Advances in Cancer Biology - Metastasis 8 (2023) 100107

Contents lists available at ScienceDirect

Advances in Cancer Biology - Metastasis

journal homepage: www.journals.elsevier.com/advances-in-cancer-biology-metastasis

Deciphering the complexities of cancer cell immune evasion: Mechanisms and therapeutic implications

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ARTICLE INFO

Keywords:
Immune evasion
Epithelial-mesenchymal transition
Micro-RNAs
Cancer stem cells
Circulating tumor cells
Immunotherapy

ABSTRACT

Cancer immune evasion is one of the principal mechanisms leading to the progression and metastatization of the disease. Despite the migration and infiltration at the tumor site of immune cells, multiple factors can influence the composition of hot or "immune-sensitive" tumors and cold or "immune-resistant" tumors. Among the multiple mechanisms responsible for the make-up of the tumor microenvironment are the expression levels of major histocompatibility molecules (MHC) and of the antigen processing machinery, the metabolic network, hypoxia, and the secretion of pro-inflammatory molecules (e.g., cytokines, chemokines, and growth factors). Moreover, the different triggered pathways can mediate the reprogramming of activated, memory, effector, or regulatory/tolerogenic subtypes of immune cells (T, NK, dendritic cells, and macrophages). Recent studies have focused on the role of cancer metabolism in evading immune surveillance through the action of the active tryptophan catabolic enzyme indoleamine 2,3-dioxygenase (IDO). Immune suppression and evasion mechanisms in cancer cells are now being extensively studied with a special focus on developing immunotherapy strategies, such as the targeting of immune checkpoints (programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1), Cytotoxic T-lymphocyte antigen-4 (CTLA-4)), adoptive cell therapy or cancer vaccines. In this review, an overview of the underlying mechanisms of cancer immune evasion and the efficacy of the therapeutic targets and agents to overcome the immune escape are described.

1. Introduction

Cancer is the second cause of mortality worldwide [1]. Gene mutations due to environmental, genetic, and infectious agents (viruses and bacteria) lead to aberrant T-cell proliferation [2–4]. Nonetheless, the intricate interaction between immune and cancer cells can either lead to the control of tumor growth or immune evasion [5] and is considered as one of the hallmarks of cancer [5].

A balanced activation and inhibition of immune response by the immune system provides protection against infected antigens and self-antigens [6]. The dysregulated crosstalk among stromal, immune, and tumor cells leads to tumor immune evasion and progression. Basophils, dendritic cells (DCs), eosinophils, macrophages, monocytes, neutrophils, and natural killer (NK) cells comprise the innate immune system, while the adaptive system is composed of lymphocytes, including B-cells and NK T-cells [7]. In the thymus, mature T-cells develop into $CD8^+$ cytotoxic lymphocytes (CTLs) and $CD4^+$ helper (Th1) T-cells which are activated by the $CD3^+$T-cell receptor (TCR) binary signals. This leads to the release of interferon gamma (IFN-γ) and factors mediating the cytotoxic functions (perforins and granzymes) which aid in effector cell development and the killing of tumor cells [8]. CTLs recognize the tumor cells *via* the interaction of TCR with major histocompatibility complex (MHC) class I molecules [9]. Antigen-specific $CD4^+$ T-cells can segregate into different T-cell subsets, including Th1, Th2, Th9, Th17, Th22, and regulatory T-cells (Tregs) [10]. During the initial phase of tumor development, NK and T-cells recognize and eradicate the highly immunogenic cancer cells [11]. However, conditions like stress, infection, or chronic inflammation help cancer cells evade these mechanisms and favor the tumor progression [12,13].

