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Immunotherapy-mediated cancer reversion: Possibilities and prospects

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ABSTRACT

Immunotherapy has revolutionized cancer treatment by enabling durable tumor control through immune activation. Emerging evidence suggests that beyond cytotoxic elimination, immune responses can reprogram malignant cells toward normalized, differentiated states, a phenomenon termed immunotherapy-mediated cancer reversion. This paradigm shift positions the immune system as a restorative rather than solely destructive force. This review synthesizes contemporary evidence on immunotherapy-mediated cancer reversion, evaluating mechanistic pathways and clinical implications across diverse malignancies to establish a conceptual framework for immune-driven phenotypic normalization. A comprehensive narrative review was conducted across PubMed, Web of Science, and Scopus databases, encompassing literature from 2015 to 2025. Evidence was synthesized thematically across immune checkpoint blockade, adoptive cell therapies, cytokine modulation, and microenvironmental remodeling. Immune-mediated reversion arises through coordinated epigenetic, metabolic, and microenvironmental reprogramming. Checkpoint inhibitors restore differentiation programs via IFNγ-driven chromatin remodeling, while CAR-T and NK-cell therapies induce metabolic normalization and epithelial restoration. Cytokine signaling and macrophage reprogramming reinforce reversion by modulating angiogenesis and stromal architecture. Clinical observations across melanoma, lung cancer, breast cancer, hematologic malignancies, and hepatocellular carcinoma support this restorative immune process. Single-cell and spatial omics identify transitional states bridging malignancy and normalcy. Immunotherapy-mediated cancer reversion represents a conceptual frontier shifting oncology from eradication to restoration. Future progress requires defining biomarkers, confirming mechanistic permanence, and redesigning clinical endpoints. As integrative immuno-epigenetic frameworks mature, immune-driven reversion may evolve from biological curiosity to clinically reproducible pathway toward durable remission and functional cure.

Abbreviations: Adoptive cell therapy, ACT; Anaplastic lymphoma kinase, ALK; Acute myeloid leukemia, AML; All-trans retinoic acid, ATRA; Chimeric antigen receptor T-cell, CAR-T; Cytokine-induced senescence, CIS; Carnitine palmitoyltransferase 1 A, CPT1A; Colony stimulating factor 1 receptor, CSF1R; Cytotoxic T-lymphocyte-associated protein 4, CTLA-4; DNA methyltransferase, DNMT; Epithelial-mesenchymal transition, EMT; Estrogen receptor, ER; Enhancer of zeste homolog 2, EZH2; Glioblastoma, GBM; Hepatocellular carcinoma, HCC; Histone deacetylase, HDAC; Human epidermal growth factor receptor 2, HER2; Hepatocyte nuclear factor 4 alpha, HNF4A; Immune checkpoint inhibitor, ICI; Interferon-gamma, IFNγ; Interleukin, IL; Interferon regulatory factor 1, IRF1; Kirsten rat sarcoma viral oncogene, KRAS; Myelodysplastic syndromes, MDS; Major histocompatibility complex, MHC; Microphthalmia-associated transcription factor, MITF; Microsatellite instability-high, MSI-H; Myelocytomatosis oncogene, MYC; Natural killer, NK; Non-small cell lung cancer, NSCLC; Programmed cell death protein 1, PD-1; Programmed death-ligand 1, PD-L1; Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, PGC-1α; Progesterone receptor, PR; Senescence-associated secretory phenotype, SASP; Small cell lung cancer, SCLC; Sirtuin 3, SIRT3; Signal transducer and activator of transcription 1, STAT1; Tumor-associated macrophage, TAM; T-cell receptor, TCR; Ten-eleven translocation 2, TET2; Transforming growth factor beta, TGFβ; Toll-like receptor, TLR; Tumor mutational burden, TMB; Tumor microenvironment, TME; Triple-negative breast cancer, TNBC; Tumor necrosis factor alpha, TNFα; Tyrosinase, TYR.

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1. Introduction

Cancer remains one of the most formidable challenges in contemporary medicine, characterized by complex molecular heterogeneity, therapeutic resistance, and immune evasion that collectively undermine curative efforts (Hanahan, 2022; Sharma et al., 2021). The past decade has witnessed the rapid evolution of immunotherapy as a transformative modality in oncology, reshaping therapeutic paradigms through immune checkpoint blockade, adoptive cell transfer, and engineered cytokine systems (Topalian et al., 2015; Ribas and Wolchok, 2018). In the context of lung cancer specifically, novel therapeutic targets and immunotherapy approaches have demonstrated remarkable clinical efficacy across non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) subtypes, with checkpoint inhibitors such as PD-1/PD-L1 and CTLA-4 blockade becoming integral components of treatment regimens (Khadela et al., 2023; O'Leary et al., 2024). These strategies have produced durable responses across several malignancies, including melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma, thereby validating the immune system as a potent determinant of cancer fate (Hodi et al., 2018). Beyond its cytotoxic effects, emerging evidence suggests that immunotherapy can influence the intrinsic state of tumor cells and their microenvironment, initiating processes that resemble cellular reprogramming or reversion toward less malignant phenotypes (Dong et al., 2021).

Cancer reversion, traditionally investigated within the framework of developmental biology and epigenetic plasticity, describes the process by which malignant cells revert to a non-malignant or less aggressive phenotype while maintaining viability and functional integrity (Feinberg, Koldobskiy and Göndör, 2016; Oisakede et al., 2025). This phenomenon is founded on key biological observations including somatic cell reprogramming, spontaneous cancer regression, and microenvironmental influences on malignant behavior. Unlike cytotoxic elimination, cancer reversion therapy aims to reprogram malignant cells toward normalized states through mechanisms including epigenetic reprogramming using HDAC inhibitors and DNA methyltransferase inhibitors, microenvironmental modulation, differentiation therapy, and targeting oncogene addiction (Hanahan, 2022; Oisakede et al., 2025). Historically, reversion was viewed as a laboratory phenomenon, supported by observations that environmental or genetic modulation could normalize cancer cell behaviour in vitro (Tripathi et al., 2021). However, the interplay between the immune system and cellular reprogramming introduces a new biological dimension on how cancer can be controlled. Recent studies show that the immune system can do more than just attack tumour cell, it can also reprogram them toward a more normal, less aggressive state. This process, known as immunologically mediated phenotype reversion, which involves restoring vital functions such as MHC-I expression, allowing the immune system to restore homeostatic regulation and promote phenotypic normalization (Auclair, 2021).

This emerging perspective redefines immunotherapy as not solely destructive but also restorative, capable of reinstating normal differentiation trajectories, reorganizing tissue architecture, and re-establishing immune-epithelial equilibrium.

Clinical and experimental studies provide evidence supporting this notion. Immune checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4 antibodies can induce transcriptional reprogramming of tumor cells, enhancing differentiation markers and reducing stem-like traits (Hugo et al., 2016; Liu et al., 2021). Similarly, adoptive T-cell therapies particularly CAR-T and TCR-T cells have been shown to remodel the tumour microenvironment, inducing metabolic and signalling changes that reflect a partial restoration of normal cell behaviour, shifting the tumour calls toward a more regulated, immune-responsive state (Xia et al., 2024; Van et al., 2024). These effects are frequently accompanied by immune-induced remodeling of stromal and vascular networks, reduction of hypoxia, and normalization of extracellular matrix interactions, all of which are conducive to reverting malignancy-associated phenotypes (Jain, 2013; Markowitz et al., 2018). Moreover, cytokine-driven immune responses, notably those mediated by interferons and interleukins, have demonstrated the capacity to induce senescence and differentiation, further implicating immune pathways in phenotypic normalization (Beyer et al., 2016; Cassetta and Pollard, 2023).

At the conceptual level, immunotherapy-mediated cancer reversion aligns with the broader biological principle that the tumor phenotype is dynamic and context-dependent rather than fixed by irreversible genetic mutations (Meacham and Morrison, 2013). The immune system, as a central regulator of tissue integrity, provides continuous surveillance and correction of aberrant cellular states. Dysregulation of this process underlies oncogenesis, while its reactivation through therapeutic intervention may re-establish normalcy. Immunotherapy thus offers a dual potential: the destruction of immunogenic malignant clones and the restoration of physiological regulation in surviving cells.

Despite these promising indications, critical questions persist. The mechanisms through which immune responses trigger or stabilize reversion remain poorly defined, and the extent to which these effects contribute to clinical remission is uncertain. Furthermore, distinguishing reversion from immune-induced cytostasis or tumor dormancy presents a major interpretative challenge. There is also limited understanding of how immune-driven epigenetic and metabolic reprogramming interacts with the intrinsic plasticity of cancer cells to sustain non-malignant phenotypes over time.

