HHS Public Access

Author manuscript

Cancer Discov. Author manuscript; available in PMC 2024 February 04.

Published in final edited form as:

Cancer Discov. 2023 August 04; 13(8): 1771–1788. doi:10.1158/2159-8290.CD-23-0225.

The transcriptional and epigenetic landscape of cancer cell lineage plasticity

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Abstract

Lineage plasticity, a process whereby cells change their phenotype to take on a different molecular and/or histological identity, is a key driver of cancer progression and therapy resistance. While underlying genetic changes within the tumor can enhance lineage plasticity, it is predominantly a dynamic process controlled by transcriptional and epigenetic dysregulation. This review explores the transcriptional and epigenetic regulators of lineage plasticity and their interplay with other features of malignancy, such as dysregulated metabolism, the tumor microenvironment and immune evasion. We also discuss strategies for the detection and treatment of highly plastic tumors.

1. Introduction

During normal development, cells undergo specific differentiation and organisation programs to produce tissues with defined functions. More specifically, multipotent embryonic progenitor cells undergo non-genetic phenotypic changes in response to environmental cues to yield lineage-specific progenitors and, eventually, terminally differentiated cells (1). It was originally postulated by Conrad Waddington that mature, differentiated cells were unable to produce progeny distinct from their committed lineage (2). While some cell types and tissues exhibit a restricted capability for phenotypic

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plasticity, later studies have revealed a remarkable level of cell state flexibility in many adult organs (3), particularly in the context of tissue repair and pathologic stress (4). Lineage plasticity can manifest via dedifferentiation, the reversal of a differentiated phenotype back to a progenitor-like state which may then re-differentiate to another cell lineage, or transdifferentiation, whereby cells switch from one lineage to another without transit via an intermediate pluripotent state.

The unlocking of phenotypic plasticity during tumor evolution is now recognised as a critical hallmark of cancer (5). By exploiting dedifferentiation and transdifferentiation, cancer cells can acquire new molecular features to facilitate metastasis and evade systemic therapies. Although genetic alterations can promote cancer cell lineage plasticity, this phenomenon is primarily driven by epigenetic and transcriptional reprogramming. Epigenetic/transcriptional mechanisms are advantageous over genetic mechanisms since they enable tumors to respond more rapidly to volatile microenvironmental pressures and therapy (6) as well as being more permissive of reversible phenotype switching, whereas genetic changes can lock cells into an evolutionary trajectory that may become disadvantageous in the future. This review describes different types of cancer cell lineage plasticity, the epigenetic and transcriptional underpinnings of such plasticity, and how cancer plasticity might be leveraged therapeutically.

2. Manifestations of lineage plasticity in cancer

Cells exist in a certain configuration – termed a cell state – based on specific molecular (e.g., gene expression) and functional (e.g., self-renewal capacity) features. Multiple regulatory levels, including epigenetic and transcriptional, are fundamental for determining and maintaining cells in a given state. However, it is becoming increasing clear that cells are not locked in a particular state but rather can be rewired and transition along a continuum of phenotypes. A key feature of this rewiring is its complexity, with transitions being frequently characterized by uncertain outcomes and ambiguity in cancer cell identity. Nevertheless, common manifestations of lineage plasticity observed in solid tumors and with documented roles in cancer growth, metastasis and therapy resistance are summarized in Figure 1A and described in more detail below.

Epithelial-mesenchymal plasticity

The loss of epithelial phenotype and acquisition of mesenchymal properties, a process referred to as epithelial-mesenchymal transition (EMT), was first described in the context of developmental genetics by Elizabeth Hay and colleagues when studying chick embryogenesis (7,8). In the intervening time, compounding evidence has pointed to EMT as a developmental program ubiquitously co-opted by cancer cells to shed epithelial cell polarity and manifest a mesenchymal, motile phenotype (9–11) (Figure 1B). This process is bi-directional; mesenchymal-like cells are capable of gaining epithelial features through a mesenchymal-epithelial transition (MET). The dynamic flexibility of these processes is collectively termed “epithelial-mesenchymal plasticity.”

The regulatory framework controlling epithelial-mesenchymal plasticity is well defined, incorporating both core intrinsic elements, namely the EMT transcription factors Slug, Snail,

Twist, and Zeb1/2, as well as context-dependent extrinsic factors such as extracellular matrix stiffness and heterotypic signals originating from tumor-associated stromal cells (9) (see Section 6). A plethora of studies have demonstrated that EMT is associated with enhanced metastatic capacity, therapy resistance and stem-like features (11). Consistent with these findings, tumors derived from tissues of mesenchymal origin are frequently highly invasive (e.g., glioblastoma) or characterized by early metastasis (e.g., melanoma) (12). However, these observations contrast with a parallel body of work showing that stable mesenchymal features can abrogate metastatic outgrowth in pre-clinical models along with reports that tumor cells with an epithelial phenotype retain complete metastatic capacity. For example, recent findings from the Brisken lab and others have demonstrated that, in mouse models of estrogen receptor-positive breast cancer, cells in an epithelial differentiation state exhibit increased fitness, anti-apoptotic signalling, and metastatic potential (13,14).

The divergent and somewhat contradictory findings surrounding epithelial-mesenchymal plasticity in cancer progression may be a result of studying extreme epithelial and mesenchymal states in a process that is likely transient and episodic. More recent evidence has shown that cells existing in a hybrid EMT (hEMT) state – that is, co-expression of epithelial and mesenchymal markers in the same cells – have the greatest malignant and metastatic potential (15,16). Moreover, isolation and sequencing of circulating tumor cells (CTCs) from breast cancer patients revealed that the hEMT state is linked to elevated expression of genes that promote a stem cell-like state (17). Notably, this hybrid phenotype is very common, with a large-scale transcriptomic profiling effort of over 7,100 human epithelial tumors uncovering a hEMT state in ~40% of tumors (18). Whether the hEMT state represents a stable phenotype or is a snapshot of the fluctuating EMT status of individual cells remains an open question, although recent single cell data from multiple tumor types suggests the existence of a continuum of cell states (19).

Neuroendocrine transdifferentiation

Histological transitions from adenocarcinoma to neuroendocrine carcinoma are frequently observed in prostate, lung and bladder tumors (Figure 1B). However, a neuroendocrine gene signature was found to be associated with metastasis and poor outcome across 21 epithelial malignancies, suggesting that this phenomenon may be underappreciated (20). The concept that the neuroendocrine cell state arises via lineage plasticity rather than expansion of pre-existing alternative lineage clones is supported by the observation that prostate tumors frequently retain the genetic hallmarks of their precursor adenocarcinoma histology (21). Validating this hypothesis, murine lineage tracing studies revealed that neuroendocrine cancer cells can arise from alveolar type 2 and tracheobronchial basal cells in the lung and luminal epithelial cells in the prostate (22–24). Moreover, in a series of elegant multiomics and spatial profiling experiments of human lung adenocarcinomas, the Ciriello lab provided additional evidence for epithelial-neuroendocrine transdifferentiation as a result of epigenetic and transcriptional reprogramming (25). Epithelial-to-neuroendocrine lineage plasticity frequently manifests following therapies targeted against driver oncogenes: anti-EGFR therapy in *EGFR*-mutant lung adenocarcinoma, ALK inhibition in *ALK*-rearranged lung cancer, and anti-androgen receptor (AR) pathway therapy in prostate adenocarcinoma (26–30). However, evidence for such plasticity in untreated tumors suggests that it

can be induced by other factors, such as microenvironmental stressors, hypoxia or oncogene dysregulation. For example, in genetically-engineered mouse models (GEMMs) of pancreatic ductal adenocarcinoma, ductal-neuroendocrine lineage plasticity is governed by deregulated MYC expression in the context of *KRAS* mutation (31). Similarly, normal epithelial cells of prostate and lung origin can be reprogrammed into neuroendocrine-like cancer cells by ectopic upregulation of AKT, c-MYC and BCL-2 concomitant with loss of the tumor suppressors *TP53* and *RB1* (32).

The recent observation of tumors with mixed adenocarcinoma/neuroendocrine features following targeted therapy is suggestive of epithelial-to-neuroendocrine plasticity occurring via transitory, metastable phenotypic state(s). Spatial profiling of a prostate tumor with distinct adenocarcinoma and neuroendocrine foci revealed cells along a continuum of plastic gene expression signatures between the two extreme differentiation states (33), a concept reinforced by the frequency of therapy-resistant prostate tumors exhibiting amphicrine phenotypes (i.e. co-expression of both AR and neuroendocrine markers) (30,34,35). Similarly, mixed/transitory high plasticity cell states emerge during lung cancer progression in GEMMs and human patient-derived xenografts (PDXs) and are postulated to underlie chemoresistance (36).

