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REVIEW ARTICLE

Reprogramming the tumour microenvironment: Emerging strategies to overcome immunotherapy resistance

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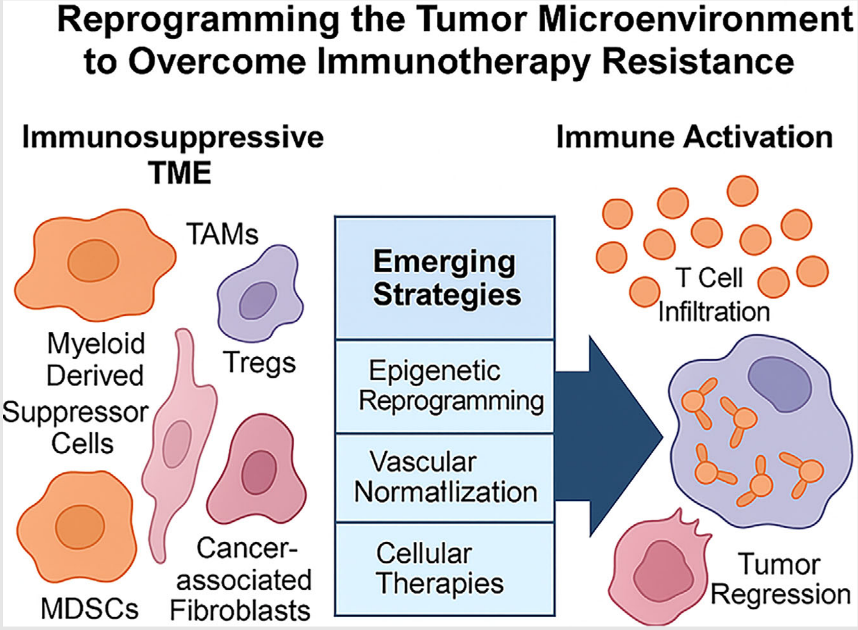
Graphical Abstract



Reprogramming the tumour microenvironment (TME) overcomes immunotherapy resistance by targeting immunosuppressive cells, abnormal vasculature and metabolic dysregulation. Emerging strategies, including epigenetic modulation, vascular normalisation and cellular therapies, transform the TME into an immune-active landscape, enhancing T-cell infiltration and promoting tumour regression.

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Abstract

Background: The advent of cancer immunotherapy, particularly immune checkpoint inhibitors, has revolutionised the treatment landscape for many malignancies. However, a significant proportion of patients exhibit primary, adaptive, or acquired resistance to these therapies, limiting their broad clinical benefit. Tumour microenvironment (TME), a complex and dynamic ecosystem of cancer cells, immune cells, stromal cells and extracellular matrix, has emerged as a critical determinant of immunotherapy response and a major driver of resistance.

Main body: This review provides a comprehensive overview of the intricate mechanisms by which the TME fosters an immunosuppressive milieu, thereby impeding effective anti-tumour immunity. We delineate the key cellular and molecular components of the TME that contribute to immunotherapy resistance, including tumour-associated macrophages, myeloid-derived suppressor cells, regulatory T cells, and cancer-associated fibroblasts. We then discuss the diverse and innovative strategies being developed to reprogram the TME and overcome these resistance mechanisms. These emerging approaches include targeting immunosuppressive cell populations, modulating tumour metabolism, epigenetic reprogramming, normalising the tumour vasculature and employing engineered cell therapies such as chimeric antigen receptor T cells and oncolytic viruses. The potential of combination therapies to synergistically dismantle the immunosuppressive TME is also explored.

Conclusion: Reprogramming the TME represents a paradigm shift in cancer treatment, moving beyond direct tumour cell targeting to modulate the entire tumour ecosystem. While significant challenges remain, including TME heterogeneity and the need for predictive biomarkers, the strategies discussed herein hold immense promise for overcoming immunotherapy resistance and improving patient outcomes. A deeper understanding of the complex interplay between the tumour and its microenvironment will be crucial for the development of next-generation, personalised immunotherapeutic strategies.

KEYWORDS
cancer immunology, CAR-T cell therapy, epigenetic modulation, immune checkpoint inhibitors, immunotherapy resistance, metabolic reprogramming, tumour-associated macrophages, tumour microenvironment

1 | BACKGROUND

The treatment of cancer has been fundamentally transformed by the rise of immunotherapy, a therapeutic modality that harnesses the power of the patient's own immune system to recognise and eliminate malignant cells. This approach stands in contrast to traditional therapies such as chemotherapy and radiation, which often cause significant collateral damage to healthy tissues. The remarkable success of immune checkpoint inhibitors (ICIs), in particular, has led to durable clinical responses in a subset of patients across a wide range of cancer types, heralding a new era in oncology.[1,2]

1.1 | Revolution of cancer immunotherapy

The concept of using the immune system to fight cancer is over a century old, but it is only in the last two decades that this idea has been translated into widespread clinical success. The development of monoclonal antibodies that block inhibitory immune checkpoint pathways, such as the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) pathways, has been a pivotal breakthrough. These checkpoints are crucial for maintaining self-tolerance and preventing autoimmunity, but they are often co-opted by tumours to evade immune surveillance.[3] By inhibiting these pathways, ICIs can unleash a pre-existing anti-tumour immune response or facilitate a new one, leading to tumour regression. The Food and Drug Administration (FDA) approval of ipilimumab, an anti-CTLA-4 antibody, in 2011 for the treatment of metastatic melanoma marked a significant milestone.[4] This was followed by the approval of several anti-PD-1 (nivolumab and pembrolizumab) and anti- programmed death-ligand 1 (PD-L1) (atezolizumab, avelumab and durvalumab) antibodies for a growing list of malignancies, including non-small cell lung cancer, renal cell carcinoma, bladder cancer and Hodgkin's lymphoma.[5] The profound and often long-lasting responses observed in some patients have solidified immunotherapy as a cornerstone of modern cancer treatment.

1.2 | Problem of immunotherapy resistance

Despite these unprecedented successes, the majority of patients do not respond to immunotherapy, and many who initially respond eventually develop resistance. This resistance can be broadly categorised into primary (innate) resistance, where the cancer does not respond from the outset; adaptive resistance, where the tumour adapts to immune pressure; and acquired (secondary) resistance, where the tumour relapses after a period of remission.[6] The high prevalence of resistance poses a major clinical challenge and underscores the urgent need for novel therapeutic strategies to broaden the reach of immunotherapy and improve its efficacy.