This review explores the emerging paradigm of immunotherapy-mediated cancer reversion by integrating current evidence from the past decade (2015–2025) with foundational immunological and oncological principles. It critically evaluates how modern immunotherapies modulate tumor cell states, remodel the microenvironment, and engage developmental or epigenetic pathways that may facilitate reversion. Specific attention is given to mechanistic insights from checkpoint blockade, adoptive cell transfer, and cytokine therapies, as well as to the technologies enabling their study, including single-cell and spatial multi-omics. Finally, the review identifies major challenges and knowledge gaps that must be addressed to translate immunological reversion from experimental observation to therapeutic strategy.

2. Methods

2.1. Search strategy and selection criteria

This narrative review synthesizes contemporary evidence on the intersection of immunotherapy and cancer reversion. A comprehensive literature search was conducted across PubMed, Web of Science, and Scopus databases to identify studies published between January 2015 and October 2025. The search strategy employed Boolean combinations of keywords, including *"immunotherapy"*, *"cancer reversion"*, *"tumor reprogramming"*, *"immune differentiation"*, *"immune-induced normalization"*, *"immune plasticity"*, *"phenotypic reversion"*, and *"tumor microenvironment modulation"*. These terms were cross-referenced with *"checkpoint inhibitors"*, *"CAR-T"*, *"cytokine therapy"*, *"immune remodeling"*, and specific cancer types (e.g., melanoma, lung, breast, hematologic malignancies).

Additionally, bibliographic searches of relevant review articles and meta-analyses were performed to identify earlier key references providing foundational insights. Grey literature, preprints, and non-peer-reviewed content were excluded. Clinical trials were identified using ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

2.2. Inclusion and exclusion criteria

Included studies met at least one of the following criteria:

1. Original research demonstrating immunotherapy-induced differentiation, senescence, or tumor phenotype normalization.
2. Preclinical or clinical studies describing immune microenvironment remodeling associated with stable phenotypic reprogramming.
3. Studies unveiling mechanisms linked to immunologic or cytokine signaling to cellular reprogramming or epigenetic modulation (Ivashkiv and Park, 2016; Pang et al., 2024).

Exclusion criteria were:

- Studies focused exclusively on cytotoxic immune mechanisms without evidence of reversion or normalization.
- Reports lacking mechanistic interpretation or failing to distinguish between tumor elimination and phenotypic reprogramming.
- Case reports without molecular or histological analysis of reversion-related phenomena.

2.3. Data extraction and thematic synthesis

Data were extracted manually and organized thematically rather than chronologically, structured around four central axes:

(a) checkpoint inhibitor-mediated transcriptional reprogramming;
(b) adoptive cell therapy and immune-driven differentiation;
(c) cytokine-induced senescence and tissue normalization; and
(d) immune microenvironmental modulation and stromal remodeling.

For each theme, findings were analyzed across mechanistic, preclinical, and translational contexts. Where available, data on clinical endpoints such as durable remission, histological normalization, and biomarker changes were integrated to assess relevance to cancer reversion.

2.4. Quality assessment

Because the review is narrative, formal meta-analytic techniques were not employed. However, methodological rigor was assessed based on study design, reproducibility, and clarity of mechanistic interpretation. Studies were prioritized when results were validated independently or supported by single-cell or spatial multi-omics data that confirmed immune-induced phenotypic transitions.

3. Conceptual framework: immunological basis of cancer reversion

3.1. Defining immunotherapy-mediated cancer reversion

Cancer reversion describes the process by which malignant cells revert to a non-malignant or less aggressive phenotype while maintaining viability and functional integrity (Oisakede et al., 2025). Within the immunological context, reversion is hypothesized to occur when immune activation restores the homeostatic and regulatory networks that control cellular differentiation, metabolism, and communication within tissues (Koelsch et al., 2024). Unlike cytotoxic elimination, this mechanism represents immune re-education of malignant cells, steering them toward phenotypic normalization through cytokine signaling, epigenetic reprogramming, and microenvironmental restructuring.

3.2. Immunological principles underpinning reversion

The immune system serves as a dynamic regulator of tissue identity, continuously monitoring and correcting aberrant cellular states. The classical “three Es” model of cancer immunoediting; Elimination, Equilibrium, and Escape originally described the phases through which immune pressure shapes tumor evolution (Dunn et al., 2004). Recent evidence, however, suggests an additional dimension called restoration, in which immune activity can reverse malignant programming without complete elimination (Škarková et al., 2024). This restorative phase is characterized by immune-mediated differentiation, senescence induction, and normalization of stromal and vascular architecture.

Cytokines such as interferon-gamma (IFNγ) and transforming growth factor-beta (TGFβ) play key roles in this process. IFNγ can promote tumor cell differentiation and antigen presentation while modulating chromatin accessibility through histone acetylation and DNA demethylation (Beyer et al., 2016). Conversely, TGFβ signaling exhibits dual roles, suppressing immune cytotoxicity yet driving differentiation and tissue remodeling in certain contexts (Mariathasan et al., 2018). Together, these pathways highlight the immune system’s capacity to recalibrate tumor phenotype rather than solely eradicate transformed cells.

3.3. Immune-microenvironmental crosstalk

Tumor progression and reversion are determined not only by intrinsic mutations but also by the microenvironmental context. The tumor microenvironment (TME) consists of immune cells, fibroblasts, endothelial networks, and extracellular matrix components that collectively shape cell fate (Binnewies et al., 2018; Hinshaw and Shevde, 2019; Wang et al., 2023). Immune activation can remodel this niche toward normalization. M1-polarized macrophages and cytotoxic lymphocytes secrete pro-differentiation cytokines (IL-12, TNFα) that can reduce epithelial-mesenchymal transition (EMT), restore E-cadherin expression, and reestablish tissue polarity (Cassetta and Kitamura, 2018). Similarly, dendritic cells and natural killer (NK) cells modulate metabolic reprogramming in tumors, promoting oxidative phosphorylation over glycolysis, a hallmark of differentiated states (Reinfeld et al., 2021).

Importantly, vascular normalization induced by immune activation enhances perfusion, oxygenation, and drug delivery, contributing indirectly to tumor cell reversion (Jain, 2013; Yu et al., 2023). These collective immune–stromal interactions underscore a bidirectional regulation where immune cells not only target malignant clones but also reconstitute the architecture and signaling fidelity of the tissue microenvironment. As illustrated in Fig. 1, immune activation simultaneously engages tumor-intrinsic and microenvironmental pathways that facilitate phenotypic normalization.

This figure summarizes the proposed multi-layered process through which modern immunotherapies induce cancer reversion. Immune checkpoint blockade, adoptive cell therapies, and innate cytokine signaling collaborate to remodel tumor-intrinsic epigenetic programs, restore antigen presentation, normalize metabolism, and reorganize the tumor microenvironment. These immune-driven pressures shift malignant cells from a dedifferentiated, glycolytic, and immunoevasive state toward a more differentiated, metabolically regulated, and immunologically integrated phenotype, consistent with functional reversion.

3.4. Epigenetic and metabolic rewiring through immune signaling

Epigenetic reprogramming represents a central mechanism through which immune activity can induce reversion. IFNγ and TNFα signaling modulate the expression of chromatin modifiers such as TET2, DNMT3A, and EZH2, thereby reshaping transcriptional landscapes toward differentiation (Cheng et al., 2024; Ivashkiv, 2018). Studies using single-cell RNA sequencing have demonstrated that tumors responding to checkpoint blockade exhibit transcriptional profiles resembling developmental intermediates rather than terminally malignant states (Miller et al., 2019; Beltra et al., 2020). Furthermore, immune-driven metabolic normalization plays a complementary role. Activated T cells and macrophages secrete metabolites such as itaconate and succinate that act as epigenetic cofactors, influencing histone and DNA methylation patterns in neighbouring tumor cells (Li, Wu and Hu, 2021). This

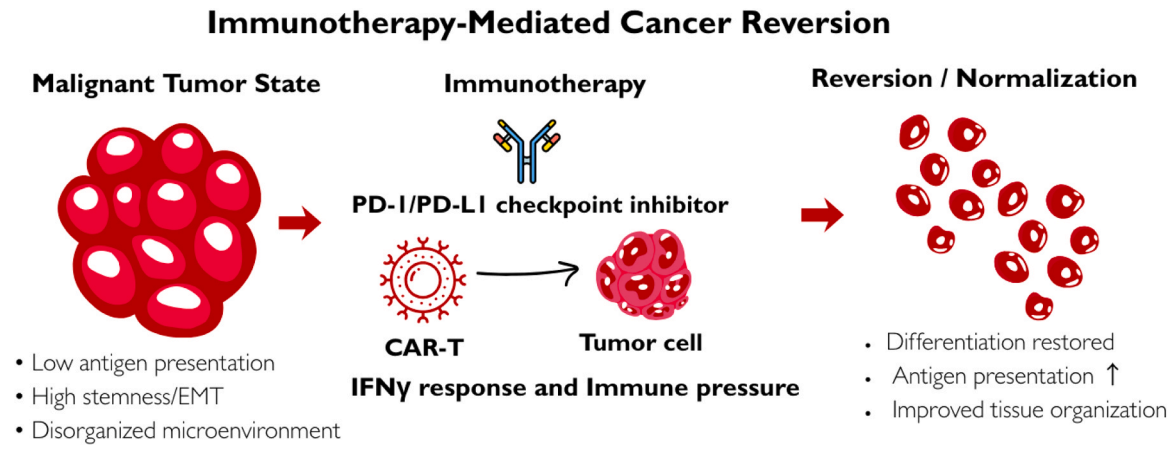

Fig. 1. Mechanistic framework of immunotherapy-mediated cancer reversion.

immunometabolism coupling can enforce stable reprogramming, limiting dedifferentiation and metastasis.