Squamous transdifferentiation

Squamous transdifferentiation represents an alternative lineage plasticity mechanism (Figure 1A) that often develops as a subpopulation within another primary histology. While adeno-squamous histology is most commonly observed to arise *de novo* in pancreatic ductal adenocarcinomas (37), squamous differentiation in the lung has been reported in the context of acquired resistance to EGFR tyrosine kinase inhibitor therapy as well as ALK inhibitors in the setting of EML4-ALK fusion positive non-small cell lung cancer (NSCLC) (38,39). Although limited in number, cases of squamous transformation with molecular profiling were found to retain the characteristic genetic features of the adenocarcinoma (e.g., *EGFR* mutation), supporting the hypothesis of lineage plasticity. This is reinforced by mouse models of Kras-driven lung adenocarcinoma whereby loss of a kinase, Lkb1, mediates epigenetic reprogramming that drives tumor cells into a plastic state to enable squamous transformation (40). More recently, squamous differentiation has been reported in human prostate tumors following AR pathway antagonism (35) and in a prostate cancer GEMM driven by *Nmyc* overexpression and *Rb1* loss (41). The observation that prostate, lung, and pancreatic adenocarcinomas with squamous differentiation are enriched for mutations in oncogenes such as *MYC* and *KRAS* (*KRAS*^{G12D}) suggests that certain genotypes may be more permissive for squamous-like identity (42–44).

Epithelial-endothelial transition

The concept of epithelial-to-endothelial transition (Figure 1A), more commonly referred to as vascular or vasculogenic mimicry, was first described by Maniotis and colleagues in 1999, who observed a neoteric blood supply in malignant melanoma formed by stem-like cancer cells transdifferentiating into an endothelial-like phenotype and forming vascular-like networks (45). Neo-vascularization via endothelial transdifferentiation has subsequently been reported in various other solid tumors, including breast, prostate, lung,

and glioblastoma (46) (Figure 1B). Conceptually, the concept of vascular mimicry is akin to vasculogenesis during embryonic development, providing a conduit for increased plasma and blood cells to meet the metabolic demands necessitated by rapid growth. Not surprisingly, therefore, cancer cells undergoing vascular mimicry have been reported to hijack embryonic vasculogenesis programs including activation of Nodal signaling (47) and upregulation of VE-cadherin (48), which functions as an "adhesion zipper" between the endothelial-like cancer cells. Interestingly, the development of Kaposi's sarcoma is characterized by transdifferentiation of endothelial cells into epithelial tumor cells (49), hinting that the epithelial-endothelial transdifferentiation axis is bidirectional.

Melanomas that are resistant to angiogenesis inhibitors display greater levels of vascular mimicry (46). This could be the result of the inability of these inhibitors to effectively suppress cancer cell-derived neo-vascular networks, a hypothesis supported by *in vitro* studies using human melanoma cell lines (50). Although definitive evidence of treatment-induced vascular mimicry has yet to be observed, it is tempting to speculate that the poor clinical efficacy of angiogenesis inhibitors could be due, at least in part, to the phenomenon of epithelial-to-endothelial transdifferentiation.

Hybrid cell states and cancer stem cells

Although there are clear distinctions between epithelial-mesenchymal, epithelial-neuroendocrine, epithelial-squamous and epithelial-endothelial plasticity, it must be noted that there is also substantial overlap between the features and mediators of these phenomena (Figure 1 and Box 1). An important concept is that these various transitions are generally associated with hybrid metastable states (Figure 1A) characterised by elevated plasticity and stem-like features. Notably, breakdown of lineage commitment and transition into a hyper-plastic state is not unique to cancer but is also observed during wound healing when stress-responsive enhancers become activated and override homeostatic enhancers that govern lineage specificity (51).

Another important concept when considering lineage plasticity is that a population of cells within a heterogenous tumor can be endowed with heightened stemness, plasticity and drug resistance, which is frequently referred to as the "cancer stem cell" or "therapy-tolerant persister" paradigm. When modelling acute responses to anti-cancer therapies across drug-sensitive human cancer cell lines, Settleman and colleagues made the initial discovery that a small population of "cancer stem-like cells (CSCs)" maintain viability (52) and serve as a reservoir from which heterogeneous drug-resistance mechanisms can evolve to enable tumor re-establishment. Notably, the persister state was found to be transiently acquired and relinquished by individual cells within a population (52), suggesting that tumor cells are constantly in flux along a continuum of "stem-ness." The intimate relationship between stem-like states and lineage plasticity is an important principle when considering transcriptional and epigenetic mechanisms governing cancer cell state transitions.

3. Transcriptional and epigenetic regulators of lineage plasticity

Transcription factor control of lineage plasticity

The coordinated actions of lineage-specific transcription factors (TFs) are essential for normal development. In contrast, this tightly coordinated process goes awry in cancer, rerouting transcriptional pathways to enhance cell plasticity and drive disease progression. In this context, a major sequela of the malignant state is activation of aberrant lineage-specific TF activities. For example, therapy-mediated epithelial-neuroendocrine transdifferentiation in prostate cancer involves activation of BRN2, ASCL1, FOXA2 and N-Myc, TFs that mediate neural differentiation programs in normal development (53–56), whereas squamous transdifferentiation of pancreatic and lung adenocarcinomas is mediated by p63, a master transcriptional regulator of the normal squamous lineage (57,58).

Perhaps the most prominent example of lineage-specific TFs that are aberrantly activated in cancer to drive plasticity are the core EMT-TFs of the Snail, Twist and Zeb families (59). These TFs enable epithelial cancer cells to acquire features associated with a mesenchymal lineage by directly repressing epithelial genes (e.g. *CDH1*, encoding E-cadherin) and activating mesenchymal genes (e.g. *CDH2*, encoding N-cadherin, and *VIM*, encoding Vimentin). However, the terminology “EMT-TF” is perhaps unfortunate since this class of factors can also mediate epithelial-neuroendocrine (60–62), epithelial-endothelial (63) and endothelial-mesenchymal (64) cell state transitions as well as eliciting dedifferentiation, in some cases independent of their EMT-inducing capacity (65–67). Thus, EMT-TFs could be regarded as “pan-plasticity” factors, at least in some cancer contexts (Box 1).

Acquisition of new lineage-specific TF activity in cancer cells often occurs concomitantly with activation of one or more of the core embryonic stem cell pluripotency TFs, OCT4, SOX2, KLF4 and NANOG. These factors not only promote cancer cell dedifferentiation to a more stem-like state (68–71), as expected, but can also promote transdifferentiation, as illustrated by SOX2-mediated epithelial-neuroendocrine plasticity and EMT (70,72,73) and KLF4-mediated acinar-to-ductal phenotype switching in pancreatic cancer (74). Thus, pluripotency TFs can enable complex transdifferentiation/dedifferentiation coalescence that engenders highly plastic cell states.

Loss of developmental TFs that specify the original tumor lineage is another feature of cancer cell lineage plasticity, with some key examples being: loss of PDX1 in pancreatic cancer, which enables tumors to suppress the epithelial state and gain mesenchymal/squamous (pancreatic) features (75); loss of the luminal epithelial lineage factor AR in prostate cancer, which can lead to neuroendocrine transdifferentiation and/or dedifferentiation to a more stem-like state (35,76); loss of GATA3 in breast cancer, resulting in acquisition of basal/mesenchymal phenotypes (77); loss of the lung epithelial lineage factor NKX2–1 in lung cancer, which is associated with switching to squamous cell states and various gut lineages (78); loss of HOXA5 and SMAD4 in colon cancer, which enables dedifferentiation to a progenitor-like state (79,80); and loss of the master regulator of melanocyte differentiation, MITF, in melanoma, leading to reactivation of a neural crest progenitor state (81). A number of noteworthy elements related to lineage plasticity arising from reduced TF expression/activity are apparent. First, in some cases the TFs that are lost

were the initial primary drivers of tumorigenesis and growth – such as AR in prostate cancer – highlighting the extreme adaptability of tumor progression. Second, targeted therapies are a significant selection pressure leading lead to TF loss and/or inactivation. Treatment of a GEMM model of melanoma with the BRAF inhibitor vemurafenib causes down-regulation of SOX10, a neural crest lineage-specifying transcription factor essential for melanocyte development, which provokes tumor dedifferentiation and therapy resistance (82). Other prominent examples are loss of the sex steroid hormone receptors AR and ERα in prostate and breast cancer, respectively, in response to hormonal therapies that directly inhibit their activity (35,83). Interestingly, the development of more potent hormonal therapies for prostate cancer has led to a substantial increase in the frequency of tumors exhibiting highly plastic phenotypes (84), a cautionary tale when applying therapies that inhibit lineage-specific TFs. Finally, paralleling other aspects of lineage plasticity (see below), epigenetic mechanisms frequently underpin loss of lineage-specific TFs. For example, hormone therapy-induced lineage switching in breast and prostate cancer has been linked to epigenetic silencing of the *ESR1* and *AR* genes (85–87). Such epigenetic mechanisms could enable oscillating loss/gain of key epithelial TFs, in turn driving complex rounds of cell state switching, in response to microenvironmental cues and therapy.