1.3 | Tumour microenvironment: a critical barrier

Increasing evidence points to the tumour microenvironment (TME) as a key player in mediating resistance to immunotherapy. The TME is a complex and heterogeneous ecosystem comprising not only cancer cells but also a diverse array of non-malignant cells, including immune cells, stromal cells (such as fibroblasts and endothelial cells) and an extensive extracellular matrix (ECM).[7] The dynamic and reciprocal interactions between these components create a unique milieu that can either support or suppress anti-tumour immunity. In many cases, the TME is profoundly immunosuppressive, creating a formidable barrier to effective immunotherapy. This immunosuppressive network is orchestrated by the tumour cells themselves, which secrete a variety of factors that recruit and activate immunosuppressive cell populations, promote the formation of a dense and disorganised ECM, and create a hostile metabolic landscape characterised by hypoxia and nutrient deprivation.[8] Understanding the intricate mechanisms by which the TME fosters immunosuppression is therefore paramount for developing strategies to

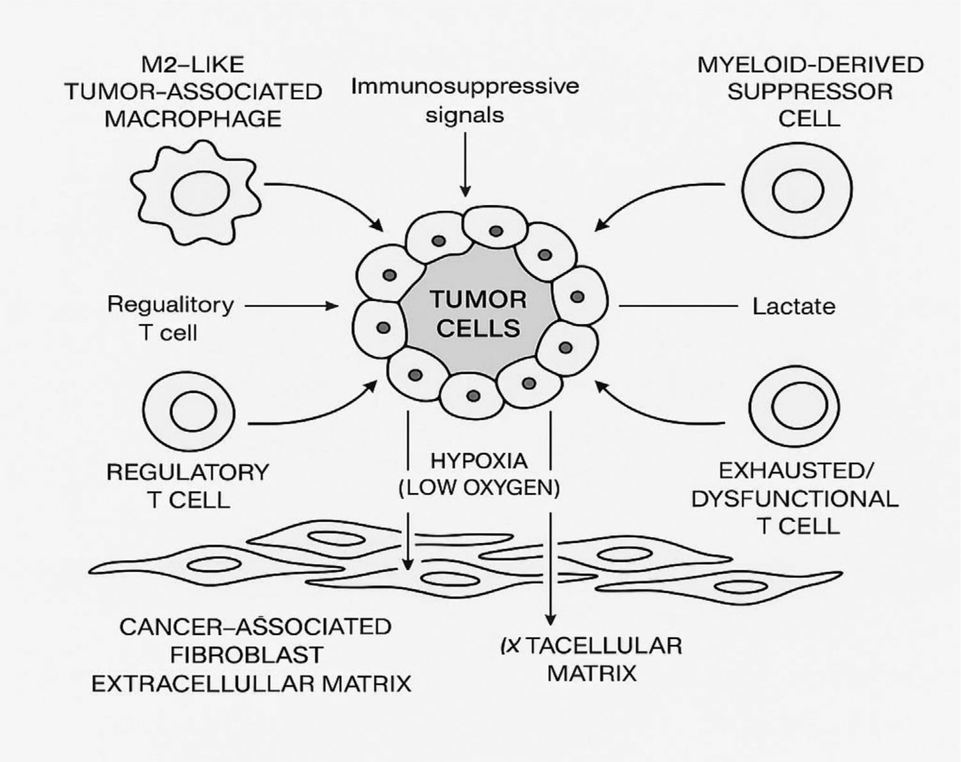

FIGURE 1 Immunosuppressive tumour microenvironment. Tumour microenvironment consists of tumour cells (purple) surrounded by various immunosuppressive cellular components including M2-like tumour-associated macrophages (TAMs, orange), myeloid-derived suppressor cells (MDSCs, yellow), regulatory T cells (Tregs, light blue) and exhausted/dysfunctional T cells (grey). Cancer-associated fibroblasts (CAFs, pink) form a dense stromal barrier with extracellular matrix. Abnormal, chaotic blood vessels contribute to hypoxia (low oxygen). Immunosuppressive signals (interleukin-10 [IL-10] and transforming growth factor-beta [TGF-β]) and metabolic factors (high lactate, glucose depletion) create a hostile environment that impedes anti-tumour immunity.

overcome resistance and unlock the full potential of cancer immunotherapy.

2 | ROLE OF TME IN IMMUNOTHERAPY RESISTANCE

The TME is a complex and dynamic ecosystem that plays a pivotal role in cancer progression and the response to therapy. The TME often evolves to create a profoundly immunosuppressive landscape, thereby facilitating immune evasion and contributing to immunotherapy resistance (Figure 1). This section will delve into the key components of the TME that mediate resistance, including immunosuppressive cells, the stromal barrier and metabolic factors.

2.1 | Immunosuppressive cellular players

A variety of immune cells with immunosuppressive functions are actively recruited to the TME, where they work in concert to dampen anti-tumour immunity (Table 1). Regulatory T cells (Tregs), a specialised subset of T cells essential for maintaining immune homeostasis, are often co-opted by tumours to suppress anti-tumour immune responses. Tumours recruit Tregs by secreting chemokines such as C–C motif chemokine ligand (CCL)22.[9] Once in the TME, Tregs employ several mechanisms to suppress the activity of effector T cells, including the secretion of inhibitory cytokines such as transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10),[10] metabolic competition through high expression of GLUT1,[11] and the expression of inhibitory receptors such as CTLA-4, PD-1 and lymphocyte-activation gene 3 (LAG-3).[12] Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells that accumulate in the TME and are potent suppressors of both innate and adaptive immunity. Their immunosuppressive functions are mediated by the depletion of L-arginine through the expression of arginase 1 (ARG1) and inducible nitric oxide synthase (iNOS),[13] the generation of reactive oxygen species (ROS),[14] and the upregulation of inhibitory receptors such as PD-L1.[15] Tumour-associated macrophages (TAMs), often polarised towards an M2-like phenotype in the TME, are associated with pro-tumoural functions

TABLE 1 Immunosuppressive components of the tumour microenvironment.

Cell type/ component	Key markers	Immunosuppressive mechanisms	Therapeutic targets	References
Tregs	CD4+, CD25+, FOXP3+	Secretion of IL-10 and TGF-β Metabolic competition via GLUT1 Expression of CTLA-4, PD-1, LAG-3	Anti-CCR4 antibodies Low-dose cyclophosphamide GITR/OX40 agonists	[9–12]
MDSCs	CD11b+, CD33+, HLA-DR-/low	L-arginine depletion via ARG1 and iNOS ROS generation PD-L1 expression	Low-dose chemotherapy ARG1/iNOS inhibitors ATRA differentiation therapy	[13–15,20]
TAMs	CD68+, CD163+, CD206+ (M2-like)	Secretion of IL-10, TGF-β, prostaglandins PD-L1/PD-L2 expression VEGF and MMP secretion	CSF-1R inhibitors CCR2 antagonists CD40 agonists Anti-CD47/SIRPα	[16–19]
CAFs	α-SMA+, FAP+, PDGFRβ+	Dense ECM deposition Secretion of TGF-β, CXCL12, IL-6 PD-L1 and FASL expression	FAP-targeted therapies CXCR4 antagonists TGF-β inhibitors	[21–23]
ECM	Collagen, fibronectin, versican	Physical barrier to T-cell infiltration Direct T-cell suppression	Matrix-degrading enzymes CAF targeting	[24]
Hypoxia	HIF-1α upregulation	PD-L1 induction Treg recruitment MDSC activation	Anti-VEGF therapy Vascular normalisation	[25]
Metabolic factors	High lactate, low glucose, acidic pH	T-cell metabolic dysfunction Amino acid depletion Inhibition of T-cell proliferation	Glycolysis inhibitors IDO/ARG1 inhibitors Lactate transport inhibitors	[11,13,26–28]