3.5. Clinical implications of immune-induced normalization

Clinically, evidence of immunotherapy-induced normalization has been observed in melanoma and NSCLC, where durable responses to checkpoint blockade are accompanied by histological differentiation, reduction of stem-like markers, and restoration of normal tissue morphology (Hugo et al., 2016; Hodi et al., 2018). Clinically, the determination of reversion or restoration of normal tissue morphology relies on multiple complementary techniques. Histological differentiation is assessed through standard hematoxylin and eosin (H&E) staining combined with immunohistochemistry for lineage-specific markers such as MITF and TYR in melanoma, or hepatocytic markers (HNF4A, albumin) in liver cancers, reflecting transcriptional and phenotypic plasticity that can be captured by high-resolution molecular profiling (Tirosh et al., 2016). ranscriptional shifts toward differentiated cellular states. Imaging modalities including contrast-enhanced CT and MRI are used to document structural normalization of tissue architecture and vascular patterns, in accordance with immune-specific response assessment frameworks such as iRECIST (Seymour et al., 2017). Treatment duration with immune checkpoint inhibitors typically ranges from 3 to 6 months for initial response assessment, with durable responders maintained on therapy for 1–2 years or until disease progression, consistent with long-term clinical outcome data from checkpoint blockade trials (Topalian et al., 2014). The commonly utilized checkpoint inhibitors include pembrolizumab and nivolumab (anti-PD-1), atezolizumab (anti-PD-L1), and ipilimumab (anti-CTLA-4), administered as monotherapy or in combination regimens.

In haematological malignancies, differentiation therapy such as ATRA combined with checkpoint-inhibitor strategies like PD-1 blockade is being explored and has shown promise in enhancing remission rates and promoting more mature phenotypes (Olson and Luke, 2023). These findings suggest that immune-mediated reversion could complement existing therapies by promoting long-term disease stability without continuous cytotoxic pressure. However, the phenomenon remains incompletely characterized at the molecular level. Distinguishing stable reversion from transient immune suppression or dormancy requires longitudinal single-cell and spatial analyses. Integrating these tools into future clinical trials will be crucial to confirm whether immunotherapy-mediated reversion represents a distinct, therapeutically exploitable biological process.

4. Immunotherapeutic pathways driving cancer reversion

The immune system influences tumor behavior through complex, multilevel mechanisms extending beyond cytotoxic destruction. Recent studies suggest that specific immunotherapeutic modalities can redirect malignant cells toward differentiated, quiescent, or functionally normalized states, thus constituting a form of therapeutic reversion. Four primary mechanistic pathways underpin this phenomenon: (i) immune checkpoint reprogramming, (ii) adoptive cell therapy–driven differentiation, (iii) microenvironmental modulation, and (iv) cytokine-mediated and innate immune reprogramming.

4.1. Immune checkpoint inhibitors and phenotypic normalization

Immune checkpoint inhibitors (ICIs) have transformed cancer therapy, primarily through restoring cytotoxic T cell activity. However, beyond immune activation, checkpoint blockade can induce direct transcriptional and epigenetic reprogramming of tumor cells. Studies in melanoma and NSCLC have demonstrated that PD-1/PD-L1 inhibition triggers IFNγ-dependent chromatin remodeling, leading to increased expression of genes associated with differentiation, antigen presentation, and epithelial identity (Hugo et al., 2016; Liu et al., 2021).

Hugo et al. (2016) identified transcriptional signatures of differentiation in melanoma biopsies from responders to PD-1 blockade, with enrichment of melanocytic lineage markers such as MITF and TYR, suggesting partial re-differentiation of previously dedifferentiated tumor cells. Similarly, beyond tumor-intrinsic changes, Kumar and Chamoto (2021) reported that PD-1 blockade also reprograms immune-cell metabolism, restoring oxidative phosphorylation over glycolysis which is a metabolic profile associated with functional and differentiated immune phenotypes.

These findings imply that checkpoint blockade can drive immune-mediated normalization by releasing immune pressure that re-establishes differentiation programs and reverses dedifferentiation signals. Mechanistically, this is attributed to IFNγ-induced activation of STAT1 and IRF1 pathways, which modulate epigenetic regulators such as DNMT1 and TET2 (Beyer et al., 2016). This dual regulation not only enhances antigen presentation but also suppresses oncogenic transcription factors that maintain stemness, including *MYC* and *SOX2*. Checkpoint inhibition may thus promote a sustained phenotypic transition spanning both immune and tumour compartments potentially explaining the durable remissions observed in certain patients long after therapy discontinuation (Hugo et al., 2016; Ribas and Wolchok, 2018).

4.2. Adoptive cell therapies and immune-driven differentiation

Adoptive cell therapies (ACT), including CAR-T, TCR-T, and NK-based systems, provide compelling evidence that immune effector cells can remodel the phenotype of surviving tumour populations. In preclinical models, CAR-T cells have been shown to modulate

epithelial–mesenchymal and stemness programs in residual tumour cells, including altered expression of E-cadherin, Vimentin, CD44, and CD133, consistent with partial differentiation and reduced stem-like potential (He et al., 2023; Zhang et al., 2024). These findings support the view that adoptive immunotherapy can drive not only cytotoxic clearance but also immune-mediated phenotypic reprogramming within the tumour microenvironment.

Single-cell transcriptomic profiling revealed that these changes correlated with Metabolic remodeling induced by immune activation, including reduced glycolytic flux and enhanced mitochondrial oxidative phosphorylation, reflects a shift toward a less glycolytic, more normalized tumour phenotype (Zhou et al., 2024). Similarly, adoptive T-cell therapies, including TCR-engineered products, can remodel tumour phenotypes through cytokine-mediated signalling. Upon tumour recognition, these effector T cells release IFN-γ and TNF-α, which upregulate MHC class I and antigen-presentation machinery in tumour cells via epigenetic and transcriptional mechanisms, thereby enhancing tumour immunogenicity and promoting partial differentiation (Qin et al., 2021; Vlková et al., 2014).

NK cell therapies further exemplify immune-induced normalization. In preclinical breast cancer models, activated NK cells released exosomes containing microRNAs (miR-186, miR-155) capable of downregulating EMT-associated genes and restoring epithelial characteristics (Abdulmalik et al., 2025). Collectively, these findings demonstrate that adoptive immune cells not only eliminate malignant clones but also remodel surviving tumor populations toward differentiation and immune compatibility.

4.3. Immune modulation of the tumor microenvironment

The tumour microenvironment (TME) constitutes a key regulator of tumour-cell and immune-cell phenotypic stability. Strategies that remodel the TME for instance by targeting tumour-associated macrophages can help re-establish a more homeostatic, immune-responsive environment and set the stage for tumour-cell reversion.

Reprogramming of tumour-associated macrophages (TAMs) from a tumour-promoting (M2) to a tumour-suppressive (M1) phenotype contributes to immune-induced normalization by restoring cytokine balance, extracellular matrix organisation, and vascular integrity. Pharmacologic or antibody-based targeting of the CSF1R and PI3Kγ pathways enhances M1 polarisation, reduces fibrosis, and promotes vascular normalization (DeNardo et al., 2011; Kaneda et al., 2016). Similarly, CD40 agonists trigger macrophage activation that remodels the tumour stroma, reducing desmoplasia and promoting a more organised epithelial architecture (Beatty et al., 2011; Byrne et al., 2021).

Moreover, immune checkpoint blockade synergizes with tumor microenvironment (TME) normalization. In murine models, immune checkpoint blockade, including PD-1–directed therapy, has been shown to promote tumour vessel normalization characterized by increased pericyte coverage, improved perfusion, and reduced hypoxia thereby enhancing antitumor immunity (Tian et al., 2017; Shigeta et al., 2020; Song et al., 2020). Perivascular macrophages, which regulate angiogenesis and vascular permeability within the perivascular niche, are a key source of IFN-γ–inducible chemokines such as CXCL9 and CXCL10, and macrophage-derived CXCL9/CXCL10 are required for optimal antitumor immune responses following immune checkpoint blockade (Lewis et al., 2016; House et al., 2019). These microenvironmental changes are mechanistically linked to metabolic stabilization and reduced epithelial–mesenchymal transition (EMT), reflecting a reversion toward more organized tissue architecture (Fukumura and Jain, 2007; Jain, 2013; Fukumura et al., 2018).