The above examples imply scenarios whereby concomitant gain of TFs that enhance cell plasticity and loss of TFs that maintain differentiated epithelial states converge to yield unequivocal binary lineage switching. However, as mentioned above, such binary phenomena are likely to be rare and associated with reduced cellular flexibility. Instead, selection pressures enable the acquisition of high plasticity hybrid states; interplay between, and opposing actions of, TFs are important mediators of such states. In the hybrid EMT setting, TFs that counteract EMT-TFs to prevent full transition have been referred to as phenotypic stability factors (59); one such factor is GRHL2, which supports the proliferation of epithelial cancer cell growth (88,89). Similarly, hybrid states are also observed in cell line models of prostate cancer and patient tumors undergoing epithelial-neuroendocrine transdifferentiation, whereby TFs mediating the luminal epithelial state (i.e. AR, FOXA1) can be co-expressed with TFs driving neuronal and stemness transcriptional circuitry (i.e. N-Myc, SOX2, ASCL1, BRN2, etc) (34,35).

In addition to gain and loss of TF function, modulation of the activity of cancer regulatory TFs to support cancer cell lineage plasticity is frequently observed, a process referred to as TF “reprogramming” or “rewiring”. One notable example is altered function of two key prostate cancer-associated TFs, AR and FOXA1, in response to AR-targeted therapies. In the normal prostate and in early-stage prostate cancer, FOXA1 and AR play complementary and critical roles in maintaining the luminal epithelial lineage (90,91). However, both chronic and acute AR-targeted therapies can cause redistribution of AR/FOXA1 cistromes from epithelial-associated to neuroendocrine-associated regulatory elements in cell lines, PDXs and patient tumors (34,92,93), illustrating a paradigm whereby TF reprogramming is a driver of cell state switching. The mechanisms underlying TF reprogramming in cancer cell lineage plasticity are complex and multifactorial but include altered expression/activity of other TFs and chromatin-modifying factors, often in a combinatorial manner. Indeed, reprogramming of FOXA1 and AR activities in prostate cancer can be mediated via

interplay with pluripotency TFs (OCT4 and NANOG) and the histone methyltransferase EZH2, leading to altered cistromes, interacting protein partners and gene targets (34,68,69).

Epigenetic regulators of lineage plasticity

A critical epigenetic mechanism underlying cancer cell lineage plasticity is the addition and removal of post-translational modifications of histones, the so-called “histone code”. In particular, a histone code state characterized by the simultaneous enrichment of transcriptionally active (e.g. histone H3 lysine 4 monomethylation [H3K4me1] or trimethylation [H3K4me3]) and transcriptionally repressive (e.g. H3K27me3) post-translational modifications, termed bivalent chromatin, plays a major role in determining expression of plasticity-associated genes. Bivalently-marked genes tend to exhibit a low level of transcription that can be activated by loss of H3K27me3 or repressed by loss of H3K4me3, a status referred to as transcriptionally “poised” (94). In normal development, chromatin bivalency is enriched at elements regulating expression of lineage-specific TFs and other developmental factors, enabling dynamic and rapid control of cell state (95,96). A general feature of lineage plasticity is hijacked control of the bivalent chromatin state, resulting in activation of genes that promote plasticity and repression of genes that block plasticity, which collectively enable dedifferentiation and transdifferentiation processes (Box 1). For example, in prostate cancer, bivalent chromatin controls genes involved in epithelial and neuronal identity; stimuli that enhance cell plasticity (i.e. androgen withdrawal or over-expression of N-Myc) cause an increased H3K27me3:H3K4me3 ratio at epithelial genes and a decreased ratio at neuronal genes, leading to acquisition of neuronal features (97). Moreover, genes encoding EMT-TFs and other plasticity-associated TFs such as N-Myc and SOX9 are dynamically regulated by bivalent chromatin during metastatic progression of melanoma, enabling dynamic control of mesenchymal cell states (98).

Enzymes responsible for controlling histone post-translational modifications, and in particular the bivalent chromatin state, are key regulators of lineage plasticity. EZH2 is the enzymatic subunit of the Polycomb-repressive complex 2 (PRC2), which catalyzes the deposition of H3K27me3. Inhibition of EZH2 activity can block and, in some cases, reverse epithelial-neuroendocrine transdifferentiation in human and mouse models of prostate cancer and SCLC (34,56,72,99–102). By regulating deposition of H3K27me3, EZH2 also promotes EMT in pancreatic (103) and prostate cancer (104), the latter via direct repression of the *CDH1* promoter. Another key mediator of chromatin bivalency and the histone code more generally is LSD1, an enzyme that demethylates H3K4me1, H3K4me2, H3K9me1 and H3K9me2. In embryonic stem cells, LSD1 regulates pluripotency and stemness by controlling chromatin bivalency at key developmental genes, including lineage-specific transcription factors such as FOXA2 (105). Given its overarching role in pluripotency, it is not surprising that dysregulation of LSD1 in cancer cells has been linked to EMT (106,107), epithelial-neuroendocrine plasticity (108,109) and maintenance of cancer stem cell states (110). EZH2 and LSD1 are increasingly recognised as therapeutic targets, a concept explored in more detail below.

Another key epigenetic factor regulating cancer cell lineage plasticity is DNA methylation, a modification that is deposited by DNA methyltransferases (DNMT1, DNMT3A and

DNMT3B) and removed by ten-eleven translocation proteins (TET1, TET2 and TET3). DNMT1, in particular, has been identified as a major mediator of plasticity. In prostate cancer, upregulation of DNMT1 in NEPC tumors is associated with dramatically altered DNA methylation patterns; neuronal, cell-cell adhesion, developmental, EMT and stem cell transcriptional programs are enriched within genes exhibiting altered methylation, providing evidence that DNMT1 is a direct mediator of plasticity in this disease context (21,111). In support of this theory, DNMT1 inhibition dampens the neuroendocrine phenotype in cell line, organoid and xenograft models of prostate cancer (112). Paralleling these observations, SCLC is characterised by elevated DNMT expression and exhibits similar DNA methylation profiles to NEPC, including hypomethylation of neuronal TFs *ASCL1*, *HES6* and *ONECUT2* (111). Elevated DNMT1 activity and specific DNA methylation profiles have also been linked to EMT and stemness in breast cancer (113,114) and pancreatic cancer (115). Although the above examples reveal a robust link between elevated DNMT1 and lineage plasticity, this principle does not appear to apply to other DNA methylation-modifying enzymes. As examples, DNMT3A loss of function mutations can drive stemness and malignant progression of leukemia cells (116,117), while TET1 can enhance self-renewal and expansion of CSCs in triple-negative breast cancer cell lines (118). The precise mechanisms underlying these complex relationships between DNA methylation and cell plasticity states remain to be elucidated.

4. Insights into cancer cell lineage plasticity from single cell analyses

The unprecedented resolution afforded by single cell profiling has deepened our understanding of the origins and transitions between transcriptional states as well as the evolutionary paths that tumors follow. Indeed, such profiling has demonstrated that cells can display both developmental and unique evolutionary trajectories, which often involve a transient increase in cellular plasticity followed by adoption of increasingly metastatic states (119).

Pseudo-temporal approaches to evaluate single cell data have reinforced the notion that perturbation of tumor suppressors or therapeutic pressure accelerates plasticity-mediated progression by creating novel cellular trajectories as well as illustrating the complexity and heterogeneity of cell state changes. For example, single cell transcriptomic/epigenomic analysis of tumor progression in a GEMM expressing an oncogenic Kras-G12D mutant in combination with *TP53* deletion, which recapitulates human lung adenocarcinoma progression, revealed a loss of fidelity of the lung lineage coincident with the acquisition of transcriptional features associated with lung progenitors, embryonic ectoderm and EMT (36,120). In contrast to embryogenesis, tumor progression in this model was characterized by persistence of earlier cell states coincident with acquisition of new cellular states, giving rise to intra-tumoral diversity. A similar phenomenon has been described in SCLC at the single cell level with multiple, concurrent plasticity-related resistance mechanisms and cell states (e.g. EMT, neuroendocrine-like phenotypes) co-existing within the same tumor (121,122). Likewise, in prostate cancer, single cell RNA and chromatin accessibility profiling of patient tumors, organoids and cell line models has demonstrated that AR-targeted hormonal therapies cause the onset of multi-lineage phenotypes comprised

of epithelial, neuroendocrine, mesenchymal and tuft-like cell states, amongst others (41,123,124).