Abbreviations: α-SMA, alpha-smooth muscle actin; ARG1, arginase 1; ATRA, all-trans retinoic acid; CAF, cancer-associated fibroblasts; CCR, C–C chemokine receptor; CSF-1R, colony-stimulating factor 1 receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ECM, extracellular matrix; FAP, fibroblast activation protein; FASL, FAS ligand; GITR, glucocorticoid-induced TNFR-related protein; HIF-1α, hypoxia-inducible factor 1-apha; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; iNOS, inducible nitric oxide synthase; LAG-3, lymphocyte-activation gene 3; MDSC, myeloid-derived suppressor cell; MMP, matrix metalloproteinase; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; ROS, reactive oxygen species; TAMs, tumour-associated macrophages; TGF-β, transforming growth factor-beta; Tregs, regulatory T cells; VEGF, vascular endothelial growth factor.

such as promoting angiogenesis, tissue remodelling and immune suppression.[16] TAMs contribute to immunotherapy resistance by secreting immunosuppressive factors such as IL-10 and TGF-β,[17] expressing inhibitory ligands such as PD-L1 and PD-L2,[18] and promoting angiogenesis and metastasis through the secretion of factors such as vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs).[19]

2.2 | Stromal barrier

The stroma, consisting of the ECM and various cellular components such as fibroblasts, can also pose a significant barrier to immunotherapy. Cancer-associated fibroblasts (CAFs), a major component of the tumour stroma, contribute to cancer progression by remodelling the ECM to create a dense physical barrier that can prevent the infiltration of T cells into the tumour,[21] secreting immunosuppressive factors such as TGF-β and CXCL12,[22] and expressing inhibitory ligands such as PD-L1 and FAS ligand (FASL).[23] The altered ECM of tumours, often denser and more disorganised than that of normal tissues, can physically impede the migration of T cells to the tumour site. Additionally, certain ECM components, such as versican, can directly suppress T-cell function.[24]

2.3 | Metabolic dysregulation in TME

The metabolic landscape of the TME is often hostile to immune cells. The high proliferative rate of tumour cells leads to a nutrient-deprived environment for immune cells. This includes glucose deprivation, which can starve effector T cells,[11] and hypoxia, which can promote the expression of immunosuppressive factors such as hypoxia-inducible factor 1-apha (HIF-1α).[25] Furthermore, the high rate of glycolysis in tumour cells leads to the production of large amounts of lactic acid, resulting in an acidic TME that can directly inhibit the function and proliferation of effector T cells.[26] The mechanisms of immunotherapy resistance mediated by the TME are illustrated in Figure 2.

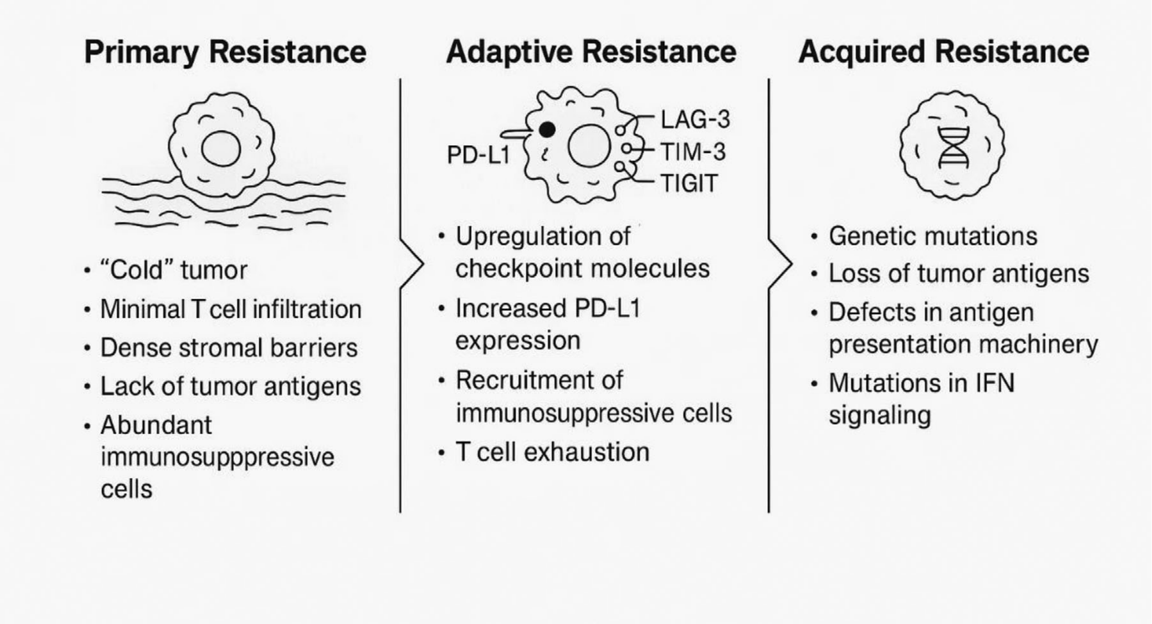

FIGURE 2 Mechanisms of immunotherapy resistance in the tumour microenvironment. Three types of resistance are shown: primary resistance is characterised by 'cold' tumours with minimal T-cell infiltration, dense stromal barriers, lack of tumour antigens and abundant immunosuppressive cells. Adaptive resistance occurs during treatment when tumours upregulate alternative checkpoint molecules (lymphocyte-activation gene 3 [LAG-3], T-cell immunoglobulin and mucin-domain containing-3 [TIM-3] and T-cell immunoreceptor with Ig and ITIM domains [TIGIT]), increase programmed death-ligand 1 (PD-L1) expression, recruit additional immunosuppressive cells and induce T-cell exhaustion. Acquired resistance develops through genetic mutations, loss of tumour antigens, defects in antigen presentation machinery and mutations in interferon (IFN) signalling pathways, leading to resistance development over time.