4.4. Cytokine and innate immune reprogramming

Cytokines represent the biochemical mediators of immune reversion. Interferons, interleukins, and tumor necrosis factors exert pleiotropic effects that integrate immune activation with cellular reprogramming.

Interferon-gamma (IFNγ) induces differentiation through transcriptional control of lineage-specific factors. In melanoma, IFNγ signaling restores expression of melanocytic markers and reduces invasive capacity, effects that are enhanced by PD-1 blockade (Landsberg et al., 2012; Benci et al., 2016). Interleukin-12 (IL-12) enhances anti-tumor immunity by activating T and NK cells and indirectly promoting vascular normalization through IFNγ-mediated mechanisms (Mirlekar and Pylayeva-Gupta, 2021). In hepatocellular carcinoma, IL-15–based agonists enhance intratumoral T-cell function and augment anti-tumor immunity when combined with PD-1 blockade (Xu et al. (2021)).

Furthermore, activation of innate immune pathways through Toll-like receptors (TLRs) contributes to tumor control by reprogramming cytokine networks and promoting immunostimulatory microenvironments. Engagement of TLR3 or TLR7 triggers NF-κB and IRF signaling cascades that enhance type I interferon and proinflammatory cytokine production, leading to activation of dendritic cells, NK cells, and cytotoxic T cells (Javaid and Choi, 2020). Preclinical and early-phase clinical studies with TLR7 agonists such as 852 A have demonstrated potent innate immune activation and increased IFN-α–driven antitumor responses in patients with advanced malignancies (Dudek et al., 2007; Weigel et al., 2012). Collectively, these findings suggest that innate immune stimulation can reprogram the tumor microenvironment toward an immunogenic and differentiated state through cytokine-mediated remodeling rather than direct lineage conversion.

4.5. Combination and sequential approaches

Integrating immunotherapy with agents targeting epigenetic and metabolic regulators enhances reversion efficacy. DNA-methyltransferase inhibitors (DNMTi) and histone-deacetylase inhibitors (HDACi) can reactivate silenced immune pathways by inducing expression of endogenous retroelements and type I interferon signaling (Chiappinelli et al., 2015). Building on this mechanism, combined epigenetic and checkpoint-blockade therapies reverse immune evasion, reduce immunosuppression, and promote durable antitumor responses in preclinical lung and ovarian cancer models (Topper et al., 2017; Stone et al., 2017).

Recent combinatorial approaches integrating oncolytic viruses or metabolic modulators (e.g., metformin) with immunotherapy have demonstrated amplified reprogramming effects, including restoration of organized tissue architecture and suppression of metastatic potential (Cao and Yan, 2020). These multimodal paradigms may help overcome intrinsic tumor heterogeneity and stabilize immune-mediated reversion. Table 1 summarizes key therapeutic modalities, underlying mechanisms, and representative findings reported over the past decade. Fig. 2 summarizes the major immunotherapeutic pathways that collectively drive phenotypic normalization and reversion.

This figure highlights four mechanistic classes through which immunotherapies shift malignant cells toward normalized phenotypes: (1) immune checkpoint inhibitors inducing IFNγ-dependent epigenetic remodeling; (2) adoptive cell therapies enforcing differentiation and metabolic correction; (3) microenvironmental modulation via macrophage reprogramming and stromal normalization; and (4) cytokine and innate immune pathways promoting lineage restoration and senescence. These pathways converge to support sustained phenotypic reversion across diverse cancer types.

5. Evidence from recent studies (2015–2025)

Over the past decade, a growing body of evidence has revealed that various forms of immunotherapy can modulate tumor phenotype and microenvironmental organization in ways that reflect cancer reversion. These effects have been documented in multiple tumor types, ranging from melanoma and NSCLC to breast, hematologic, glioblastoma and hepatic malignancies. While many observations remain correlative,

Table 1
Key immunotherapeutic pathways implicated in cancer reversion (2015–2025).

Therapeutic Modality	Mechanistic Basis of Reversion	Representative Findings	Key References
Checkpoint Inhibitors (PD-1/PD-L1, CTLA-4)	IFNγ-driven epigenetic remodeling; restoration of differentiation programs; suppression of stemness genes	Melanoma and NSCLC biopsies show increased *MITF* and *TYR* expression in responders; oxidative metabolic reprogramming	Hugo et al., 2016; Jiang et al., 2025
CAR-T/TCR-T/NK Cell Therapies	Cytokine-induced differentiation; metabolic normalization; EMT reversal	CAR-T cells induce E-cadherin restoration in residual tumor cells; NK- derived exosomes revert EMT	Xia et al., 2024; Cassetta and Pollard, 2023
Macrophage Modulation (CSF1R, CD40)	M2→M1 transition; matrix remodeling; vascular normalization	TAM reprogramming reduces fibrosis, restores epithelial polarity	Byrne et al., 2021; Cassetta and Kitamura, 2018; Xia et al., 2024
Cytokine Therapy (IFNγ, IL-12, IL-15)	Lineage-specific differentiation; vascular and metabolic normalization	IFNγ enhances differentiation in melanoma; IL-15 induces maturation in HCC	Landsberg et al., 2012; Benci et al., 2016
Combination Epigenetic-Immunotherapy	Dual targeting of DNA methylation and immune checkpoints	Synergistic reactivation of tumor suppressors and immune recognition	Chiappinelli et al., 2015; Cao and Yan, 2020; Li, Wu and Hu, 2021

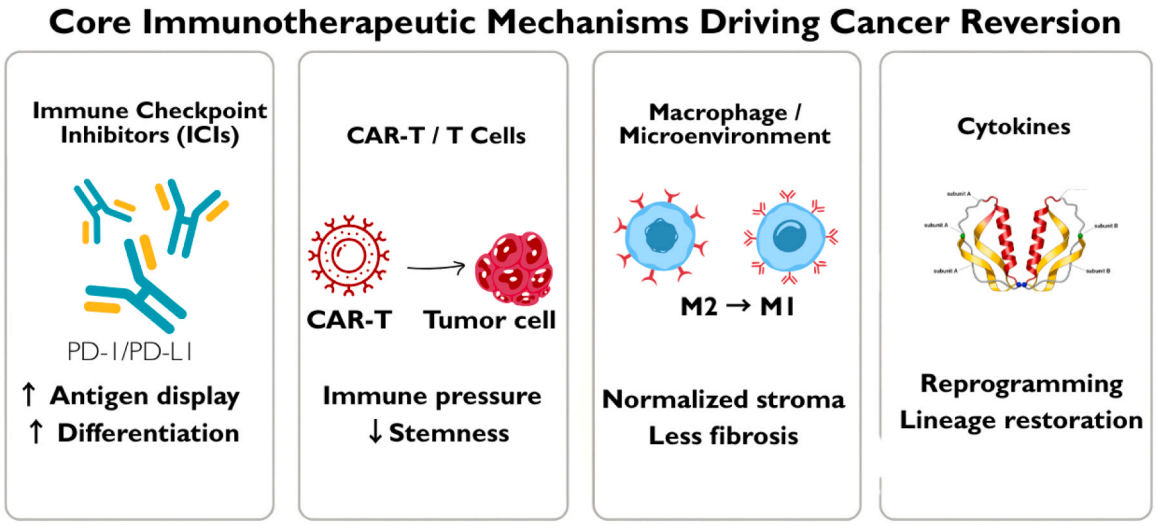

Fig. 2. Major immunotherapeutic pathways implicated in cancer reversion.

cumulative data indicate that immunological reprogramming and microenvironmental normalization are integral to the therapeutic durability observed with modern immunotherapies.

5.1. Melanoma

Melanoma represents the prototypical model for immune-mediated tumor regression and reprogramming. Long-term responders to checkpoint blockade exhibit re-expression of melanocytic lineage markers, enhanced antigen presentation, and transcriptional normalization suggestive of partial differentiation (Hugo et al., 2016; Liu et al., 2019).

Hugo et al. (2016) analyzed tumor biopsies from patients treated with anti-PD-1 therapy and found upregulation of *MITF*, *TYR*, and *PMEL17*, alongside decreased expression of *AXL* and *NGFR*, which mark invasive, dedifferentiated states. Responding lesions also displayed enriched $CD8^+$ T-cell signatures and enhanced antigen-presentation pathways, indicative of a microenvironment conducive to reversion. Subsequent single-cell analyses confirmed that checkpoint blockade reshapes tumor-cell heterogeneity, expanding subpopulations with intermediate differentiation phenotypes rather than fully proliferative states (Jerby-Arnon et al., 2018).