Single cell profiling has also provided new insight into the mediators of cancer cell lineage plasticity, uncovering evolutionary bottlenecks and vulnerabilities that could pave the way for new anti-plasticity therapies. Using single cell chromatin accessibility profiling, heterogenous self-renewing populations of stem-like cells were detected in human glioblastoma multiforme (GBM) tumors (125). Further work revealed that YAP/TAZ signalling is responsible for instilling stem-like properties; inhibition of this pathway irreversibly locked differentiated GBM cells in a non-tumorigenic state, preventing plasticity and regeneration of the stem-like cell compartment (126). Likewise, intratumoral subtype switching in SCLC has been reported as a mechanism of acquired resistance to platinum-based chemotherapy (127). Longitudinal single-cell transcriptome analysis of SCLC tumors uncovered a role for MYC-mediated Notch signalling activation in promoting a temporal shift from ASCL1-positive SCLC to a non-neuroendocrine YAP1-positive state, a subtype switch that could be blocked with a Notch inhibitor (128). Finally, single-cell studies in prostate and breast cancer have implicated JAK/STAT and FGFR signalling in lineage plasticity from luminal epithelial to neuroendocrine and mesenchymal states, revealing pharmacological inhibition of JAK/STAT as a viable therapeutic strategy (123,124,129).

Despite the increasing catalogue of single cell data, findings in relation to cellular trajectories inferred by pseudo-temporal approaches should be taken with caution as they make the assumption that transcriptional similarity denotes a developmental relationship. The next wave of single cell technologies that enable lineage barcoding (for review, see (130)) will provide more robust capture of plasticity, cell state transitions and clonal mosaicism. Indeed, application of a lineage recorder system that exploits CRISPR-Cas9-induced insertions and deletions (“indels”) to a mouse xenograft model of metastatic pancreatic cancer reinforced the notion – originally proposed from bulk transcriptomic data – that cells occupy a continuum of EMT states and that “late-hybrid” cells have the highest metastatic potential (131). More recently, an equivalent CRISPR-Cas9-based lineage tracing system was incorporated into the Kras-G12D mutant/*TP53* deletion lung cancer GEMM, yielding an autochthonous mouse model that provided important insights into tumor evolution, plasticity and subclonal origins (119).

5. Interplay between cancer cell lineage plasticity and metabolism

The intimate relationship between metabolism and tumor cell plasticity is evident by the distinct metabolic profile between stem-like and differentiated cell populations within a heterogeneous tumor. In general, stem-like cells exhibit suppression of oxidative phosphorylation (OXPHOS), resulting in redox niches with low reactive oxygen species (ROS) levels. Multiple epigenetic and transcriptional drivers of lineage plasticity have been demonstrated to control this metabolic reprogramming (Figure 2). For example, in mouse models of liver cancer, Nanog directly represses OXPHOS genes and concomitantly activates fatty acid oxidation to support cancer cell self-renewal and drug resistance (132). Similarly, JAK/STAT pathway activation (described above as a feature of lineage plasticity) promotes fatty acid β-oxidation activity to sustain breast cancer stem-like cells (133). A

switch from OXPHOS to glycolysis is also a common feature of lineage plasticity in tumors. The Snail-G9a-DNMT1 complex mediates promoter methylation and repression of fructose-1,6-biphosphatase (*FBP1*) in breast cancer cell lines, leading to a switch from mitochondrial OXPHOS to glycolysis that supports EMT, stemness and tumorigenicity (134). Acquisition of enhanced glycolysis is also associated with epithelial-neuroendocrine plasticity in prostate cancer, mediated at least in part by aberrant epigenetic/transcriptional activities of the histone lysine demethylase KDM8 and HIF1α (135).

The above examples describe how epigenetic enzymes and TFs mediate metabolic reprogramming concomitant with increased cancer cell plasticity. However, the interplay between these processes is very much a two-way street, perhaps best epitomised by the fact that the lineage-shaping activities of chromatin modifying enzymes are dependent on metabolic pathways and oncometabolites that provide the “fuel” for epigenetic modifications, particularly DNA and histone methylation (Figure 2). For example, one-carbon metabolism is central to lineage plasticity due to its role in the synthesis of substrates for methylation reactions. The methionine cycle controls the conversion of methionine into S-Adenosyl methionine (SAM), the universal methyl donor for histone and DNA methyltransferase enzymes, such as EZH2. Accordingly, regulation of SAM metabolism dictates a cell’s ability to impart histone and DNA modifications to support lineage reprogramming (136,137). Indeed, methionine has been reported to be required for maintenance of human embryonic stem cells (138). Similarly, in malignancy, stem-like cells rely on methionine and SAM biosynthesis for their self-renewal and tumor-forming capacity (139,140). In triple-negative breast cancer, methionine deprivation is associated with H3K4me3 demethylation and suppression of the pro-plasticity/developmental transcription factor Sox9, effects that were partially rescued by SAM supplementation (140). Increased SAM levels have also been reported during prostate cancer epithelial-neuroendocrine transdifferentiation (112). Beyond SAM, other oncometabolites that support lineage plasticity via dysregulation of DNA and histone methylation include fumarate and 2-hydroxyglutarate, both of which can inhibit TET DNA demethylases and histone demethylases: by suppressing TET-mediated DNA demethylation of miR-200 promoters, fumarate was found to stabilise EMT-related transcription factors (141), whereas 2-hydroxyglutarate was recently demonstrated to mediate an altered chromatin landscape that drives breast cancer cell state transitions and heterogeneity (142).

6. Interplay between the tumor microenvironment and lineage plasticity

The microenvironment in which a tumor grows can have a profound impact on cancer cell lineage plasticity. These external cues have been referred to as extrinsic regulators of plasticity (143), as opposed to cell-intrinsic factors that are predominantly described above. Although in many cases the precise mechanisms underlying the cross-talk between the microenvironment and cancer cell plasticity remain to be uncovered, an emerging body of work is elucidating epigenetic and transcriptional mechanisms underlying this phenomenon.

Growth factor secretion by cancer-associated fibroblasts (CAFs) can have a profound influence on the transcriptional and epigenetic regulators of cancer cell plasticity. For example, Lau and colleagues demonstrated that hepatocyte growth factor (HGF) release by

CAFs induced the AP-1 transcription factor *FOSL1* (FRA1) in liver cancer cells; subsequent transcriptional changes mediated by FRA1, including induction of the NOTCH signalling factor *HEY1*, resulted in enhanced plasticity, stemness and cancer-initiating capacity (144). Acidic fibroblast growth factor (FGF1) derived from pancreatic cancer CAFs can signal through AKT and GSK-3β to increase Myc half-life in tumor cells, which increases Myc promoter occupancy and transcriptional activity (145). Another study found that NSCLC CAFs release various growth factors, most notably insulin-like growth factor 2, to induce the stem TF Nanog in lung cancer, which drives transcriptional programs associated with stemness and plasticity (146). Collectively, this body of evidence supports the concept that paracrine signals play a major role in establishing transcriptional and epigenetic programs required for cancer cell plasticity. Importantly, the composition of such signals and subsequent impact on cancer cell state will depend on the specific microenvironmental niche; lung cancer brain metastases exhibited epithelial-neuroendocrine lineage switching but this was reversed when the tumor cells were separated from brain stroma (147).

Rapid tumor growth frequently outstrips the process of vascularization, resulting in a hypoxic microenvironment. An emerging knowledge base has linked hypoxia to epigenetic and transcriptional reprogramming of plasticity in cancer cells. Arguably the most well-studied mechanism underlying this relationship is induction of the transcription factor HIF-1α, which occurs in response to hypoxia and can directly activate genes encoding mediators of EMT, such as Twist, ZEB1, Snail and lysyl oxidase and TGF-β (148–151). HIF-1α can also regulate other forms of cancer cell lineage plasticity: in hypoxic GEMM prostate tumors, HIF-1α protein is stabilised and can interact with the transcription factor FOXA2 to drive expression of a gene expression program that mediates epithelial-neuroendocrine plasticity and metastasis (152). Beyond cell-autonomous mechanisms, hypoxia can also influence stroma to influence plasticity of cancer cells. For example, hypoxia induces expression of VEGF by stromal cells, which can activate stem-related transcriptional programs in breast and lung cancer cell lines via Myc and SOX2 (153).