2.4 | Role of cancer stem cells in TME-mediated immunosuppression

Cancer stem cells (CSCs), a subpopulation of tumour cells with self-renewal and differentiation capabilities, play a crucial role in tumour initiation, progression and therapy resistance. CSCs actively shape the TME to create an immunosuppressive niche that protects them from immune-mediated clearance. They recruit and activate immunosuppressive cells such as TAMs, MDSCs and Tregs, while inhibiting the function of effector T cells and natural killer (NK) cells. For instance, CSCs can secrete factors such as TGF-β and IL-10 to promote the polarisation of TAMs towards the M2 phenotype and induce the expansion of Tregs.[29] Moreover, the interaction between CSCs and the TME is bidirectional; the TME, in turn, provides a supportive niche for CSC survival and self-renewal. This reciprocal relationship creates a vicious cycle that promotes tumour growth and resistance to immunotherapy. CSC-derived factors such as CCL2 and exosomes can recruit immunosuppressive myeloid cells and reprogram them into tumour-promoting phenotypes. Conversely, TAMs and MDSCs release cytokines such as IL-6 and CXCL8 that enhance CSC stemness and epithelial–mesenchymal transition, further reinforcing the immunosuppressive milieu.[30] CSC-rich zones in tumours are often associated with hypoxic and nutrient-deprived regions that disable effector T cells, with hypoxia-inducible factors not only maintaining stemness but also upregulating immune checkpoints and metabolic enzymes such as indoleamine 2,3-dioxygenase (IDO) that thwart T-cell function. Therefore, targeting the CSC–TME axis represents a promising strategy to overcome immunotherapy resistance by eliminating a key source of tumour regeneration and immunosuppression.[29]

3 | EMERGING STRATEGIES TO REPROGRAM TUMOUR MICROENVIRONMENT

Given the central role of the TME in mediating immunotherapy resistance, a major focus of current research is the development of strategies to reprogram this immunosuppressive landscape into one that is more permissive to anti-tumour immunity. These strategies aim to deplete or repolarise immunosuppressive cell populations, normalise the tumour vasculature, and alleviate the metabolic and physical barriers that impede immune attack (Table 2).

TABLE 2 Emerging therapeutic strategies to reprogram the tumour microenvironment (TME).

Strategy category	Specific approach	Mechanism of action	Clinical stage	Representative agents/examples	References
TAM targeting	Recruitment inhibition	Block CCR2–CCL2 axis to prevent monocyte recruitment	Phase I/II	CCR2 antagonists (PF-04136309)	29
	Depletion	Inhibit CSF-1R to eliminate TAMs	Phase I/II	Pexidartinib, emactuzumab	30
	Repolarisation	Reprogram M2-like to M1-like phenotype	Phase I/II	CD40 agonists, TLR agonists, PI3Kγ inhibitors	31
	Phagocytosis enhancement	Block 'don't eat me' signal	Phase I/II	Anti-CD47 (magrolimab), anti-SIRPα	32
MDSC targeting	Depletion	Selective elimination of MDSCs	Preclinical/phase I	Low-dose 5-FU, gemcitabine	33
	Functional inhibition	Restore L-arginine levels	Phase I/II	ARG1 inhibitors, iNOS inhibitors	34
	Differentiation induction	Force maturation to non-suppressive cells	Phase I/II	ATRA	35
Treg targeting	Depletion	Selective elimination of Tregs	Phase I/II	Low-dose cyclophosphamide, anti-CCR4	36
	Functional modulation	Enhance effector T-cell function	Phase I/II	GITR agonists, OX40 agonists	37
	Checkpoint blockade	Deplete Tregs via ADCC	FDA approved	Ipilimumab (anti-CTLA-4)	38
CAF targeting	CAF depletion	Target FAP-expressing CAFs	Preclinical/phase I	FAP-targeted CAR-T cells	39
	Signalling inhibition	Block CAF-derived factors	Phase I/II	CXCR4 antagonists	40
	ECM normalisation	Reduce stromal density	Phase II/III	TGF-β inhibitors	41
Metabolic reprogramming	Glucose metabolism	Reduce tumour glucose consumption	Preclinical/phase I	Glycolysis inhibitors	27
	Amino acid metabolism	Restore amino acid availability	Phase II/III	IDO inhibitors, ARG1 inhibitors	28
	Lipid metabolism	Modulate fatty acid oxidation	Preclinical	FAO inhibitors	42
Epigenetic modulation	DNA methylation	Upregulate tumour antigens and MHC	FDA approved	Azacitidine, decitabine	43
	Histone modification	Enhance immune gene expression	Phase I/II	HDAC inhibitors	44
	Chromatin remodelling	Downregulate PD-L1 and oncogenes	Phase I/II	BET inhibitors	45
Vascular normalisation	Anti-angiogenic therapy	Improve vessel function and perfusion	FDA approved	Bevacizumab (low dose)	46,47
Oncolytic viruses	Viral oncolysis	Induce ICD and TME inflammation	FDA approved	T-VEC	48–50

(Continues)

TABLE 2 (Continued)

Strategy category	Specific approach	Mechanism of action	Clinical stage	Representative agents/examples	References
Engineered cell therapies	Armoured CAR-T cells	Overcome TME immunosuppression	Phase I/II	IL-12-secreting CAR-T, PD-1 KO CAR-T	[51]
	CAR-NK cells	Off-the-shelf immunotherapy	Phase I	CD19-CAR-NK	[52]
	CAR-macrophages	Enhanced phagocytosis and APC function	Preclinical	HER2-CAR-M	[53]
Bispecific antibodies	T-cell engagers	Redirect T cells to tumour	FDA approved	Blinatumomab (CD19×CD3)	[54]
	Dual checkpoint blockade	Simultaneous inhibition of two pathways	Phase I/II	PD-1×CTLA-4 bispecific	[55]
Nanomedicine	Targeted delivery	TME-specific drug delivery	Preclinical/phase I	pH-responsive nanoparticles	[56–58]
	Co-delivery	Synergistic multi-agent delivery	Preclinical	Antigen + adjuvant nanoparticles	[57]

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; APC, antigen-presenting cell; ARG1, arginase 1; ATRA, all-trans retinoic acid; BET, bromodomain and extra-terminal domain; CAF, cancer-associated fibroblast; CAR, chimeric antigen receptor; CAR-NK, chimeric antigen receptor-natural killer; CCL, C–C motif chemokine ligand; CCR, C–C chemokine receptor; CSF-1R, colony-stimulating factor 1 receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ECM, extracellular matrix; FDA, Food and Drug Administration; GITR, glucocorticoid-induced TNFR-related protein; HDAC, histone deacetylase; ICD, immunogenic cell death; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; iNOS, inducible nitric oxide synthase; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; NK, natural killer; PD-L1, programmed death-ligand 1; TAMs, tumour-associated macrophages; TGF-β, transforming growth factor-beta; TLR, Toll-like receptor; Tregs, regulatory T cells; T-VEC, talimogene laherparepvec.