Complementary findings from adoptive T-cell therapy models show that effector cytokines can impose durable growth arrest on residual tumor cells. In murine systems, IFNγ and TNF produced by tumor-reactive T cells induce cytokine-induced senescence (CIS), stabilizing disease control even after treatment and providing a mechanism for long-term immune conditioning of tumor phenotype (Braumüller et al., 2013; Brenner et al., 2020). Consistently, in human melanoma models, IFNγ + TNF trigger stable senescence programs with a characteristic SASP, supporting the concept of immune-conditioned, durable tumor arrest (Homann et al., 2022). These observations align with the idea that checkpoint blockade restores lineage programs while T-cell cytokines enforce durable arrest, as summarized in Table 2.

5.2. Non-Small Cell Lung Cancer (NSCLC)

In NSCLC, immune checkpoint blockade has been shown to induce not only tumor regression but also molecular reprogramming suggestive of phenotypic reversion. Transcriptomic analyses of tumors treated with PD-1 inhibitors such as nivolumab revealed increased expression of

Table 2
Representative evidence of immunotherapy-mediated reversion in melanoma (2015–2025).

Study	Immunotherapy Type	Mechanistic Findings	Phenotypic Outcome
Hugo et al., 2016	Anti-PD-1	IFNγ-induced activation of differentiation genes (*MITF*, *TYR*)	Re-expression of melanocytic markers, decreased invasiveness
Jerby-Arnon et al., 2018	PD-1 blockade (single-cell RNA-seq)	Immune-induced state transitions toward developmental intermediates	Partial differentiation, reduced stemness
Liu et al., 2021	CAR-T (anti-gp100)	IFNγ/TNFα-mediated senescence and oxidative metabolic reprogramming	Durable phenotypic normalization

epithelial differentiation genes and suppression of EMT-associated markers, indicating partial reversal of mesenchymal states (Riaz et al., 2017). Moreover, studies of the tumor microenvironment demonstrate that immunotherapy can promote vascular normalization and reduce fibroblast activation, consistent with restoration of tissue homeostasis (Jain, 2013).

Combination PD-1 and CTLA-4 blockade can promote durable tumor control through coordinated immune and metabolic reprogramming rather than cytotoxicity alone. Neoadjuvant checkpoint blockade studies describe a characteristic regression bed featuring immune activation, tumor cell clearance, neovascular remodeling, and proliferative fibrosis (Cottrell et al., 2018; Rawson et al., 2021). At the metabolic level, checkpoint inhibition enhances mitochondrial oxidative phosphorylation and fatty-acid oxidation in effector T cells, sustaining antitumor immunity (Kumar and Chamoto, 2021) . Moreover, tumor-intrinsic metabolic states such as mtDNA-driven glycolytic dependence can influence responsiveness to immune checkpoint blockade (Mahmood et al., 2024). Collectively, these findings indicate that immunotherapy-induced metabolic and structural reprogramming contributes to sustained disease control beyond direct immune cytotoxicity. Table 3 summarizes key mechanistic pathways and phenotypic outcomes associated with checkpoint blockade and microenvironmental remodeling.

5.3. Breast cancer

Triple-negative breast cancer (TNBC), characterized by absent expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), represents the most aggressive breast cancer subtype with limited therapeutic options beyond cytotoxic chemotherapy and surgery. The advent of immune checkpoint blockade, particularly PD-1/PD-L1 inhibitors such as pembrolizumab and atezolizumab, has introduced a paradigm shift in TNBC management. Clinical trials including IMpassion130 demonstrated improved progression-free survival when atezolizumab was combined with nab-paclitaxel in PD-L1–positive metastatic TNBC (Emens et al., 2021), while the KEYNOTE-355 study further established pembrolizumab plus chemotherapy as an effective first-line treatment in PD-L1–expressing advanced TNBC (Schmid et al., 2020). However, conventional immunotherapy faces significant cytotoxic shortcomings including limited overall response rates (approximately 20–40 % in unselected populations), immune-related adverse events affecting multiple organ systems, and the challenge of overcoming the immunosuppressive tumor microenvironment characteristic of breast cancer (Oisakede et al., 2025; Sharma et al., 2017).

The epithelial–mesenchymal transition (EMT) phenotype prevalent in aggressive breast cancers actively drives immunosuppression through recruitment of myeloid-derived suppressor cells and regulatory T cells, while simultaneously reducing tumor immunogenicity (Dongre and Weinberg, 2018). These limitations have prompted investigation of combination strategies and alternative approaches including macrophage reprogramming and stromal remodeling to enhance therapeutic efficacy, reflecting growing interest in modulating the tumor microenvironment rather than relying solely on direct tumor cell killing (Khadela et al., 2022; Mantovani et al., 2017). Understanding these cytotoxic limitations provides critical context for exploring immune-mediated reversion as a complementary therapeutic strategy that may overcome resistance mechanisms inherent in purely destructive approaches, consistent with evolving frameworks that view malignancy as a dynamically regulated and potentially normalizable state (Barkley et al., 2021).

Immunotherapy-driven normalization in breast cancer involves macrophage reprogramming and stromal remodeling. Clinical and preclinical models demonstrate that immune activation can reverse EMT and restore epithelial features. In triple-negative breast cancer (TNBC) models, blockade of CSF1R reprograms immunosuppressive M2-type macrophages toward pro-inflammatory M1 phenotypes and remodels the fibrotic stroma (Guo et al., 2025; DeNardo et al., 2011). When combined with PD-1 or CTLA-4 inhibition, CSF1R blockade enhances antitumor immunity and improves therapeutic efficacy by relieving myeloid-driven suppression within the tumor microenvironment (Holmgaard et al., 2016; Gómez-Roca et al., 2022). Similarly, NK-cell–derived exosomes enriched with miR-155 and miR-186 have been shown to suppress ZEB1 and SNAI2, thereby reversing epithelial–mesenchymal transition (EMT) and reducing invasiveness in aggressive breast cancer models (Abdulmalik et al., 2025). Across cancers, EMT-high gene programs are associated with enrichment of immune checkpoint targets, and in breast cancer, quasi-mesenchymal states actively drive an immunosuppressive microenvironment that can be therapeutically reversed (Mak et al., 2016; Dongre et al., 2021).

5.4. Hematologic malignancies

In hematologic cancers, differentiation therapy has long been recognized (e.g., ATRA in acute promyelocytic leukemia). In acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), targeting the PD-1/PD-L1 pathway has emerged as a potential strategy to overcome immune evasion and enhance treatment efficacy (Yang et al., 2022). Additionally, CAR-T cell therapies targeting CD19 and CD22 exert potent immune pressure that reshapes the transcriptional landscape of residual leukemia cells. Studies show that such pressure can drive lineage remodeling and partial differentiation, characterized by altered expression of B-cell transcription factors (including *PAX5* and *EBF1*) and reduced proliferative signaling pathways such as *MYC* (Jacoby et al., 2016; Eagle et al., 2022). These findings suggest that immune modulation may promote stabilization of more differentiated hematopoietic states, thereby lowering relapse potential.

5.5. Hepatocellular Carcinoma (HCC)

Immunotherapy in hepatocellular carcinoma (HCC) has revealed signs of immune-mediated differentiation and metabolic restoration. In preclinical models, an IL-15 super agonist fused to anti-PD-1 enhanced intratumoral T-cell activity, reduced α-fetoprotein expression, and promoted re-expression of hepatocytic genes consistent with partial tumor differentiation (Xu et al., 2021). PD-1 or TIGIT co-blockade further improved T-cell effector function and shifted metabolism from glycolytic toward oxidative, indicating restoration of efficient immune energetics within the tumor microenvironment (Ge et al., 2021).

These immune-mediated effects coincided with re-expression of hepatocytic differentiation markers and metabolic regulators, suggesting re-engagement of hepatic transcriptional networks governed by factors such as HNF4A and PPARα. Collectively, these findings highlight the capacity of immune modulation to restore tissue-specific programs and differentiation states in solid organ malignancies.

Table 3
Immunotherapy-induced reversion evidence in NSCLC.

Study	Therapy	Key Mechanisms	Phenotypic Signatures
Zappasodi et al., 2018	PD-1 blockade	Downregulation of EMT genes (*SNAI1*, *TWIST*), upregulation of epithelial adhesion markers	EMT reversal, increased differentiation
Wang et al., 2023	PD-1 + CTLA-4 blockade	Metabolic normalization, mitochondrial activation	Reduced proliferation, restored polarity
Zheng et al., 2021	Vascular normalization (TME remodeling)	Improved perfusion and oxygenation	Reduced hypoxia, restored architecture

5.6. Glioblastoma

Glioblastoma (GBM) remains among the most recalcitrant of human cancers, with median survival seldom exceeding fifteen months despite maximal surgical resection, radiotherapy, and temozolomide chemotherapy. The introduction of immunotherapeutic strategies, particularly checkpoint inhibitors, has thus far shown limited efficacy due to the tumour's profound immune exclusion, low mutational burden, and highly suppressive microenvironment (Liu et al., 2024). Nevertheless, isolated reports of exceptional responses suggest that, in rare cases, immune modulation may elicit differentiation-like or reversional phenotypes rather than simple disease stabilization.

