, C. & Leutz, A. Chromatin remodeling in development and differentiation. *Curr. Opin. Genet. Dev.* **11**, 167–174 (2001).
11. Kluger, Y., Lian, Z., Zhang, X., Newburger, P. E. & Weissman, S. M. A panorama of lineage-specific transcription in hematopoiesis. *Bioessays* **26**, 1276–1287 (2004).
12. Nagamura-Inoue, T., Tamura, T. & Ozato, K. Transcription factors that regulate growth and differentiation of myeloid cells. *Int. Rev. Immunol.* **20**, 83–105 (2001).
13. Warburton, D. *et al.* The molecular basis of lung morphogenesis. *Mech. Dev.* **92**, 55–81 (2000).
14. Fraga, M. F. *et al.* Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer. *Nature Genet.* **37**, 391–400 (2005).
15. Strahl, B. D. & Allis, C. D. The language of covalent histone modifications. *Nature* **403**, 41–45 (2000).
16. Wolffe, A. P. & Hayes, J. J. Chromatin disruption and modification. *Nucleic Acids Res.* **27**, 711–720 (1999).
17. Bird, A. DNA methylation patterns and epigenetic memory. *Genes Dev.* **16**, 6–21 (2002).
18. Vignali, M., Hassan, A. H., Neely, K. E. & Workman, J. L. ATP-dependent chromatin-remodeling complexes. *Mol. Cell. Biol.* **20**, 1899–1910 (2000).
19. Ringrose, L. & Paro, R. Epigenetic regulation of cellular memory by the Polycomb and Trithorax group proteins. *Annu. Rev. Genet.* **38**, 413–443 (2004).
20. Wolpert, L. Positional information and pattern formation in development. *Dev. Genet.* **15**, 485–490 (1994).
21. Davis, P. K. & Brackmann, R. K. Chromatin remodeling and cancer. *Cancer Biol. Ther.* **2**, 22–29 (2003).
22. Versteeg, I. *et al.* Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. *Nature* **394**, 203–206 (1998).
23. Sevenet, N. *et al.* Spectrum of hSNF5/INI1 somatic mutations in human cancer and genotype-phenotype correlations. *Hum. Mol. Genet.* **8**, 2359–2368 (1999).
24. Grand, F. *et al.* Frequent deletion of hSNF5/INI1, a component of the SWI/SNF complex, in chronic myeloid leukemia. *Cancer Res.* **59**, 3870–3874 (1999).
25. Sawa, M. *et al.* BMI-1 is highly expressed in M0-subtype acute myeloid leukemia. *Int. J. Hematol.* **82**, 42–47 (2005).
26. Dukers, D. F. *et al.* Unique polycomb gene expression pattern in Hodgkin's lymphoma and Hodgkin's lymphoma-derived cell lines. *Am. J. Pathol.* **164**, 873–881 (2004).
27. Abate-Shen, C. Deregulated homeobox gene expression in cancer: cause or consequence? *Nature Rev. Cancer* **2**, 777–785 (2002).
28. Grier, D. G. *et al.* The pathophysiology of HOX genes and their role in cancer. *J. Pathol.* **205**, 154–171 (2005).
29. Kho, A. T. *et al.* Conserved mechanisms across development and tumorigenesis revealed by a mouse development perspective of human cancers. *Genes Dev.* **18**, 629–640 (2004).
This paper shows that certain tumour subsets may be characterized by their molecular similarity to a particular developmental stage.
30. Hahn, W. C. & Weinberg, R. A. Rules for making human tumor cells. *N. Engl. J. Med.* **347**, 1593–1603 (2002).
31. Weber, B. L. Cancer genomics. *Cancer Cell* **1**, 37–47 (2002).
32. Davies, H. *et al.* Mutations of the *BRAF* gene in human cancer. *Nature* **417**, 949–954 (2002).
This paper represents one of the first large-scale sequencing efforts to identify a novel oncogene mutation.
33. Sieber, O. M., Tomlinson, S. R. & Tomlinson, I. P. Tissue, cell and stage specificity of (epi)mutations in cancers. *Nature Rev. Cancer* **5**, 649–655 (2005).
34. Sharpless, E. & Chin, L. The *INK4a/ARF* locus and melanoma. *Oncogene* **22**, 3092–3098 (2003).
35. Sharpless, N. E., Kannan, K., Xu, J., Bosenberg, M. W. & Chin, L. Both products of the mouse *Ink4a/Arf* locus suppress melanoma formation *in vivo*. *Oncogene* **22**, 5055–5059 (2003).
36. Keyomarsi, K. & Pardee, A. B. Redundant cyclin overexpression and gene amplification in breast cancer cells. *Proc. Natl Acad. Sci. USA* **90**, 1112–1116 (1993).
37. Bringuier, P. P., Tamimi, Y., Schuurin, E. & Schalken, J. Expression of cyclin D1 and EMS1 in bladder tumours; relationship with chromosome 11q13 amplification. *Oncogene* **12**, 1747–1753 (1996).
38. Slamon, D. J. *et al.* Human breast cancer: correlation of relapse and survival with amplification of the *HER-2/neu* oncogene. *Science* **235**, 177–182 (1987).
39. Wong, A. J. *et al.* Increased expression of the epidermal growth factor receptor gene in malignant gliomas is invariably associated with gene amplification. *Proc. Natl Acad. Sci. USA* **84**, 6899–6903 (1987).