3.1 | Comparative analysis of TAM-targeting and Treg depletion strategies

Both TAMs and Tregs are key immunosuppressive cell populations in the TME, and targeting them has shown promise in preclinical and clinical studies. However, these two strategies have distinct toxicity and efficacy profiles that warrant careful consideration. TAM-targeting approaches, such as colony-stimulating factor 1 receptor (CSF-1R) inhibitors or CD40 agonists, generally aim to relieve macrophage-mediated immunosuppression without directly removing regulatory lymphocytes. In clinical trials, TAM-targeted therapies have shown moderate anti-tumour efficacy as monotherapies, with responses often improving when combined with other treatments such as checkpoint inhibitors. One advantage of TAM targeting is that it has not typically precipitated the severe systemic autoimmunity seen with Treg depletion. For instance, small-molecule CSF-1R inhibitors mainly cause on-target effects such as skin rash or liver enzyme changes rather than generalised autoimmunity.[31] However, certain TAM-depletion methods can carry their own toxicities, and thus TAM-targeting strategies often focus on partial reprogramming of TAMs (e.g., M2 to M1 polarisation) or localised delivery to maximise tumour efficacy while minimising collateral damage. In contrast, Treg-depletion strategies, such as low-dose cyclophosphamide, anti-CD25 antibodies or anti-CTLA-4 checkpoint blockade, can unleash powerful anti-tumour immunity by removing central suppressors of anti-tumour T-cell responses. The prototypical Treg-depleting agent, ipilimumab (anti-CTLA-4), can deplete intratumoural Tregs via Fc-mediated mechanisms and provides durable responses in some patients, but at the cost of considerable toxicity. By removing inhibitory constraints on the immune system, it frequently triggers autoimmune-like adverse events including immune-related dermatitis, colitis and endocrinopathies. This underscores that broad Treg depletion is a double-edged sword: while it may produce a more potent anti-tumour effect than TAM targeting, it carries a high risk of systemic autoimmunity due to the loss of immune self-tolerance.[32] Researchers are seeking ways to mitigate these toxicities, for example, by targeting Tregs more selectively using antibodies against Treg-specific markers such as C–C chemokine receptor (CCR)4, or by functionally reprogramming Tregs through epigenetic modulation rather than outright depletion. The efficacy of both strategies depends on the specific tumour type and the composition of the TME. In some tumours, Tregs may be the dominant immunosuppressive cell population, while in others, TAMs may play a more critical role. Therefore, a personalised approach, guided by biomarkers that can predict the dominant immunosuppressive mechanisms in individual patients, is needed to maximise the efficacy of these therapies. In practice, combination approaches that simultaneously modulate TAMs and Tregs are being explored to capitalise on their complementary roles in immunosuppression while potentially allowing lower doses of each agent to minimise toxicity.[31]

3.2 | Clinical bottlenecks in translating metabolic reprogramming agents

Metabolic reprogramming of the TME is a promising therapeutic strategy, but its translation to the clinic has been slow. Several bottlenecks have hindered the clinical development of metabolic reprogramming agents. The metabolic landscape of the TME is highly complex and dynamic, with significant heterogeneity between different tumour types and even within the same tumour. This complexity makes it challenging to identify metabolic vulnerabilities that can be effectively targeted without causing significant toxicity to normal tissues. A major bottleneck is the redundancy and adaptability of tumour metabolism: tumours often bypass a blocked metabolic pathway by upregulating alternatives, diminishing the efficacy of single-pathway inhibitors. The high-profile case of IDO1 inhibitors illustrates these challenges. IDO1 enzyme in tumours creates an immunosuppressive, tryptophan-depleted environment for T cells, and inhibiting IDO1 was expected to synergise with PD-1/PD-L1 checkpoint blockade. However, the phase III ECHO-301 trial combining the IDO inhibitor epacadostat with pembrolizumab failed to improve outcomes in melanoma. The failure has been attributed to multiple factors including incomplete target inhibition in vivo, compensatory immunosuppressive pathways (e.g., other enzymes such as TDO), and patient selection issues. This taught investigators that single-agent metabolic therapy might not suffice in an inherently plastic TME.[33]

Another bottleneck is the lack of robust biomarkers that can predict which patients are most likely to respond to metabolic reprogramming agents. This makes it difficult to design clinical trials and to select the right patients for treatment. Tumours vary in their dominant immunosuppressive metabolic pathways, and without biomarkers to identify tumours that rely heavily on specific pathways (such as the IDO/kynurenine pathway), trials can appear negative. Furthermore, metabolic pathways are ubiquitous, and completely shutting down a pathway systemically can harm normal tissues. Effective targeting requires either tumour-specific delivery or finding dosing regimens that preferentially affect immune cells and tumour cells over normal cells. Achieving this selectivity is difficult, and many metabolic drugs have narrow therapeutic windows where they help immune cells without causing undue toxicity. Current research is focusing on combinatorial metabolic interventions (targeting more than one pathway) and integrating them with immunotherapies. Early-phase trials are ongoing for combinations such as adenosine receptor blockers with anti-PD-1, or lactic acid transport inhibitors alongside T-cell therapies. In summary, the major bottlenecks in metabolic reprogramming are the selection of the right target(s) for the right patient, avoiding systemic toxicity, and conquering the tumour's metabolic flexibility. Overcoming these will likely require personalised and multi-targeted metabolic strategies, as well as better real-time imaging or biomarkers to monitor metabolic changes in the TME.[33,34]

3.3 | Targeting immunosuppressive cell populations

Strategies to counteract the pro-tumoural functions of TAMs include inhibiting their recruitment by targeting the CCR2–CCL2 axis,[35] depleting existing TAMs by targeting the CSF-1R,[36] and repolarising them to an anti-tumour phenotype using CD40 agonists or Toll-like receptor (TLR) agonists.[37] Additionally, blocking the phagocytosis checkpoint CD47–SIRPα has been shown to enhance the ability of macrophages to engulf and destroy cancer cells.[38] These strategies are illustrated in Figure 3.

Similarly, targeting the potent immunosuppressive functions of MDSCs is another critical strategy, with approaches including their depletion with low-dose chemotherapy,[39] inhibition of their function with ARG1 or iNOS inhibitors,[40] and promoting their differentiation with agents like all-trans retinoic acid (ATRA).[41] Given their central role in suppressing anti-tumour immunity, depleting or inactivating Tregs in the TME is a major goal of cancer immunotherapy. Strategies to target Tregs include their depletion with low-dose cyclophosphamide or anti-CCR4 antibodies,[27] targeting Treg-specific markers such as glucocorticoid-induced TNFR-related protein (GITR) and OX40,[28] and inhibiting their function with anti-CTLA-4 antibodies such as ipilimumab.[42]

3.4 | Reprogramming the tumour stroma and metabolism

CAFs are key architects of the tumour stroma and contribute significantly to the immunosuppressive TME. Strategies to counteract their influence include targeting