Inflammation is another important microenvironmental factor that is intimately connected to lineage plasticity. Early lineage tracing studies were key in establishing this relationship. For example, a murine model of bacteria-induced prostatic inflammation resulted in basal-luminal transdifferentiation that was linked to carcinogenesis (154). Although the epigenetic and transcriptional bases that link inflammation and cancer cell plasticity remain to be fully established, one emerging theme is activation of transcriptional regulators such as NF-κB, JAK-STAT3 and Notch by pro-inflammatory chemokines and cytokines (e.g., TNFα, IL-1β, IL-6, IL-8 and CXLC8). Indeed, IL-6 can elicit stemness by activating JAK-STAT3 and Notch in breast cancer models *in vitro* and *in vivo* (155,156). More recent studies have also highlighted the essential role of JAK-STAT inflammatory signalling in prostate cancer lineage plasticity, whereby this pathway is essential for establishing complex admixed cellular phenotypes (including neuroendocrine-like and stem-like populations) and resistance to AR-targeted therapies (123,124). Soluble pro-inflammatory factors are frequently produced at high levels in cancer cells but can also be derived from other tumor microenvironmental components, most notably myeloid cells (156,157) and CAFs (158).

Mechanical features of the TME can also regulate cancer cell transcriptional and epigenetic plasticity. Integrins in cancer cells sense TME stiffness and mediate activation of key plasticity TFs, such as Twist and YAP/TAZ, leading to EMT transcriptional programs (159,160). YAP/TAZ-mediated mechanotransduction was also reported to enhance stem-like traits in breast and pancreatic cancer cell lines via modulating autophagy (161).

Two other aspects of tumor:microenvironment interplay in relation to cancer cell plasticity are worth noting. First, although our discussion has had a unidirectional focus – i.e. microenvironmental cues that influence transcriptional and epigenetic regulators of plasticity – this is of course a bidirectional relationship. An elegant example of such bidirectionality was provided by Somerville and colleagues, who demonstrated that squamous transdifferentiation of human and mouse pancreatic cancer cells results in conversion of pancreatic stellate cells into inflammatory CAFs; mechanistically, this was mediated by p63-mediated transcription of genes encoding pro-inflammatory secreted factors in the cancer cells (37). Thus, p63 regulates a transcriptional program that simultaneously drives squamous transdifferentiation (57,58) and fibroblast reprogramming (37). Second, experimental conditions can dramatically influence cancer cell plasticity, which has significant implications for studying the influence of the microenvironment on this process. Indeed, cell states of pancreatic adenocarcinoma cell lines and organoids were highly sensitive to culture medium and artificial states altered anti-cancer drug responses (162). Additionally, non-malignant and neoplastic mammary epithelial cells can gain stem-like characteristics via epigenetic mechanisms when grown in 2-dimensional culture but this phenomenon is mitigated if cells are cultured within 3-dimensional matrices (163). Thus, approaches to study the impact of the tumor microenvironment on transcriptional and epigenetic mechanisms underlying cancer cell plasticity should use models and optimise culture conditions that faithfully recapitulate patient-relevant cell states (162,164).

7. Cancer cell plasticity as a driver of immune escape

The ability of cancer cells to evade attack and elimination by immune cells is a hallmark of cancer and emerging evidence points to a critical role for non-genetic cell tumor plasticity in promoting non-immunogenic cell states (Figure 3 and Box 1). This concept was first established via the identification of a relationship between epithelial-mesenchymal plasticity and an immunosuppressive phenotype (165,166). Surveying clinical data from lung cancer, a strong correlation between “tumor EMT score” (based on expression of 76 canonical EMT genes) and expression of the immune checkpoint PD-L1 was uncovered (165). This finding was validated in a subsequent large-scale analysis of eleven cancer types, which demonstrated that tumors with a high EMT score exhibited elevated expression of immune checkpoint proteins, including PD-1, PD-L1, PD-L2, and CTLA-4 (166). Subsequent work has begun to provide mechanistic insight into the link between EMT and immune evasion. For example, an elegant set of experiments from the Weinberg lab using a SNAIL-driven fluorescent reporter in the MMTV-PyMT breast cancer mouse model demonstrated the relevance of this EMT-TF in directly mediating resistance to immune checkpoint inhibitors (ICIs) (167,168). While $SNAIL^{lo}$ epithelial cells were immunogenic, $SNAIL^{hi}$ mesenchymal-like cells promoted an immunosuppressive tumor microenvironment characterized by cytotoxic T lymphocyte exclusion, M2 pro-tumor

macrophage polarization, and decreased response to anti-CTLA-4 therapy. Interestingly, in mixed SNAIL^{lo}/SNAIL^{hi} tumors, only a small proportion (<10%) of mesenchymal-like cells were required to shield the surrounding epithelial cells from immune attack (167), likely due to secretion of immunosuppressive factors, such as TGFβ, by mesenchymal-like cells (169). SNAIL directly binds to the promoters of key immunosuppressive paracrine factors, including CD73 (Nt5e), macrophage colony-stimulating factor (Csf1), and Spp1, identifying a putative mechanism by which it inhibits anti-tumor immune activity (168). A similar immunosuppressive mechanism was identified in ovarian cancer whereby SNAIL directly binds to and upregulates the expression of genes encoding the CXCL1 and CXCL2 chemokines, leading to infiltration of myeloid-derived suppressor cells (MDSCs) (170). Direct transcriptional regulation by ZEB1 can activate expression of immunosuppressive factors (PD-L1 and CD47) (171) and repress expression of T cell-attracting chemokines, such as CXCL10 (172). Thus, direct transcriptional control of immunoregulatory factors by EMT-TFs could be a key contributor to tumor immune evasion and response to immunotherapy. Interestingly, positive feedback loops between tumor cells and immune cell populations can enhance this phenomenon: for example, MDSCs can reinforce a EMT/stemness phenotype and facilitate metastasis in syngeneic mouse models of breast cancer (173).

Epigenetic programs associated with high plasticity tumor states also play a critical role in regulating cancer cell immunogenicity. For example, bivalent chromatin or DNA methylation at the promoters of key immune regulators, including major histocompatibility complex (MHC) class I genes, the type III interferon receptor IFNLR1 and T cell-attracting chemokines (CCL5, CXCL9 and CXCL10), are associated with transcriptional repression and evasion of T cell-mediated immunity in leukaemia, SCLC, various types of squamous cell carcinoma and tripe-negative breast cancer (99,174–176). Collectively, these studies demonstrate that epigenetic reprogramming associated with lineage plasticity can mediate immune escape and reveal immunosensitization therapies for cancer, as discussed below.

8. Detection of cancer cell lineage plasticity for patient benefit

Clinically, lineage plasticity in cancer is not always recognizable, particularly since changes may be dynamic and occur at the cellular level. The most obvious recognition of lineage plasticity is when a primary tumor or metastatic biopsy shows mixed histology or a change in phenotype that differs from the original tumor histology. In the case of histologic transformation (e.g., SCLC or NEPC conversion), clinical genomic assays such as targeted exome sequencing may be performed to exclude a second primary cancer, which confirms similarities with the original cancer's gene alterations (e.g., *EGFR* mutation in NSCLC) and sometimes acquisition of additional alterations associated with plasticity or treatment resistance (e.g., loss of *RB1* and/or *TP53*) (21,177). Tumor protein assessment may be performed by immunohistochemistry to confirm loss of target expression (for example, loss of the luminal epithelial lineage factor AR in a subset of prostate tumors undergoing neuroendocrine transdifferentiation (30)) and acquisition of alternative lineage markers (e.g., neuroendocrine markers such as chromogranin, synaptophysin), although mixed luminal/neuroendocrine features are frequently observed. Often, the clinical detection of transdifferentiation is after it has already occurred; early detection strategies are important

to identify susceptible individuals and for the development of novel approaches to target the lineage plasticity process.

Serial biopsies are not always feasible to perform in patients, and therefore a comprehensive understanding of the timing of activation of transcriptomic and epigenetic drivers of lineage plasticity in individual patients has been a major challenge. Non-invasive approaches such as liquid biopsies and molecular imaging are in early development and hold promise as tools for early detection and monitoring of lineage plasticity. For example, loss of luminal programs may be suspected in prostate cancer based on features such as progressive disease with low or non-rising serum prostate specific antigen (PSA) or loss of prostate specific membrane antigen, the latter evaluated using PET/CT imaging (178,179). Circulating tumor cell (CTC) analyses across varied cancer types have revealed heterogeneity in epithelial marker expression, pointing to EMT changes that may contribute to metastasis (180). Cell free DNA (cfDNA) also holds significant promise for detecting both genetic and epigenetic changes associated with lineage plasticity. Indeed, cfDNA methylation can distinguish NEPC from prostate adenocarcinoma (181), and other emerging approaches such as cfDNA nucleosome footprinting (182) and 5-hydroxymethylcytosine (5hmC) sequencing (183) may more robustly identify lineage plasticity changes as well as other epigenetic drivers of disease progression. Additional studies applying liquid biopsy platforms to evaluate lineage plasticity, with the aim of improving early detection strategies, disease monitoring and therapy selection, are warranted.