40. Reissmann, P. T., Koga, H., Figlin, R. A., Holmes, E. C. & Slamon, D. J. Amplification and overexpression of the cyclin D1 and epidermal growth factor receptor genes in non-small-cell lung cancer. *J. Cancer Res. Clin. Oncol.* **125**, 61–70 (1999).
41. Garraway, L. A. *et al.* Integrative genomic analyses identify *MITF* as a lineage survival oncogene amplified in malignant melanoma. *Nature* **436**, 117–122 (2005).
This paper demonstrated the power of combining genomic data sets for lineage-associated cancer gene discovery, and characterized the first lineage-survival oncogene.
42. Zhao, X. *et al.* Homozygous deletions and chromosome amplifications in human lung carcinomas revealed by single nucleotide polymorphism array analysis. *Cancer Res.* **65**, 5561–5570 (2005).
43. Garraway, L. A. *et al.* 'Lineage addiction' in human cancer: lessons from integrated genomics. *Cold Spring Harb. Symp. Quant. Biol.* **70**, 1–10 (2005).
44. Weinstein, I. B. Addiction to oncogenes — the Achilles heel of cancer. *Science* **297**, 63–64 (2002).
45. Kantarjian, H. *et al.* Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N. Engl. J. Med.* **346**, 645–652 (2002).
46. Demetri, G. D. *et al.* Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N. Engl. J. Med.* **347**, 472–480 (2002).
47. Paez, J. G. *et al.* EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* **304**, 1497–1500 (2004).
48. Lynch, T. J. *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med.* **350**, 2129–2139 (2004).
49. Morales, A. V., Barbas, J. A. & Nieto, M. A. How to become neural crest: from segregation to delamination. *Semin. Cell Dev. Biol.* **16**, 655–662 (2005).
50. Dupin, E. & Le Douarin, N. M. Development of melanocyte precursors from the vertebrate neural crest. *Oncogene* **22**, 3016–3023 (2003).
51. Widlund, H. R. & Fisher, D. E. Microphthalmia-associated transcription factor: a critical regulator of pigment cell development and survival. *Oncogene* **22**, 3035–3041 (2003).
52. Goding, C. R. *MITF* from neural crest to melanoma: signal transduction and transcription in the melanocyte lineage. *Genes Dev.* **14**, 1712–1728 (2000).
53. Garraway, L. A. & Sellers, W. R. From integrated genomics to tumor lineage dependency. *Cancer Res.* **66**, 2506–2508 (2006).
54. Du, J. *et al.* Critical role of CDK2 for melanoma growth linked to its melanocyte-specific transcriptional regulation by *MITF*. *Cancer Cell* **6**, 565–576 (2004).
55. McGill, G. G. *et al.* Bcl2 regulation by the melanocyte master regulator *Mitf* modulates lineage survival and melanoma cell viability. *Cell* **109**, 707–718 (2002).
This paper was the first to suggest a mechanism by which *MITF*, the master melanocyte transcription factor, might exert a lineage-survival role.
56. Loercher, A. E., Tank, E. M., Delston, R. B. & Harbour, J. W. *MITF* links differentiation with cell cycle arrest in melanocytes by transcriptional activation of *INK4A*. *J. Cell Biol.* **168**, 35–40 (2005).
57. Carreira, S. *et al.* *Mitf* cooperates with Rb1 and activates p21^{Cip1} expression to regulate cell cycle progression. *Nature* **433**, 764–769 (2005).
References 56 and 57 showed that *MITF* induces growth arrest in non-transformed cells, and that this arrest was dependent on the integrity of key cell-cycle inhibitory pathways.
58. Chin, L. The genetics of malignant melanoma: lessons from mouse and man. *Nature Rev. Cancer* **3**, 559–570 (2003).
59. Hemesath, T. J., Price, E. R., Takemoto, C., Badalian, T. & Fisher, D. E. MAP kinase links the transcription factor *Microphthalmia* to *c-Kit* signalling in melanocytes. *Nature* **391**, 298–301 (1998).
60. Ohholt, K., Platz, A., Kanter, L., Ringborg, U. & Hansson, J. *NRAS* and *BRAF* mutations arise early during melanoma pathogenesis and are preserved throughout tumor progression. *Clin Cancer Res* **9**, 6483–6488 (2003).
61. Reifemberger, J. *et al.* Frequent alterations of Ras signaling pathway genes in sporadic malignant melanomas. *Int. J. Cancer* **109**, 377–384 (2004).
62. Heinlein, C. A. & Chang, C. Androgen receptor in prostate cancer. *Endocr. Rev.* **25**, 276–308 (2004).
63. Waltregny, D. *et al.* Androgen-driven prostate epithelial cell proliferation and differentiation *in vivo* involve the regulation of p27. *Mol. Endocrinol.* **15**, 765–782 (2001).