A recent report from University College London Hospitals (UCLH) described a 40-year-old male with newly diagnosed glioblastoma (WHO Grade IV, IDH-wildtype) who participated in the neoadjuvant NeAT-GLIO/Win-Glio clinical effort investigating pre-treatment with ipilimumab prior to planned chemoradiotherapy and surgery. The patient received ipilimumab (anti-CTLA-4) before standard therapy, and pre-treatment MRI showed an enhancing lesion in the right temporal lobe consistent with glioblastoma. Following immunotherapy and subsequent standard care, serial MRI scans have reportedly shown no evidence of active tumour more than two and a half years later, with imaging consistent with restoration of normal-appearing parenchyma in the regions previously involved by tumour (UCLH News, 2025). Formal histopathological confirmation and comprehensive biomarker analyses including TMB and MSI were not detailed in these reports. It is critical to distinguish this exceptional outcome from conventional pathological complete response (pCR), which requires histological confirmation of absent viable tumor cells following neoadjuvant therapy and cannot be established without surgical resection. In the absence of tissue confirmation, sustained radiological clearance must be interpreted cautiously, particularly in glioblastoma where imaging alone cannot definitively distinguish tumor eradication from immune-mediated control or phenotypic alteration (Wen et al., 2010). Nevertheless, given the extreme rarity of durable responses to immunotherapy in glioblastoma, this case serves as proof-of-principle that immune activation may, in exceptional circumstances, induce long-term tumor control or functional normalization even in highly refractory central nervous system malignancies (Sharma and Allison, 2015).

Other studies, however, have failed to reproduce similar outcomes. Phase II evaluations of ipilimumab in newly diagnosed or recurrent GBM have not demonstrated significant improvements in overall survival, reflecting the challenges of achieving durable immune engagement in the central nervous system (Brown et al., 2025). Mechanistic analyses underscore the formidable barriers posed by the glioma microenvironment, including macrophage-dominant immunosuppression, limited cytotoxic T-cell infiltration, and restricted antibody penetration across the blood-brain barrier (Liu et al., 2024). Consequently, while the UCLH case suggests that immune activation can, in principle, induce a reversion-like outcome in GBM, such responses remain anecdotal and unrepresentative of broader clinical experience. For now, the phenomenon serves as a conceptual reference point, such as an exceptional proof of principle illustrating how immune activation, even within the central nervous system, may in rare circumstances re-establish phenotypic equilibrium in malignant tissue.

5.7. Integrated interpretation

Across tumor types, immunotherapy-induced reversion appears to converge on common mechanistic axes:

1. Epigenetic restoration of lineage-specific transcriptional programs.
2. Reversal of metabolic deregulation (glycolysis to oxidative metabolism).
3. Immune-stromal normalization of the microenvironment.
4. Reduction in stemness and EMT markers, promoting differentiation.

While not universal, these convergent signatures suggest that reversion is an adaptive response to sustained immune pressure, potentially explaining why durable responders often maintain remission despite minimal residual disease.

6. Mechanistic insights and emerging technologies

6.1. Unravelling the molecular logic of immune-mediated reversion

Recent advances in single-cell, spatial, and computational biology have begun to decode the molecular logic by which immunotherapy induces phenotypic normalization. Evidence now suggests that immune-mediated reversion involves coordinated transcriptional, epigenetic, and metabolic rewiring driven by both adaptive and innate immune cues. These processes appear to converge on the restoration of lineage fidelity, chromatin accessibility, and microenvironmental equilibrium, resembling tissue repair and developmental regulation more than cytotoxic eradication (Liu et al., 2021; Burkhardt et al., 2022).

At the genomic level, checkpoint blockade and cytokine signaling activate transcription factors such as STAT1, IRF1, and NFκB, which interface with epigenetic regulators including TET2, DNMT3A, and EZH2 to reshape chromatin landscapes (Sen et al. (2016); Grasso et al. (2020)). In melanoma, single-cell sequencing revealed that PD-1 blockade induces expression of differentiation-associated enhancers previously silenced by DNA methylation, suggesting that immune cues can reopen closed chromatin regions linked to normal cellular identity (Hugo et al., 2016). Similar transcriptional reactivation has been observed in lung and liver cancers, where immunotherapy reinstates cell–cell adhesion and suppresses stemness programs (Zappasodi et al., 2018; Ge et al., 2021). These findings indicate that immune activation may transiently re-establish an embryonic-like plasticity followed by lineage stabilization, a phenomenon analogous to "developmental rebooting" rather than dedifferentiation. The interplay between immune signaling and chromatin remodeling thus provides the molecular substrate for reversion stability, allowing transformed cells to reacquire regulated growth and differentiation characteristics.

6.2. Immunometabolic reprogramming as a driver of normalization

Metabolic remodeling has emerged as both a cause and consequence of immune-mediated reversion. Tumor cells typically adopt aerobic glycolysis (the Warburg effect), a state favoring proliferation and immune evasion. In contrast, effective immunotherapy shifts this equilibrium toward oxidative phosphorylation and lipid metabolism, hallmarks of differentiated, non-proliferative states (Liu et al., 2024).

Activated immune cells contribute directly to metabolic shifts within the tumor microenvironment through the secretion of immunoregulatory metabolites. A key example is itaconate, produced by activated macrophages, which exerts anti-inflammatory effects by activating the Nrf2 antioxidant pathway. Mills et al. (2018) demonstrated that itaconate achieves this by alkylating the Nrf2 repressor KEAP1, thereby reducing reactive oxygen species (ROS) accumulation and restoring redox homeostasis. These redox-stabilizing effects help reprogram cellular metabolism toward a less inflammatory state and promote conditions that support cellular differentiation and metabolic quiescence.

Recent in vivo CRISPR–Cas9 screens have highlighted nutrient-signaling and metabolic pathways as key determinants of immune-driven differentiation, particularly in $CD8^+$ T cells (Huang et al., 2021). Complementary functional studies identify mitochondrial regulators such as PGC-1α, CPT1A and SIRT3 as central nodes linking bioenergetics to immune control: enforced PGC-1α expression enhances mitochondrial fitness and durable antitumor T-cell responses (Dumauthioz et al., 2021), CPT1A-dependent fatty acid oxidation confers tumor resistance to immune-mediated cytolysis (Liu et al., 2023), and SIRT3 acts as a metabolic sensor shaping T-cell differentiation in

cancer (Hou et al., 2024). Collectively, these data position immuno-metabolic coupling as a mechanistic bridge between immune pressure and durable reprogramming.

6.3. Spatial and single-cell technologies in mapping immune reversion

The heterogeneity of tumor-immune interactions has historically obscured evidence of reversion. Single-cell and spatial transcriptomic technologies have now provided unprecedented resolution in mapping cellular trajectories during therapy. Integration of single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics has revealed transitional tumor states that emerge only after immune activation. In responders to checkpoint blockade, these cells exhibit hybrid features, which are partial restoration of lineage markers alongside retained antigenicity, suggesting intermediate stages of reprogramming (Jerby-Arnon et al., 2018). Spatially resolved immunophenotyping using multiplex imaging has identified immune niches in which cytotoxic T-cells and macrophages cluster in tumour micro-regions of remodelling (Kumar et al., 2023).

The application of time-resolved clonal lineage tracing is beginning to clarify how immune checkpoint blockade reshapes tumor cell populations. In preclinical syngeneic tumor models, DNA barcoding of cancer cells followed by anti–PD-1 and anti–CTLA-4 therapy has shown that immune pressure does not simply eradicate all malignant clones uniformly; instead, it markedly restricts clonal diversity and selects for pre-existing subclones that persist and generate stable progeny with distinct transcriptional programs (Gu et al., 2020; Baldwin et al., 2022). These experiments provide direct empirical evidence that immune surveillance actively sculpts tumor-cell lineages over time rather than acting as a purely stochastic filter, consistent with models in which phenotypic remodeling and potential reversion-like states can emerge alongside selective elimination.

6.4. Organoid and co-culture models as experimental proxies

Organoid-based tumor–immune co-cultures and microfluidic platforms are emerging as powerful systems for modeling immune–tumor interactions. These bioengineered technologies recapitulate key structural and signaling features of the tumor microenvironment, enabling controlled, high-resolution study of how immune cells engage and modulate tumor cells over time (Olawade at al., 2025). While still largely exploratory, such platforms have the potential to illuminate dynamic processes, including phenotypic adaptation and differentiation during immunotherapeutic challenge.