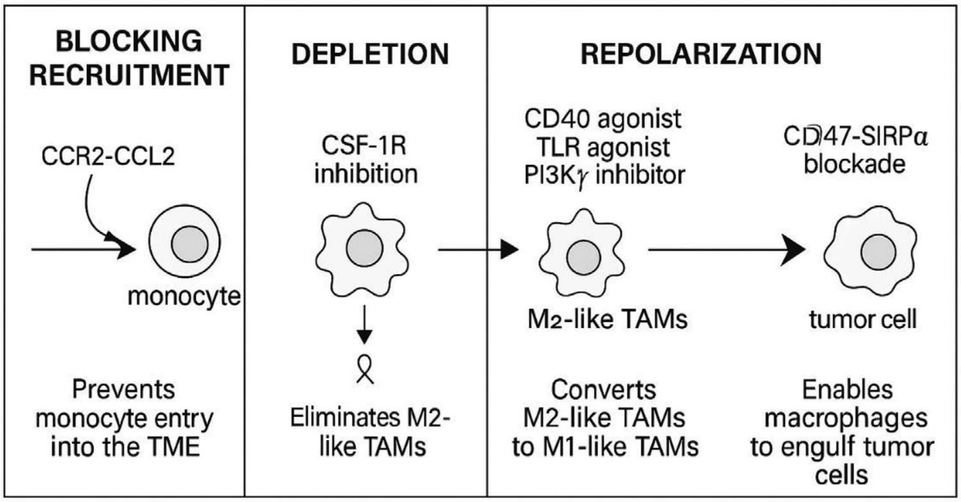

FIGURE 3 Strategies for reprogramming tumour-associated macrophages. Three main approaches are shown: blocking recruitment prevents monocytes from entering the tumour microenvironment (TME) by inhibiting the CCR2–CCL2 axis. Depletion eliminates M2-like tumour-associated macrophages (TAMs) through colony-stimulating factor 1 receptor (CSF-1R) inhibition, leading to apoptosis. Repolarisation transforms M2-like TAMs into anti-tumour M1-like TAMs using CD40 agonists, Toll-like receptor (TLR) agonists and PI3Kγ inhibitors. Enhanced phagocytosis is achieved through CD47–SIRPα blockade, enabling macrophages to engulf tumour cells. CCL, C–C motif chemokine ligand; CCR, C–C chemokine receptor.

CAF-specific markers such as fibroblast activation protein (FAP),[43] inhibiting CAF-derived factors such as CXCL12 and TGF-β,[44,45] and normalising the ECM. The hostile metabolic landscape of the TME is another major barrier to effective anti-tumour immunity (Figure 4). Strategies to reprogram tumour metabolism aim to alleviate nutrient competition and reverse the immunosuppressive effects of metabolic byproducts. These include targeting glucose metabolism with glycolysis inhibitors,[46] modulating amino acid metabolism with IDO or arginase inhibitors,[47] and interfering with lipid metabolism.[48]

3.5 | Epigenetic and vascular modulation

Epigenetic modifications play a crucial role in regulating gene expression in both tumour cells and immune cells. Targeting the epigenetic machinery with DNA methyltransferase (DNMT) inhibitors,[49] histone deacetylase (HDAC) inhibitors,[50] or bromodomain and extra-terminal domain (BET) inhibitors[51] is a novel strategy to reverse the immunosuppressive TME and enhance the efficacy of immunotherapy. The tumour vasculature is often chaotic and leaky, leading to hypoxia and poor perfusion. Vascular normalisation, which aims to restore a more normal and functional vasculature, has emerged as a promising strategy to enhance the efficacy of immunotherapy, often through the use of anti-angiogenic therapy at normalising doses.[52,53]

3.6 | Novel therapeutic modalities: chimeric antigen receptor T cells, oncolytic viruses and nanotechnology

Novel therapeutic modalities are being developed to overcome the limitations of current immunotherapies. These include advanced cell therapies, oncolytic viruses (OVs), and nanomedicine platforms that can reprogram the TME and enhance anti-tumour immunity.

3.6.1 | Engineered cell therapies

The adoptive transfer of genetically engineered immune cells, particularly chimeric antigen receptor (CAR) T cells, has revolutionised the treatment of hematological malignancies. However, their success in solid tumours has been limited by challenges such as TME-mediated exhaustion, antigen escape and poor tumour infiltration. To address these limitations, several innovative strategies are being explored. Targeting the TME with CAR-T cells: a promising approach is to engineer CAR-T cells to target specific components of the TME rather than tumour cells directly. For example, CAR-T cells targeting FAP, a marker expressed on CAFs, have shown the ability to remodel the tumour stroma and enhance the infiltration and activity of other immune cells. In preclinical models of pancreatic cancer, sequential treatment with FAP-targeted CAR-T cells followed by tumour-specific CAR-T cells led to greater

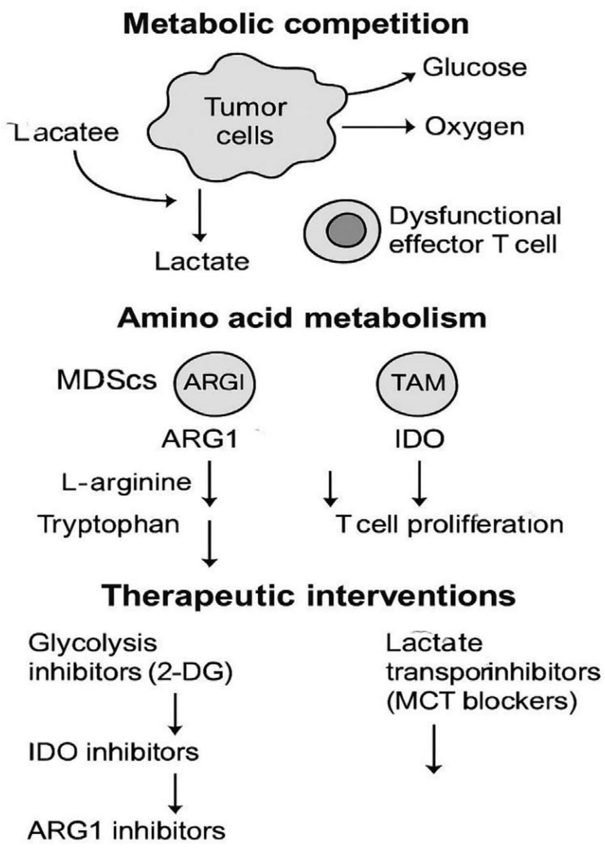

FIGURE 4 Metabolic reprogramming of the tumour microenvironment. Top: metabolic competition shows tumour cells consuming glucose and oxygen, producing lactate, leading to glucose-starved and dysfunctional effector T cells. Middle: amino acid metabolism depicts myeloid-derived suppressor cells (MDSCs) and tumour-associated macrophages (TAMs) expressing arginase 1 (ARG1) and indoleamine 2,3-dioxygenase (IDO) enzymes that deplete L-arginine and tryptophan, preventing T-cell proliferation. Bottom: therapeutic interventions include glycolysis inhibitors (2-DG), IDO inhibitors, ARG1 inhibitors and lactate transport inhibitors (monocarboxylate transporter [MCT] blockers), which restore T-cell function and enable anti-tumour activity by normalising pH and nutrient availability.