64. Berger, R. *et al.* Androgen-induced differentiation and tumorigenicity of human prostate epithelial cells. *Cancer Res.* **64**, 8867–8875 (2004). **This paper showed that the androgen receptor, which triggers reduced prostate cell growth *in vitro* upon androgen stimulation, also promotes tumorigenesis in immortalized prostate epithelia following orthotopic injection.**
65. Sicinski, P. *et al.* Cyclin D1 provides a link between development and oncogenesis in the retina and breast. *Cell* **82**, 621–630 (1995).
66. Fantl, V., Stamp, G., Andrews, A., Rosewell, I. & Dickson, C. Mice lacking cyclin D1 are small and show defects in eye and mammary gland development. *Genes Dev.* **9**, 2364–2372 (1995).
67. Chodosh, L. A. The reciprocal dance between cancer and development. *N. Engl. J. Med.* **347**, 134–136 (2002).
68. Gilliland, D. G. & Griffin, J. D. Role of FLT3 in leukemia. *Curr. Opin. Hematol.* **9**, 274–281 (2002).
69. Stirewalt, D. L. & Radich, J. P. The role of FLT3 in haematopoietic malignancies. *Nature Rev. Cancer* **3**, 650–665 (2003).
70. Kumar, V. *et al.* Functional domains of the human estrogen receptor. *Cell* **51**, 941–951 (1987).
71. Clarke, R. B., Anderson, E. & Howell, A. Steroid receptors in human breast cancer. *Trends Endocrinol. Metab.* **15**, 316–323 (2004).
72. Anzick, S. L. *et al.* AIB1, a steroid receptor coactivator amplified in breast and ovarian cancer. *Science* **277**, 965–968 (1997).
73. Tanner, M. M. *et al.* Frequent amplification of chromosomal region 20q12-q13 in ovarian cancer. *Clin. Cancer Res.* **6**, 1833–1839 (2000).
74. Bingle, C. D. Thyroid transcription factor-1. *Int. J. Biochem. Cell Biol.* **29**, 1471–1473 (1997).
75. Stenhouse, G., Fyfe, N., King, G., Chapman, A. & Kerr, K. M. Thyroid transcription factor 1 in pulmonary adenocarcinoma. *J. Clin. Pathol.* **57**, 383–387 (2004).
76. Byrd-Gloster, A. L. *et al.* Differential expression of thyroid transcription factor 1 in small cell lung carcinoma and Merkel cell tumor. *Hum. Pathol.* **31**, 58–62 (2000).
77. Hecht, J. L., Pinkus, J. L., Weinstein, L. J. & Pinkus, G. S. The value of thyroid transcription factor-1 in cytologic preparations as a marker for metastatic adenocarcinoma of lung origin. *Am. J. Clin. Pathol.* **116**, 483–488 (2001).
78. Freund, J. N., Domon-Dell, C., Keding, M. & Duluc, I. The *Cdx-1* and *Cdx-2* homeobox genes in the intestine. *Biochem. Cell Biol.* **76**, 957–969 (1998).
79. Soubeyran, P. *et al.* Homeobox gene *Cdx1* regulates Ras, Rho and PI3 kinase pathways leading to transformation and tumorigenesis of intestinal epithelial cells. *Oncogene* **20**, 4180–4187 (2001).
80. de la Chapelle, A. Genetic predisposition to colorectal cancer. *Nature Rev. Cancer* **4**, 769–780 (2004).
81. Classon, M. & Harlow, E. The retinoblastoma tumour suppressor in development and cancer. *Nature Rev. Cancer* **2**, 910–917 (2002).
82. Nishi, T. & Saya, H. Neurofibromatosis type 1 (NF1) gene: implication in neuroectodermal differentiation and genesis of brain tumors. *Cancer Metastasis Rev.* **10**, 301–310 (1991).
83. Salti, G. I. *et al.* Microphthalmia transcription factor: a new prognostic marker in intermediate-thickness cutaneous malignant melanoma. *Cancer Res.* **60**, 5012–5016 (2000).
84. Birtle, A. J., Freeman, A., Masters, J. R., Payne, H. A. & Harland, S. J. Clinical features of patients who present with metastatic prostate carcinoma and serum prostate-specific antigen (PSA) levels < 10 ng/mL: the 'PSA negative' patients. *Cancer* **98**, 2362–2367 (2003).