Organoid platforms have become powerful systems for dissecting how immune pressure reshapes tumor-cell states. Patient-derived tumor organoids co-cultured with autologous T cells exhibit IFNγ-dependent transcriptional remodeling, including induction of antigen-presentation genes and re-engagement of lineage-associated differentiation programs (Neal et al., 2018). In several models, withdrawal of immune pressure reveals that a subset of tumor cells retains these induced states, consistent with the acquisition of partially stabilized epigenetic programs (Benci et al., 2019). Recent CRISPR perturbation studies in organoid systems further demonstrate that chromatin-regulatory factors including components of the SWI/SNF complex and histone-modifying enzymes govern the persistence of such remodelled phenotypes by shaping accessibility at interferon-responsive and lineage-defining loci (Ringel et al., 2020). Together, these findings support the view that immune-driven tumor "normalization" can be reconstructed in engineered organoid platforms and is maintained through defined epigenetic regulators. These models are now being integrated with live-cell imaging and single-cell multi-omic readouts to quantify reversion probability under defined immune stimuli. They also provide a framework for drug discovery, allowing screening of adjuvants (e.g., epigenetic or metabolic modulators) that amplify or stabilize immune-mediated reprogramming.

6.5. Computational and AI-driven modelling of immune reprogramming

The advent of AI–based modelling has enabled the integration of large multi-omic datasets to predict immunotherapy responses and infer immune-driven phenotypic transitions. Multi-omics machine-learning frameworks now combine genomic, transcriptomic, and tumour-microenvironment features to stratify patients and identify immunotherapy-relevant cellular states (Li et al., 2024). Pathway-informed graph neural networks, including IRnet and melanoma-specific GNN predictors, integrate transcriptomic profiles with biological interaction networks to forecast checkpoint-inhibitor responsiveness and highlight pathway signatures associated with immune-inflamed versus immune-cold tumour phenotypes (Jiang et al., 2025). Single-cell and spatial analyses have further applied graph-based architectures such as GraphSAGE to encode the tumour ecosystem and reconstruct distinct response trajectories under anti–PD-1–based therapy, in some cases closely mirroring radiological and histological patterns of regression or resistance (Shiao et al., 2024).

Similarly, interpretable probabilistic approaches including tree-augmented naïve Bayes classifiers and related Bayesian-network models trained on clinical, genomic, and immune-profiling variables have demonstrated strong performance in predicting durable benefit from immune checkpoint blockade while uncovering mechanistic dependencies among predictive immunologic and cytokine features (Hozumi and Shimizu, 2023). Together, these computational frameworks offer a principled route for identifying biomarkers associated with more differentiated, immune-regulated tumour states and for designing immunotherapy combinations that bias responses toward durable control rather than unchecked progression.

6.6. Translational implications

The integration of these mechanistic and technological insights substantiates cancer reversion as a tangible, quantifiable endpoint in immunotherapy. By coupling immune activation with molecular and metabolic stabilization, therapeutic strategies could be redirected from indiscriminate destruction toward functional normalization of malignant tissues. Advances in single-cell analysis, organoid co-culture, and computational modelling collectively enable the measurement, prediction, and eventual therapeutic harnessing of immune-mediated reversion. As such, the field stands at a pivotal juncture: the transition from anecdotal reports of spontaneous regression to a systems-level understanding of how the immune system can re-establish normalcy in malignant contexts. The coming decade is likely to redefine the objective of cancer immunotherapy, from elimination of disease to the restoration of cellular identity and tissue equilibrium.

7. Limitations and challenges

Despite growing evidence supporting the concept of immunotherapy-mediated cancer reversion, several fundamental limitations temper both its mechanistic certainty and its translational feasibility. Current observations, while intriguing, are largely derived from post-hoc analyses, small patient subsets, or preclinical models that incompletely represent the spatiotemporal complexity of human tumors. These challenges fall broadly into three interrelated domains: mechanistic ambiguity, biomarker insufficiency, and translational uncertainty.

7.1. Mechanistic ambiguity

A principal limitation lies in distinguishing genuine phenotypic reversion from other immunologically induced states such as dormancy, cytostasis, or incomplete senescence. Many studies infer reversion from transcriptional or histological normalization without demonstrating the functional restoration of regulatory circuitry characteristic of non-malignant tissue (Meacham and Morrison, 2013). The transient nature

of many immune-induced differentiation markers complicates this interpretation. In melanoma and NSCLC, for instance, the re-expression of lineage or differentiation markers following checkpoint blockade may represent an adaptive, reversible phenotype rather than a stable reversion (Jerby-Arnon et al., 2018; Hugo et al., 2016).

Furthermore, most available models cannot disentangle whether immune-mediated normalization arises from direct cell-autonomous reprogramming or from the selective survival of subclones with inherently less malignant potential. The absence of longitudinal lineage tracing in clinical contexts prevents definitive attribution of phenotype changes to immune-driven molecular remodeling rather than clonal selection. Until dynamic single-cell or spatial multi-omic analyses are routinely integrated into clinical trials, assertions of stable reversion must remain provisional.

7.2. Biomarker and endpoint deficiency

Unlike cytotoxic response metrics, reversion lacks validated biomarkers or histopathological criteria. Current endpoints in immunotherapy trial's objective response rate, progression-free survival, and overall survival are ill-suited to capture functional normalization of tumor cells or microenvironmental repair. While reversion is frequently associated with the re-expression of differentiation genes or metabolic normalization (Baylin and Jones, 2016; Faubert et al., 2020), these signatures are neither universally applicable nor easily quantifiable across cancer types.

Moreover, the absence of standardized "reversion scores" impedes comparative assessment between studies. Epigenetic or metabolic hallmarks, such as restoration of oxidative phosphorylation or chromatin accessibility at lineage enhancers, have been proposed as surrogate indicators (Burkhardt et al., 2022), yet they require validation against functional outcomes and long-term stability. Without reliable biomarkers, reversion remains a descriptive rather than measurable therapeutic endpoint, limiting its incorporation into clinical trial design.

7.3. Dependence on small sample sizes and preclinical data

A significant limitation of the current evidence base is the reliance on small patient cohorts, single-institution case reports, and preclinical models that may not fully recapitulate human tumor biology. Many mechanistic claims regarding immune-driven reversion are derived from a limited subset of studies, often conducted in murine systems or patient-derived organoid cultures that lack the complexity of intact human immune–tumor ecosystems and have historically demonstrated limited predictive power for clinical translation (Mak et al., 2014). For instance, observations of IFNγ-driven differentiation or metabolic reprogramming are frequently extrapolated from in vitro co-culture experiments or immunocompromised xenograft models, which may overestimate therapeutic efficacy and fail to capture context-dependent immune regulation observed in patients (Ivashkiv, 2018).

Furthermore, exceptional clinical responses such as the glioblastoma case described herein represent rare outliers rather than reproducible phenomena, and the molecular determinants distinguishing responders from non-responders remain poorly characterized. The heterogeneity of tumor types, disease stages, and treatment regimens across reported studies further complicates meta-analysis and generalization of findings, while many mechanistic insights rely on exploratory analyses of very small patient subsets ($n < 10$–20), precluding robust statistical validation and limiting confidence in causality versus correlation.

Large-scale, prospective clinical trials incorporating standardized biomarker assessment, longitudinal multi-omic profiling, and uniform response criteria are therefore essential to validate these preliminary observations and establish immune-mediated reversion as a reproducible therapeutic endpoint rather than an anecdotal phenomenon. Until such evidence is generated, claims of immune-mediated reversion should be interpreted cautiously as hypothesis-generating rather than clinically actionable paradigms.

7.4. Model system limitations

Experimental models of immune reversion frequently rely on simplified in vitro co-cultures or immunodeficient xenografts that fail to replicate the reciprocal dynamics of human immunity and tumour architecture. Mouse models, while indispensable, possess fundamental differences in immune composition and tumour evolution that restrict extrapolation (Cogels et al., 2021; Chen et al., 2023). Humanised mouse platforms and patient-derived organoids have advanced mechanistic understanding, yet they remain constrained by short culture lifespans and limited immune complexity (Grönholm et al., 2021; Wang et al., 2023).

Another challenge is the temporal resolution of reversion studies. The kinetics of immune-induced normalization i.e., its initiation, stability, and potential reversibility are poorly defined. Current experimental timelines capture transient remodeling but not long-term maintenance of the normalized phenotype. Consequently, it is uncertain whether immune-induced reversion represents a permanent epigenetic reset or a reversible equilibrium contingent on sustained immune surveillance.

7.5. Clinical and translational barriers

At the clinical level, the translation of reversion from concept to therapeutic goal is impeded by both biological and regulatory factors. Tumor heterogeneity ensures that immune pressure yields divergent outcomes: cytotoxic clearance in some subclones, immune editing in others, and transient normalization in the remainder. The durability of reversion remains unpredictable, and relapse following immune withdrawal is not uncommon (Gubin and Vesely, 2022).

Immunotherapy toxicity further complicates this paradigm. Strategies potent enough to induce profound immune remodeling risk triggering autoimmunity or tissue damage that undermines homeostatic restoration. Moreover, the absence of consensus criteria for "reversion responses" prevents recognition of such outcomes within existing clinical trial frameworks, discouraging systematic investigation. Ethical constraints also limit longitudinal tissue sampling necessary to confirm phenotypic reversal in situ.