tumour control, as the FAP-CAR-T cells first eliminated CAFs and suppressed MDSC recruitment, thereby improving the efficacy of subsequent CAR-T cells. Similarly, CAR-T cells targeting CD70, a costimulatory molecule expressed on some tumour cells and immune cells, are being investigated for their potential to eliminate both tumour cells and immunosuppressive cells in the TME. In a phase I clinical trial, an allogeneic anti-CD70 CAR-T cell product (CTX130) showed encouraging results in advanced clear-cell renal cell carcinoma, with 81% of patients achieving disease control and no dose-limiting toxicities observed. This underscores that targeting CD70 can yield significant anti-tumour activity in solid cancers while maintaining a manageable safety profile. Chimeric antigen receptor-natural killer T (CAR-NKT) cells: CAR-NKT cells are an emerging class of engineered immune cells that combine the tumour-targeting capabilities of CARs with the intrinsic anti-tumour and immunomodulatory properties of NKT cells. CAR-NKT cells can recognise and kill tumour cells in a CAR-dependent manner, and they can also modulate the TME through their invariant T-cell receptor, which recognises the non-polymorphic CD1d molecule on antigen-presenting cells. This dual-targeting mechanism allows CAR-NKT cells to not only directly kill tumour cells but also to activate other immune cells and reshape the TME to be more favorable for an anti-tumour response. In preclinical models of ovarian cancer, allogeneic CAR-NKT cells demonstrated superior activity compared to conventional CAR-T cells, with enhanced tumour homing, concurrent TME modulation and reduced exhaustion.[54] Notably, these CAR-NKT cells showed minimal cytokine release syndrome or graft-versus-host disease, indicating a promising off-the-shelf cell therapy approach.[55]

In vivo CAR engineering: another exciting development is the in vivo engineering of CAR-T cells using lipid nanoparticle (LNP) or viral-based delivery systems. This approach avoids the need for ex vivo cell manufacturing and allows for the direct reprogramming of T cells within the patient's body. In proof-of-concept studies, intravenous injection of targeted LNPs carrying CAR-encoding mRNA successfully generated functional CAR-T cells in mice, resulting in tumour regression. In vivo CAR engineering has the potential to be a more cost-effective and scalable approach to CAR-T cell therapy, and it may also lead to the generation of CAR-T cells with improved persistence and function. Early preclinical data show that transient CAR expression can be induced in circulating T cells via LNPs without severe systemic toxicity.[54]

3.6.2 | Oncolytic viruses

OVs are naturally occurring or genetically engineered viruses that can selectively infect and kill cancer cells while sparing normal cells. Beyond their direct oncolytic effects, OVs are potent immunotherapeutic agents that can remodel the TME and trigger a robust anti-tumour immune response by inducing immunogenic cell death and TME inflammation. The FDA approval of talimogene laherparepvec (T-VEC), an oncolytic herpes simplex virus, for the treatment of melanoma has validated this approach. OVs can convert immunologically 'cold' tumours into 'hot' tumours by promoting the release of tumour-associated antigens and danger signals, thereby enhancing T-cell infiltration and activation.[56]

3.6.3 | Nanotechnology

Nanotechnology offers exciting new possibilities for TME reprogramming by enabling the targeted delivery of therapeutic agents and the development of novel immunomodulatory platforms. Nanoparticles can be designed to carry a wide range of payloads, including drugs, cytokines and nucleic acids, and they can be targeted to specific cell types or components of the TME. This allows for the precise and localised delivery of therapeutic agents, which can minimise off-target toxicity and enhance therapeutic efficacy. Recent advances in nanomedicine have demonstrated the potential to reprogram the TME through multiple mechanisms. For instance, dendritic nanomedicines with boronate bonds have been developed for augmented chemo-immunotherapy via synergistic modulation of the tumour immune microenvironment, integrating immunogenic cell death-inducing agents with IDO1 inhibitors to evoke robust immune responses while remodelling the immunosuppressive TME.[57] Metformin-based nanomedicines have shown promise in reprogramming the TME by altering tumour metabolism and repolarising suppressive myeloid cells, with mannose-functionalised nanoparticles delivering metformin specifically to TAMs, resulting in M2-to-M1 phenotype switching and increased CD8+ T-cell infiltration.[58] Furthermore, prodrug-based combinational nanomedicines can remodel lipid metabolism to reinforce ferroptosis and immune activation, with nanoplatforms co-delivering chemotherapeutic agents and photosensitisers to disrupt tumour lipid metabolism, induce extensive ferroptosis and activate adaptive immunity with elevated CD8+ T-cell infiltration. These nanomedicine approaches represent a versatile toolkit to modulate the TME in a multifaceted way, delivering immune agonists, metabolic drugs and therapeutic agents precisely where needed to convert immunotherapy-resistant tumours into responsive ones.[59]

4 | COMBINATION STRATEGIES: PATH TO SYNERGISTIC TME REPROGRAMMING

The complexity and redundancy of the immunosuppressive mechanisms within the TME make it unlikely that targeting a single pathway will be sufficient to overcome resistance in most patients. Consequently, a major focus of current clinical development is the use of combination therapies that can simultaneously attack multiple nodes of the immunosuppressive network (Figure 5). The goal is to achieve synergistic effects, where the combination is more effective than the sum of its parts. Given their central role in modern cancer immunotherapy, ICIs are the backbone of many combination strategies, and are often combined with chemotherapy,[60] radiation therapy[61] or targeted therapies.[62] As our understanding of the TME deepens, more sophisticated combination strategies are being developed that target multiple components of the TME simultaneously.

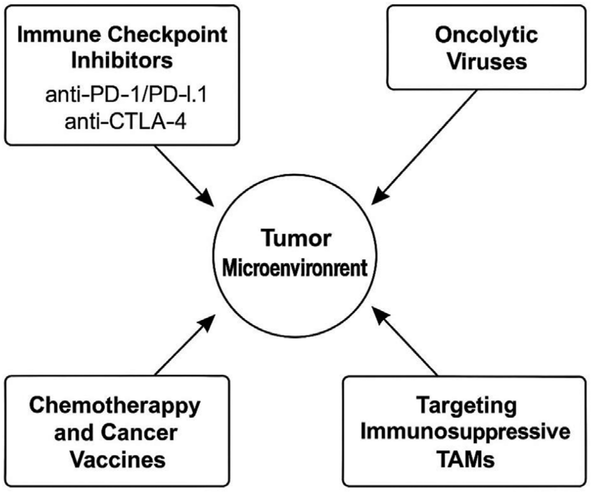

FIGURE 5 Synergistic combination strategies for tumour microenvironment (TME) reprogramming. Multiple therapeutic modalities converge on the immunosuppressive TME to achieve synergistic anti-tumour effects. Immune checkpoint inhibitors (anti-programmed cell death protein 1 [PD-1]/programmed death-ligand 1 [PD-L1] and anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]) unleash T-cell activity. Chemotherapy and cancer vaccines induce immunogenic cell death and antigen presentation. Oncolytic viruses trigger TME inflammation and immune activation. Targeting immunosuppressive tumour-associated macrophages (TAMs) depletes or repolarises these cells. Combination of these approaches dismantles the immunosuppressive TME and enables effective anti-tumour immunity.