Distinguishing early facilitators, key drivers, and downstream consequences of lineage plasticity has important biomarker and therapeutic implications. For instance, an early facilitator such as *RB1* loss may not be sufficient to drive a change in phenotype but might still be a useful biomarker for strategies geared toward the prevention of lineage plasticity (184). Identifying key drivers or markers of lineage plasticity such as TF activity, stem cell features, transcriptome and/or DNA methylation changes, may serve to guide strategies geared towards targeting or reversing the plasticity process. Detecting downstream consequences of lineage plasticity, such as INSM1 or DLL3 expression that only emerges when a neuroendocrine differentiated state occurs, may be leveraged to target the new emergent phenotype (185).

9. Targeting lineage plasticity to treat cancer

Since lineage plasticity most often emerges as a mechanism for cancers to metastasize and/or bypass therapy, patients developing lineage plasticity often have a poor prognosis. There are no current strategies specifically tailored toward targeting the lineage plasticity process. As new therapies are developed in the context of lineage plasticity, the goal of treatment may be to prevent, reverse, or treat the new lineage. For example, based on the hypothesis that RB1 and TP53 alterations occur “before” the onset of SCLC lineage plasticity, an ongoing trial is using these markers to intervene early in patients with NSCLC with SCLC-chemotherapy regimens to potentially prevent cell state conversions and improve outcomes (NCT03567642). Approaches to target EMT-TFs or other lineage determinant TFs has been particularly challenging but, with advances in drug development including protein degraders, are looking increasingly feasible (186,187).

Using epigenetic therapies to reverse cancer cell lineage plasticity and induce ‘re-differentiation’, which in some cases can re-sensitize tumors to standard-of-care therapies, is a compelling concept. Notably, this strategy would only be effective in the context of cancer cell states that are capable of transitioning and not ‘locked in’ to new lineages. One prominent example is prostate cancer, whereby acquired neuroendocrine-like states can be reversed by EZH2 inhibition, which in some cases results in re-expression of the AR and re-sensitization to AR-targeted therapies (34,72). This effect is in part due to the catalytic function of EZH2 (i.e. H3K27 trimethylation) but also via a non-canonical role of EZH2 in driving lineage plasticity by forming transcriptional complexes with N-Myc and AR (34,56). LSD1 inhibitors can reverse neuroendocrine phenotypes in prostate cancer and SCLC and are also emerging as a viable strategy to re-differentiate cancer cells for therapeutic benefit (109,188). Various epigenetic therapies including EZH2 inhibitors (eg., tazemetostat, valemetostat, PF-06821497, CPI- 0209) and LSD1 inhibitors (e.g., CC-90011, seclidemstat, JBI-802) are in clinical development across solid tumors but trials are currently in biomarker-unselected populations. Since these epigenetic therapies target factors with pleiotropic functions, understanding how they modulate lineage plasticity and/or act to ‘re-differentiate’ tumors, and in which context, will be critical. Co-targeting epigenetic pathways along with lineage-specific drivers in patients at high risk of developing lineage plasticity, or sequentially cycling between these distinct therapeutic approaches, are intriguing possibilities but are yet to be tested clinically.

Arguably the most exciting application of plasticity-suppressing epigenetic therapies is to prime tumors for immune rejection. As described above, key epigenetic mediators of lineage plasticity (i.e. EZH2, LSD1 and DNMT1) play a critical role in establishing chromatin states that result in repression of immune-activating genes and activation of immune-inhibitory genes (Figure 3). It is therefore unsurprising that targeting these enzymes potentiates response to ICIs (99,174–176,189,190). Furthermore, epigenetic therapies can also activate immune signaling through the viral defense pathway, a process referred to as “viral mimicry”. More specifically, inhibitors of EZH2, DNMT1 and LSD1 lead to de-repression of endogenous retroviruses, resulting in accumulation of dsRNA and anti-tumor type-I interferon (IFN) responses, a phenomenon that can be harnessed to improve tumor response to ICIs (191–197). Importantly, combining DNMT inhibitors with histone deacetylase inhibitors (HDACis) was found to enhance viral mimicry and immunotherapy responses in non-small cell lung cancer and ovarian cancer models (193,194). Collectively, these studies demonstrate that epigenetic reprogramming associated with lineage plasticity can mediate immune escape and uncover novel therapeutic strategies for immunosensitization.

Could lineage plasticity be harnessed to treat cancer? Historical and emerging evidence suggests that highly plastic malignant cells may be susceptible to enforced transdifferentiation into post-mitotic differentiated cells. This strategy has been applied for decades in acute promyelocytic leukemia by treatment with the retinoid all-trans retinoic acid, which induces terminal differentiation of leukaemic cells into granulocytes via activation of retinoic acid receptor-α (198). The application of differentiation therapy in solid tumors has been long studied with several agents including retinoids, histone deacetylase inhibitors, and PPARγ agonists inducing differentiation in solid tumor models (198). While this approach has been challenging to translate to clinical benefit, an

increased understanding of differentiation and lineage plasticity processes has resulted in new opportunities. For example, in preclinical models of breast cancers developing EMT *in vivo*, forced transdifferentiation of cancer cells into post-mitotic adipocytes via the combination of MEK inhibition and the PPAR-gamma agonist rosiglitazone resulted in cell cycle arrest and repression of tumor growth and metastasis (199). Another breast cancer study demonstrated that retinoids can reverse EMT (i.e. promote MET) and thereby block metastasis of breast cancer, which occurs at least in part by causing a metabolic switch whereby fatty acids are directed towards lipid storage rather than β-oxidation (200). In *IDH1*-mutant glioma organoids or models of *IDH1*-mutant biliary cancer that exhibit dedifferentiation due to accumulation of 2-hydroxyglutarate, inhibition of IDH1 or DNA methylation using azacytidine enables tumor control at least in part by promoting differentiation (201,202). Chemotherapy-mediated lineage plasticity in urothelial carcinoma leads to semi-squamatization and targeting of cathepsin H promoted terminal squamous differentiation and cell death via pyroptosis (203).

Since lineage plasticity is often detected late after changes in phenotype manifest clinically, patients are typically treated based on their new histology extrapolated from other cancer types. Nonetheless, they still might harbor features of their ancestral tumor of origin, which should also be considered for disease management. The prognosis of lineage plasticity tends to be poor regardless of tumor type or mechanism of plasticity. An increased understanding of the biology of lineage plasticity and collaborative efforts across cancer types will hopefully lead to better biomarkers and therapies for this growing subgroup of cancer patients.

10. Conclusions and future perspectives

Lineage plasticity is a hallmark of cancer and a critical facilitator of other oncogenic features such as metastasis, therapy resistance, dysregulated metabolism, TME reprogramming and immune evasion. The centrality of phenotypic plasticity in cancer progression necessitates dissection of the molecular mediators and regulators of this phenomenon and development of strategies to effectively target them. Herein, we have focussed on the transcriptional and epigenetic mechanisms that mediate cell state transitions in cancer, in the process highlighting features of these phenomena that may be exploited for patient benefit.

Given the extreme epigenomic/transcriptomic heterogeneity in cell states that can be found in highly plastic tumors, the advent of high-throughput single cell and spatial profiling techniques alongside tools to trace individual cells are anticipated to drive progress in this field. Similarly, tumor models that accurately recapitulate the various manifestations of plasticity and which can be sampled at relevant time-points are critical. However, one major challenge will be to effectively unravel and exploit the cell atlases that will arise from these comprehensive large-scale approaches; high-throughput genetic perturbation strategies will assist in this respect.

Achieving a more complete understanding of the fundamental epigenetic/transcriptional mechanisms underlying cell state transitions in cancer will unlock new therapeutic strategies to target, and tools to monitor, lineage plasticity. In this respect, a key question that remains

poorly understood is whether plasticity is a cause or consequence of therapy resistance. We propose that evaluation of rational combinatorial strategies will provide major insights into this question and are likely to be necessary to realise significant benefit for patients. Using epigenetic therapies to sensitize tumors to immunotherapies and/or re-sensitize tumors to drugs that block distinct oncogenic signalling pathways is a compelling possibility that is under clinical evaluation. Of course, context will be key for effective targeting of lineage plasticity for patient benefit. While a goal of precision cancer medicine is to treat patients with the right treatment at the right time, excess plasticity enables cancer cells to effectively deal with environmental stressors, signals and therapy by switching on the right phenotype(s) at the right time. Since epigenetics and TFs play a major role in this extreme adaptability, understanding their context-dependent activities will be crucial to improve precision cancer medicine.