7.6. Conceptual and philosophical constraints

Beyond empirical limitations, a conceptual challenge persists: the oncology community remains oriented toward eradication rather than normalization. The notion of curing cancer through reversion challenges entrenched paradigms of therapy design and regulatory approval. Convincing evidence that restored phenotypes can remain indefinitely stable without ongoing immune surveillance is still lacking. As such, while immunotherapy-mediated reversion offers a compelling theoretical complement to cytotoxic paradigms, it has yet to achieve definitional clarity or clinical validation.

Overall, the translation of immune-mediated reversion into a clinically actionable strategy requires: (1) rigorous mechanistic delineation distinguishing reversion from dormancy; (2) validated molecular and imaging biomarkers of phenotypic normalization; (3) long-term, multi-omic tracking to confirm stability of reversion states; and (4) adaptive clinical frameworks that recognize restoration of normalcy as a therapeutic success equivalent to cytotoxic remission. Until these are achieved, reversion will remain a promising but speculative frontier, an intersection of immunology, epigenetics, and systems biology poised for maturation through integrative experimental and clinical innovation.

8. Future directions

The prospect of immunotherapy-mediated cancer reversion marks a

paradigm shift in oncology, from tumor eradication toward restoration of normalcy. Future research must bridge the gap between anecdotal observation and mechanistic validation, integrating immunology, epigenetics, and systems biology into a cohesive framework that defines, quantifies, and therapeutically stabilizes the reversion phenotype.

8.1. Integrative immuno-epigenetic frameworks

A priority for future investigation lies in elucidating the epigenetic architecture of immune-induced normalization. Immune signaling orchestrates broad transcriptional remodeling through cytokine-dependent activation of chromatin regulators such as TET2, DNMT3A, and HDAC1 (Burkhardt et al., 2022). Yet the reversibility and hierarchy of these epigenetic transitions remain poorly defined. Multi-omic studies combining chromatin accessibility (ATAC-seq), DNA methylation profiling, and transcriptional mapping are needed to identify epigenetic "switches" that demarcate reversible immune adaptation from permanent reversion.

Therapeutically, rational integration of epigenetic modulators with checkpoint blockade or adoptive cell therapy could stabilize normalized states. Early clinical studies combining DNA methyltransferase inhibitors (DNMTi) or histone deacetylase inhibitors (HDACi) with PD-1 blockade have demonstrated enhanced immune infiltration and sustained differentiation (Chiappinelli et al., 2015; Cao and Yan, 2020). Extending this strategy to incorporate next-generation epigenetic drugs, targeting chromatin remodelers or non-coding RNA pathways could potentiate durable immune-driven reprogramming across heterogeneous tumor types.

8.2. Multi-omic and spatial profiling of reversion states

The next decade of discovery will depend on high-resolution mapping of immune-induced cell state transitions. Integration of single-cell transcriptomics, spatial proteomics, and metabolomics can delineate the trajectory from malignant to normalized states with unprecedented precision (Jerby-Arnon et al., 2018; Keren et al., 2019). Longitudinal profiling of patient biopsies pre- and post-immunotherapy will enable the definition of molecular coordinates of reversion, including key transcriptional regulators, metabolic signatures, and stromal interactions.

The development of computational atlases linking immune phenotypes with differentiation trajectories will be essential for biomarker discovery. Such atlases can generate reversion "signatures" applicable across cancer types, guiding both patient stratification and therapeutic monitoring. Furthermore, machine learning approaches integrating these datasets could forecast reversion likelihood, identifying patients most likely to achieve durable normalization.

8.3. Synthetic immunobiology and reversion engineering

The convergence of immunology and synthetic biology provides a new platform for programmatic induction of reversion. Advances in gene circuit engineering and cytokine design now permit construction of immune cells capable of delivering differentiation-inducing signals with spatiotemporal precision (Roybal et al., 2016). CAR-T or TCR-T cells could be engineered to co-express epigenetic regulators or metabolic enzymes that promote reprogramming of target cells following antigen engagement.

Similarly, synthetic cytokine switches, such as engineered IL-2 or IL-15 analogues could be tuned to favor tissue repair over cytotoxicity, promoting immune-epithelial re-equilibration. These strategies may establish an entirely new therapeutic category: immune reversion therapy, in which immune cells act not as killers but as architects of phenotypic normalization.

8.4. Biomarker development and reversion metrics

Operationalizing cancer reversion requires robust biomarkers and quantifiable endpoints. Candidate markers include restoration of lineage transcription factors (e.g., MITF, HNF4A, PAX5), reversal of metabolic deregulation (glycolytic to oxidative transition), and microenvironmental normalization (vascular remodeling, reduced fibrosis). Integration of circulating tumor DNA (ctDNA), exosomal RNA, and metabolomic profiling may provide zliquid-biopsy correlates of reversion, enabling non-invasive monitoring of immune-induced normalization in real time (Tripathi et al., 2021).

Developing "Reversion Index Scores" composite measures incorporating epigenetic, metabolic, and microenvironmental parameters could allow clinical trials to evaluate normalization alongside tumor regression. This would redefine success in immunotherapy, acknowledging that survival can be achieved through re-establishment of homeostatic equilibrium, not merely cytotoxic elimination.

8.5. Translational pathways and clinical trial redesign

The clinical translation of immune reversion will depend on innovative trial designs capable of capturing non-traditional outcomes. Adaptive protocols incorporating serial biopsies, spatial multi-omic profiling, and dynamic imaging (e.g., metabolic MRI or hyperpolarized 13 C MRI) could identify structural and functional correlates of reversion.

Future studies might adopt a two-phase approach: an initial induction phase to trigger immune activation and epigenetic remodeling, followed by a maintenance phase aimed at stabilizing the normalized phenotype. Clinical endpoints should evolve beyond conventional response criteria (RECIST) to include metrics of tissue reconstitution, immune–stromal balance, and long-term metabolic normalization. Such frameworks would also necessitate ethical and regulatory adaptation, recognizing immune-driven normalization as a legitimate therapeutic goal. This shift parallels the evolution of differentiation therapy in leukaemia, a once radical idea that became a cornerstone of curative treatment. The conceptual leap required in solid tumors is similar, though biologically more complex.

8.6. Prospective vision

Ultimately, the trajectory of immunotherapy may converge on the principle that restoration is more sustainable than eradication. By learning from developmental and regenerative immunology, researchers can design interventions that harness the immune system not as a weapon of destruction but as a mediator of balance and renewal.

The transition from "killing cancer" to "reverting cancer" represents both a scientific and philosophical reorientation, one that aligns oncology with the broader biological goal of restoring harmony to perturbed systems. As multi-disciplinary technologies mature, and as our capacity to modulate immune-epigenetic feedback deepens, immunotherapy-mediated cancer reversion may evolve from a rare anomaly into a reproducible, clinically exploitable therapeutic reality.

9. Conclusion

The evolving landscape of immuno-oncology has redefined the relationship between immunity and malignancy, shifting from eradication to regulation. Evidence accumulated over the past decade demonstrates that immune activation can not only destroy malignant clones but also recondition surviving cells toward physiological normalcy. Across diverse malignancies including melanoma, lung, breast, hematologic, hepatic, and even glioblastoma, immunotherapy has revealed the potential for immune-mediated reversion, a process in which transcriptional, epigenetic, metabolic, and microenvironmental circuits are re-aligned to approximate non-malignant states.

This review has outlined the mechanistic foundations of that process. Checkpoint blockade, adoptive cell therapy, cytokine modulation, and immune-driven microenvironmental remodeling converge on shared molecular pathways that restore lineage fidelity, metabolic equilibrium, and stromal organization. The immune system emerges not merely as a defensive network but as a contextual architect of tissue identity, capable of reinstating homeostasis in the aftermath of oncogenic disruption.

Yet reversion remains an emerging and incompletely characterized outcome. The field still lacks definitive biomarkers, temporal criteria, and mechanistic consensus distinguishing true normalization from dormancy or immune-mediated stasis. Establishing the epigenetic and metabolic permanence of reversion will be essential to its clinical validation. Similarly, conceptual realignment within oncology is required: therapy success must be measured not solely by absence of disease but by restoration of self-regulatory balance.

Technological advances, such as single-cell and spatial multi-omics, organoid co-culture systems, and AI-driven modelling now provide the experimental infrastructure to map immune-driven phenotypic transitions with unprecedented fidelity. These tools will define the molecular coordinates of reversion, reveal its stability conditions, and guide design of therapies that deliberately favor normalization over destruction.

The ultimate promise of immunotherapy may therefore extend beyond tumour elimination. By co-opting the immune system's evolutionary role in tissue maintenance, future interventions could achieve curative equilibrium; a state in which cancer is not annihilated but reassimilated into the body's physiological order. Realizing this vision will require interdisciplinary synthesis across immunology, epigenetics, systems biology, and clinical medicine. When that integration is achieved, cancer reversion may stand as the next transformative chapter in precision immunotherapy, redefining cure not as the absence of malignancy but as the restoration of biological harmony.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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