85. Hainsworth, J. D. & Greco, F. A. Poorly differentiated carcinoma and poorly differentiated adenocarcinoma of unknown primary tumor site. *Semin. Oncol.* **20**, 279–286 (1993).
86. Ramaswamy, S. *et al.* Multiclass cancer diagnosis using tumor gene expression signatures. *Proc. Natl Acad. Sci. USA* **98**, 15149–15154 (2001). **This paper showed how gene-expression profiles could classify tumours largely on the basis of lineage-differentiation signatures; however, poorly differentiated cancers were not as easily classified by this approach.**
87. Zhang, M. & Rosen, J. M. Stem cells in the etiology and treatment of cancer. *Curr. Opin. Genet. Dev.* **16**, 60–64 (2006).
88. Kulesa, P. M. *et al.* Reprogramming metastatic melanoma cells to assume a neural crest cell-like phenotype in an embryonic microenvironment. *Proc. Natl Acad. Sci. USA* **103**, 3752–3757 (2006).
89. Lu, J. *et al.* MicroRNA expression profiles classify human cancers. *Nature* **435**, 834–838 (2005). **This paper showed that miRNA profiles could classify tumours across multiple lineages, regardless of their differentiation patterns.**
90. Kroll, E. S., Hyland, K. M., Hieter, P. & Li, J. J. Establishing genetic interactions by a synthetic dosage lethality phenotype. *Genetics* **143**, 95–102 (1996).
91. Kaelin, W. G. The concept of synthetic lethality in the context of anticancer therapy. *Nature Rev. Cancer* **5**, 689–698 (2005).
92. Hartman, J. L., Garvik, B. & Hartwell, L. Principles for the buffering of genetic variation. *Science* **291**, 1001–1004 (2001).
93. Kaelin, W. G. Choosing anticancer drug targets in the postgenomic era. *J. Clin. Invest.* **104**, 1503–1506 (1999).
94. Cairncross, J. G. *et al.* Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J. Natl Cancer Inst.* **90**, 1473–1479 (1998).
95. Sawyers, C. L. Finding the next Gleevec: FLT3 targeted kinase inhibitor therapy for acute myeloid leukemia. *Cancer Cell* **1**, 413–415 (2002).
96. Tamm, I., Dorken, B. & Hartmann, G. Antisense therapy in oncology: new hope for an old idea? *Lancet* **358**, 489–497 (2001).
97. Morris, M. J. *et al.* Phase I trial of BCL-2 antisense oligonucleotide (G3139) administered by continuous intravenous infusion in patients with advanced cancer. *Clin. Cancer Res.* **8**, 679–683 (2002).
98. Nahta, R. & Esteva, F. J. Bcl-2 antisense oligonucleotides: a potential novel strategy for the treatment of breast cancer. *Semin. Oncol.* **30**, 143–149 (2003).
99. Genasense FDA review team. *Genasense (Oblimersen) for metastatic melanoma* [online], <http://www.fda.gov/ohrms/dockets/ac/04/slides/403751_02_FDA-Kane-Yang%20.ppt> (2004).
100. Wang, J. C. & Dick, J. E. Cancer stem cells: lessons from leukemia. *Trends Cell Biol.* **15**, 494–501 (2005).
101. Dean, M., Fojo, T. & Bates, S. Tumour stem cells and drug resistance. *Nature Rev. Cancer* **5**, 275–284 (2005).
102. Garraway, L. A. & Sellers, W. R. Array-based approaches to cancer genome analysis. *Drug Discov. Today* **2**, 171–177 (2005).
103. Engle, L. J., Simpson, C. L. & Landers, J. E. Using high-throughput SNP technologies to study cancer. *Oncogene* **25**, 1594–1601 (2006).
104. Beroukhi, R. *et al.* Inferring loss-of-heterozygosity from tumor-only samples using high-density oligonucleotide SNP arrays. *PLoS Comput. Biol.* **2**, e41 (2006).
105. Zhao, X. *et al.* An integrated view of copy number and allelic alterations in the cancer genome using single nucleotide polymorphism arrays. *Cancer Res.* **64**, 3060–3071 (2004).
106. Jiang, J. *et al.* Identifying and characterizing a novel activating mutation of the FLT3 tyrosine kinase in AML. *Blood* **104**, 1855–1858 (2004).