Acknowledgements

This study was supported by: the Cancer Council of South Australia (2012127 to LAS); a joint grant from the Freemasons Centre for Male Health and Wellbeing and Flinders Foundation (LAS); Cancer Council New South Wales (23-04 to LAS); Terry Fox New Frontier Program Project (F22-00589 to AZ); the Canadian Institutes of Health Research (CIHR-169173 to AZ); U.S. Department of Defense (W81XWH-17-1-0653 to HB; W81XWH-18-1-0690 to AZ); the Prostate Cancer Foundation; and the National Institutes of Health (NIH) / National Cancer Institute (NCI) (R37CA241486 to HB; P50-CA211024 to HB). LAS is supported by a Principal Cancer Research Fellowship awarded by Cancer Council's Beat Cancer project on behalf of its donors, the state Government through the Department of Health, and the Australian Government through the Medical Research Future Fund. The authors apologize that, due to space limitations, many important studies in the field could not be cited.

Author disclosures

AD is employed by and holds stock in Pfizer, Inc. HB has served as consultant/advisory board member for Janssen, Astellas, Astra Zeneca, Merck, Pfizer, Foundation Medicine, Blue Earth Diagnostics, Amgen, Bayer, Oncorus, LOXO, Daicchi Sankyo, Curie Therapeutics, and has received research funding (to institution) from Janssen, AbbVie/Stemcentrx, Eli Lilly, Astellas, Millennium, Bristol Myers Squibb, Circle Pharma, Daicchi Sankyo and Novartis. No disclosures were reported by the other authors.

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Box 1.

Shared transcriptional and epigenetic features of lineage plasticity and implications for cancer treatment

The diversity and breadth of oncogenic lineage plasticity – whereby tumors exhibit diverse manifestations of plasticity in response to the unique set of external pressures to which they are exposed, with the consequent possibility being almost limitless unique cellular states – creates a formidable barrier to fully understanding and effectively targeting this phenomenon to improve patient outcomes. Although the explosion of research in this field in the past 2 decades or so has exacerbated the complexity of this issue, it has also revealed convergent transcriptional and epigenetic mechanisms and principles that can guide the development of tools to monitor and target cancer cell lineage plasticity.

The Snail, Twist, and Zeb families of EMT-TFs represent one such convergent mechanism. As outlined in Section 3, these factors mediate a diverse array of cell state transitions beyond EMT. The mechanisms underlying the “pan-plasticity” activity of EMT-TFs remain to be fully elucidated, although one possibility is that these factors directly promote distinct oncogenic transdifferentiation events in a context-dependent manner: for example, Twist can repress the E-cadherin (*CDH1*) gene to drive EMT and can also activate vascular endothelial (VE)-cadherin (*CDH5*) expression during epithelial-endothelial transition (see Section 3). Another (non-mutually exclusive) mechanism is that EMT-TFs promote dedifferentiation and rely on other transcriptional and epigenetic regulators to endow cells with new lineage states, a concept supported by well-described roles for EMT-TFs in enhancing dedifferentiation and stemness in cancer, in some cases independent of their EMT-inducing capacity (see Section 3). Whatever the mechanism, “pan-plasticity” EMT-TF activity would enhance the adaptability of cancer cells and thereby maintain fitness in the face of environmental pressures such as therapies, nutrient deprivation and immune attack. It follows that suppressing the activity of these factors may be an effective approach to block multiple aggressive features of tumors; initially thought to be “undruggable”, it is now recognised that oncogenic TFs are *bona fide* targets (see Section 9).

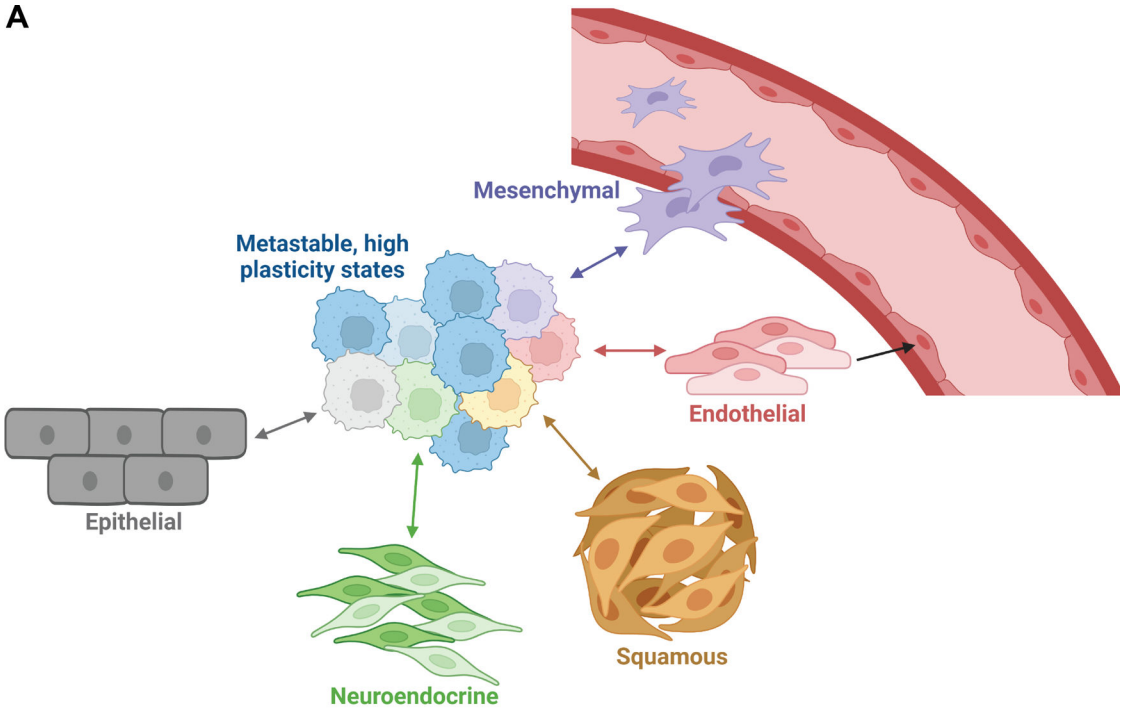
Another molecular principle underpinning cancer cell plasticity is the ability to rapidly modulate gene expression programs by reprogramming chromatin states, with one prominent example being the exploitation of bivalent chromatin (see Section 3). Elevated activity of enzymes and other factors that regulate epigenetic topographies in cancer cells enables activation of pro-plasticity genes and repression of genes responsible for maintaining the original differentiated state, a phenomenon that is a prominent feature of malignancy-associated cell state transitions. The druggability of epigenetic enzymes, as well as the availability of molecular tools to monitor their activity, has facilitated the development of therapeutic strategies to counter plasticity-associated chromatin reprogramming (see Sections 8–9).

Lineage plasticity is also frequently associated with acquisition of immune-evasive phenotypes. In multiple cancer types and across distinct manifestations of cell state

transitions, plasticity-promoting TFs and epigenetic enzymes have been found to suppress immune-activating genes and induce immune-inhibitory genes (see Section 7). This may have important implications for application of immunotherapies. More specifically, therapies that suppress lineage plasticity could induce anti-tumor immune responses and be fast-tracked into immunotherapy combination trials; additionally, markers of lineage switching and stemness could be used to identify patients unlikely to respond to immunotherapies and thereby guide treatment decision-making.

Significance

Lineage plasticity is a hallmark of cancer and a critical facilitator of other oncogenic features such as metastasis, therapy resistance, dysregulated metabolism and immune evasion. It is essential that the molecular mechanisms of lineage plasticity are elucidated to enable the development of strategies to effectively target this phenomenon. In this review, we describe key transcriptional and epigenetic regulators of cancer cell plasticity, in the process highlighting therapeutic approaches that may be harnessed for patient benefit.



B

	Epithelial ↔ Mesenchymal	Epithelial ↔ Neuroendocrine	Epithelial ↔ Squamous	Epithelial ↔ Endothelial
Cancer types	Ubiquitous in epithelial cancers	Prostate, lung, bladder, pancreas	Pancreas, lung, prostate, bladder, esophageal	Melanoma, lung, breast, prostate, glioblastoma
Key lineage-determining factors	Snail, Slug, Twist, ZEB1/2, GRHL2	SOX2, BRN2, ASCL1, FOXA2, N-Myc	TP63, SOX2, Myc, c-FOS	Twist, ZEB1, Slug, VE-cadherin
Genomic aberrations	*KRAS* GOF	*RB1*, *TP53*, *AR* LOF *MYC* OE	*KRAS* GOF, *KDM6A* LOF, *MYC* OE	Unknown
Reversibility	Yes (MET)	Pre-clinical evidence	Pre-clinical evidence	Pre-clinical evidence

Figure 1. Lineage plasticity triggers phenotypic and histological diversity within a tumor.