5 | CLINICAL TRANSLATION AND CHALLENGES

The translation of these innovative TME-reprogramming strategies from the laboratory to the clinic is a complex and challenging process (Table 3). A growing number of clinical trials are evaluating TME-reprogramming agents, both as monotherapies and in combination with ICIs. Early phase trials have provided proof-of-concept for several of these strategies, with some showing promising signs of clinical activity.[63] However, a major challenge in the clinical development of TME-reprogramming therapies is the identification of predictive biomarkers that can identify the patients who are most likely to respond (Table 4). The TME is highly heterogeneous, and the development

TABLE 3 Selected clinical trials of tumour microenvironment (TME)-reprogramming agents in combination with immunotherapy.

Agent/ combination	Target	Cancer type	Phase	Key findings	Status	Reference
Bevacizumab + atezolizumab	VEGF + PD-L1	Hepatocellular carcinoma	III	Improved OS and PFS versus sorafenib	FDA approved	47,63
T-VEC + pembrolizumab	Oncolytic virus + PD-1	Melanoma	Ib/II	Enhanced response rate (62% vs. 33%)	Approved combination	50
CCR2 inhibitor + FOLFIRINOX	CCR2 + chemotherapy	Pancreatic cancer	Ib	Reduced TAMs, improved survival	Completed	29
CSF-1R inhibitor + anti-PD-1	CSF-1R + PD-1	Solid tumours	I/II	Depleted TAMs, enhanced T-cell infiltration	Ongoing	30
Atezolizumab + Nab-paclitaxel	PD-L1 + chemotherapy	Triple-negative breast cancer	III	Improved PFS in PD-L1+ patients	FDA approved	60
BRAF/MEK inhibitors + anti-PD-1	BRAF/MEK + PD-1	Melanoma	II	Synergistic anti-tumour activity	Ongoing	62
Anti-CD47 + rituximab	CD47 + CD20	Non-Hodgkin lymphoma	I	Enhanced phagocytosis, clinical responses	Ongoing	32
Azacitidine + nivolumab	DNMT + PD-1	Myelodysplastic syndrome	II	Improved response rates	Ongoing	43

Abbreviations: CCR, C–C chemokine receptor; CSF-1R, colony-stimulating factor 1 receptor; DNMT, DNA methyltransferase; FDA, Food and Drug Administration; OS, overall survival; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; PFS, progression-free survival; TAMs, tumour-associated macrophages; T-VEC, talimogene laherparepvec; VEGF, vascular endothelial growth factor.

TABLE 4 Biomarkers for tumour microenvironment (TME) profiling and patient selection.

Biomarker category	Specific markers	Assessment method	Clinical utility	References
Immune cell infiltration	CD8+ T cells, CD4+ T cells, NK cells	IHC, multiplex IHC, flow cytometry	Predict ICI response; 'hot' versus 'cold' tumours	64
Immunosuppressive cells	TAMs (CD68+, CD163+), MDSCs (CD33+), Tregs (FOXP3+)	IHC, multiplex IHC, flow cytometry	Identify patients for TAM/MDSC/Treg targeting	16,17
Checkpoint expression	PD-L1, PD-1, CTLA-4, LAG-3, TIM-3	IHC, RNA-seq	Predict ICI response; guide combination therapy	5,6
TMB	Number of somatic mutations	Whole-exome sequencing, targeted panels	High TMB predicts ICI response	2
MSI	MSI-high status	PCR, IHC (MMR proteins)	Strong predictor of ICI response	2
IFN signalling	IFN-γ signature, STAT1, IRF1	RNA-seq, qPCR	Indicates active anti-tumour immunity	7
Metabolic markers	Lactate, glucose, HIF-1α	Metabolomics, imaging (FDG-PET)	Identify metabolic reprogramming needs	25,26
Stromal markers	CAFs (α-SMA, FAP), collagen density	IHC, imaging (MRI, ultrasound)	Predict response to CAF-targeting therapies	21,22
Vascular markers	VEGF, CD31, vessel density	IHC, imaging (DCE-MRI)	Guide vascular normalisation strategies	46
Gene expression signatures	T-cell-inflamed signature, immune gene panels	RNA-seq, NanoString	Comprehensive TME profiling	64

Abbreviations: α-SMA, alpha-smooth muscle actin; CAF, cancer-associated fibroblast; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FAP, fibroblast activation protein; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; FDG-PET, fluorodeoxyglucose positron emission tomography; HIF-1α, hypoxia-inducible factor 1-apha; ICI, immune checkpoint inhibitor; IFN, interferon; IHC, immunohistochemistry; LAG-3, lymphocyte-activation gene 3; MDSC, myeloid-derived suppressor cell; MMR, mismatch repair; MSI, microsatellite instability; NK, natural killer; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; TAMs, tumour-associated macrophages; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TMB, tumour mutational burden; Tregs, regulatory T cells; VEGF, vascular endothelial growth factor.

of robust biomarkers that can accurately profile the TME of individual patients is crucial for the success of these therapies.[64] Other challenges include managing the toxicity of combination therapies, overcoming the redundancy of immunosuppressive mechanisms, and addressing the tumour type-specific differences in the TME.

6 | CONCLUSIONS

TME represents a major barrier to the success of cancer immunotherapy. The complex and dynamic interplay between cancer cells, immune cells, stromal cells and the ECM creates a profoundly immunosuppressive landscape that can foster immune evasion and promote resistance to therapy. However, our growing understanding of the TME has opened up a new frontier in cancer treatment, with a plethora of emerging strategies that aim to reprogram this hostile environment into one that is more conducive to anti-tumour immunity. The future of cancer immunotherapy lies in the development of rational combination therapies that can simultaneously attack the tumour and dismantle the immunosuppressive TME. The next generation of clinical trials will likely focus on personalised combinations, guided by sophisticated biomarker analysis. Emerging technologies such as spatial proteomics are revolutionising our ability to deconstruct the TME with single-cell resolution, revealing novel therapeutic targets and predictive signatures of response. Furthermore, advanced preclinical models, particularly patient-derived organoids co-cultured with immune cells, are providing unprecedented insights into tumour–immune interactions and enabling high-throughput screening of novel therapeutic combinations. As these technologies mature, they will be instrumental in designing more effective, personalised immunotherapeutic strategies. By embracing a more holistic view of cancer as a complex ecosystem and leveraging these powerful new tools to understand and manipulate it we can hope to overcome the challenge of immunotherapy resistance and bring the benefit of these transformative therapies to a greater number of patients.

AUTHOR CONTRIBUTIONS

Mohammed Elmujtba Adam Essa conceived and designed the review, supervised the overall project and drafted the manuscript. Shahd Elbadri contributed to data interpretation, literature analysis and manuscript revision. Hamid Noori contributed to the critical revision of the sections on immunotherapy resistance mechanisms and assisted in figure improvement. Abdelkareem A. Ahmed. participated in literature collection, data verification and drafting of selected sections. All authors contributed to the discussion, reviewed the final manuscript, and approved it for submission.

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The authors declare they have no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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