Acknowledgements

This work was supported by grants from the US National Cancer Institute to L.A.G. and W.R.S.

Competing interests statement

The authors declare **competing financial interests**. See web version for details.

DATABASES

The following terms in this article are linked online to:
Entrez Gene: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene>
 ABL | APC | AR | BCL2 | BCR | BMI1 | BRAF | CCND1 | CDK2 | CDKN2A | CDX1 | EGFR | ERBB2 | ERK | ESR1 | FLT3 | FOXD3 | KIT | MITF | NF1 | NRAS | PIK3CA | PML | PSA | RARA | RB | SNAI2 | SNF5 | SOX9 | SOX10 | TP53 | TITF1
National Cancer Institute: <http://www.cancer.gov>
 brain tumours | breast adenocarcinoma | colon adenocarcinoma | gastrointestinal stromal tumours | leukaemia | lung adenocarcinoma | ovarian cancer | prostate cancer

FURTHER INFORMATION

Affymetrix: <http://www.affymetrix.com>
COSMIC database: <http://www.sanger.ac.uk/genetics/CGP/cosmic>
William R. Sellers's homepage: <http://research.dfci.harvard.edu/sellerslab/index.html>
Access to this links box is available online.

ERRATUM

Lineage dependency and lineage-survival oncogenes in human cancer

Levi A. Garraway and William R. Sellers

Nature Rev. Cancer **6**, 593–602 (2006)

On page 596 of this article the statement 'The lineage-dependency model (FIG. 1) therefore offers a counterpoint to oncogene addiction...' should have cited Figure 3 rather than Figure 1. The online version of the article has been corrected.