(A) During cancer progression, malignant cells can lose their epithelial identity and enter a hybrid state characterized by heightened plasticity that is primed for multi-lineage differentiation. Varying combinations of transcriptional and epigenetic changes within these hyper-plastic cells, as well as microenvironmental influences, drive transdifferentiation into divergent lineages. Active and bi-directional reprogramming supports tumor growth, metastasis and escape from lineage-directed therapies. **(B)** Major features of distinct manifestations of cancer cell lineage plasticity. GOF, gain of function; LOF, loss of function; MET, mesenchymal-epithelial transition; OE, overexpression. Created with BioRender.com.

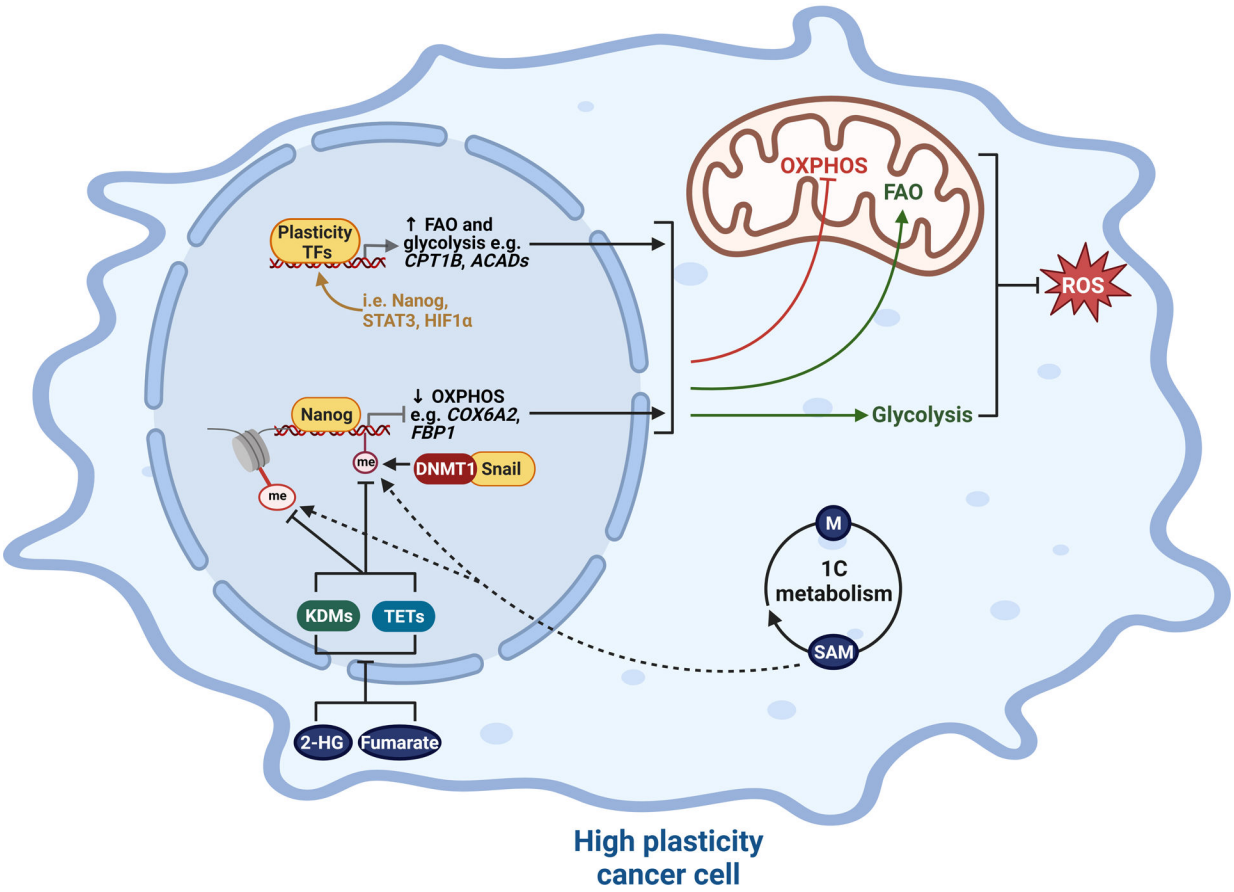


Figure 2. Interplay between transcriptional and epigenetic mediators of lineage plasticity and cancer cell metabolism.

Plasticity-enhancing transcription factors (TFs) and epigenetic enzymes regulate a gene expression program that favors fatty acid oxidation (FAO) and glycolysis over oxidative phosphorylation (OSPHOS), one consequence of which is suppression of ROS production. Concomitantly, oncometabolites impinge on multiple transcriptional/epigenetic mechanisms, prominent examples being dysregulation of histone and DNA methylation by elevated levels of S-Adenosyl methionine (SAM), 2-Hydroxyglutarate (2-HG) and fumarate. 1C metabolism = one carbon metabolism; ACADs = acyl-CoA dehydrogenases; KDMs, lysine demethylases; me, methyl groups; TETs, ten-eleven translocation methylcytosine dioxygenases. Created with BioRender.com.

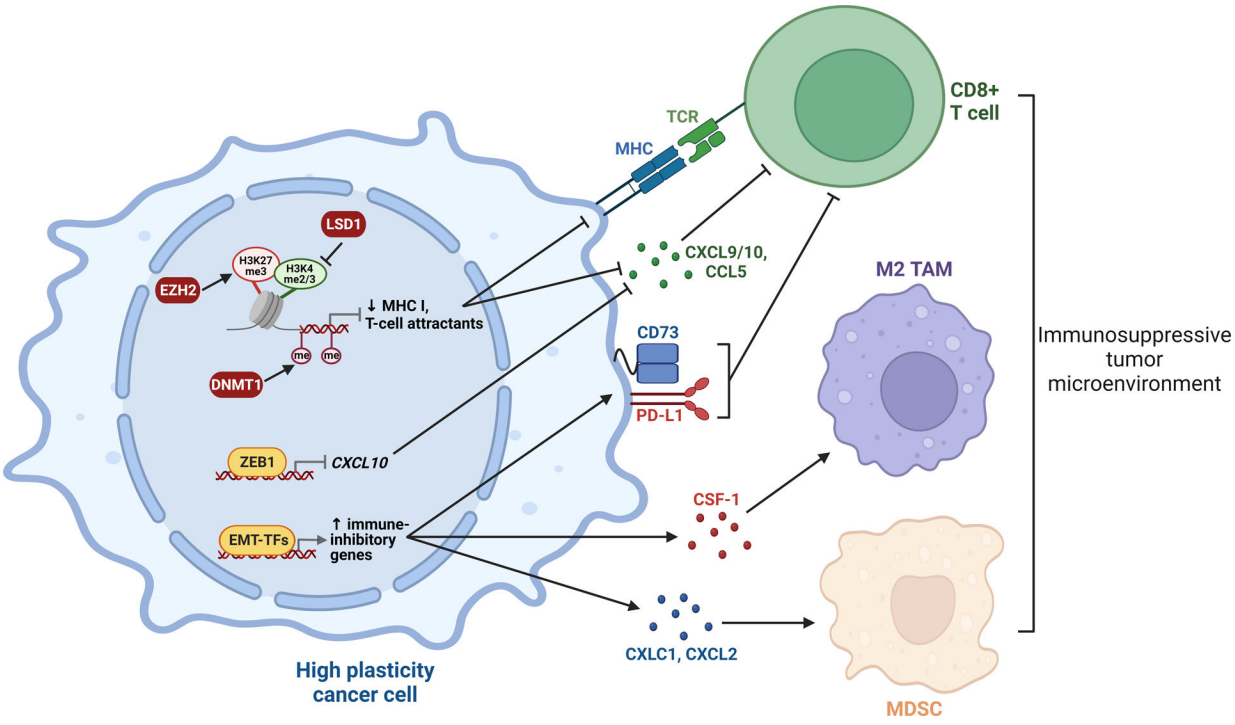


Figure 3. Cancer cell plasticity as a driver of immune escape.

Plasticity-enhancing transcription factors and epigenetic enzymes downregulate immune-activating genes and upregulate immune-inhibitory genes, resulting in escape or exclusion of tumor-killing CD8+ T cells and recruitment of M2 tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs). Thus, the high plasticity state is associated with cancer cell evasion of the immune system. EMT-TFs, EMT transcription factors; MHC, major histocompatibility complex; me, methyl groups; TCR, T cell receptor. Created with BioRender.com.