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https://doi.org/10.1016/j.adcanc.2023.100107
Received 9 June 2023; Accepted 1 August 2023
Available online 3 August 2023
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List of abbreviations

1-MT 1-methyl tryptophan
2DG 2-deoxyglucose
ABC ATP-binding cassette
ACT Adoptive cell therapy
AFAP-AS1 Actin filament-associated protein 1 antisense RNA1
AFP Alpha-fetoprotein
Ahr Aryl hydrocarbon receptor
ALDH1 Aldehyde dehydrogenase
ALL Acute lymphocytic leukemia
APCs Antigen-processing cells
APM Antigen processing machinery
Akt Ak strain forming
ATM Adenosine 5′-triphosphate
β2M beta-2-microglobulin
BAGE B Melanoma antigen
BC Breast cancer
BCMA B cell maturation antigen
BIN1 Bridging integrator 1
BTLA B and T lymphocyte attenuator
CAFs cancer-associated fibroblasts
cAMP Cyclic adenosine 3′,5′-monophosphate
CAR Chimeric Antigen Receptor
CCL CC chemokine ligand
CDH1 Cadherin 1
CEA Carcinoembryonic antigen
CH13L1 Chitinase-3-like protein 1
circFGFR1 circular RNA fibroblast growth factor receptor 1
CLDN1 Claudin 1
CRC Colorectal cancer
CREB cAMP-response element binding protein
CICs Cancer initiating cells
cSCC Cutaneous squamous-cell carcinoma
CSCs Cancer stem cells
CTCs Circulating tumor cells
CtDNA Circulating tumor DNA
CTLA-4 Cytotoxic T-lymphocyte antigen-4
CTLs Cytotoxic T lymphocytes
CXCL Chemokine (C-X-C motif) ligand
CXCR C-X-C chemokine receptor
DCs Dendritic cells
dMMR Deficient mismatch repair
DNMT DNA methyltransferase
DR5 Death receptor 5
ECM Extracellular matrix
EGF Epidermal growth factor
EMA European Medicines Agency
EMT epithelial-mesenchymal transition
EpCAM Epithelial cellular adhesion molecule
EphA3 Ephrin type-A receptor 3
ERK Extracellular signal-regulated kinase
FAS Fas Cell Surface Death Receptor
FDA Food and Drug Administration
FL Follicular lymphoma
FOX Forkhead box
GM-CSF Granulocyte-Macrophage Colony-Stimulating Factor
HBV Hepatitis B virus
HCC Hepatocellular carcinoma
HDAC Histone deacetylase
HIF Hypoxia-inducible factor
HK2 Hexokinase-2
HL Hodgkin's Lymphoma
HLA Human leukocyte antigen
HNSCC Head and neck squamous cell carcinoma
HOTAIR HOX transcript antisense intergenic RNA
HOTTIP HOXA Distal Transcript Antisense RNA
HOX Homeobox
HPV Human papillomavirus
ICAM1 Intracellular adhesion molecule 1 receptor
ICPs Immune checkpoints
ICP-Is Immune checkpoint inhibitors
IDO Indoleamine 2,3-dioxygenase
IFN-γ Interferon gamma
IL Interleukin
ILCs Innate lymphoid cells
iNOS Inducible nitric oxide synthase
IRF Interferon regulatory factor
JAK/STAT Janus kinase/signal transducers and activators of transcription
KYN Kynurenine acid
LAG3 Lymphocyte-activation gene 3
LCN2 Lipocalin 2
LMP Latent membrane protein
lncRNAs Long non-coding RNAs
LOH Loss of heterozygosity
MAGE Melanoma Antigen gene
MALAT1 Metastasis-associated lung adenocarcinoma transcript 1
MAPK Mitogen-activated protein kinase
MART1 Melanoma-associated antigen recognized by T cells
MCC Merkel cell carcinoma
MCT4 Monocarboxylate transporter 4
MDM2 Murine double minute 2
MDSCs Myeloid-derived suppressor cells
MEK Mitogen-activated extracellular kinase
MHC Major histocompatibility complex
MICA/B Major histocompatibility complex class I chain-related protein A or B
miRs Micro-RNAs
MMPs Matrix metalloproteinases
MSI-H Microsatellite instability
mTOR Mammalian target of rapamycin
MUC Mucin
NADH reduced Nicotinamide adenine dinucleotide
NF-κB Nuclear factor kappa light chain enhancer of activated B cells
NEAT1 Nuclear-enriched autosomal transcript 1
NETs Neutrophil extracellular traps
NHL Non-Hodgkin's lymphoma
NK Natural killer
NKG2D Natural killer group 2 D
NKX2-AS1 NK2 homeobox family member 2 antisense RNA 1
NR4A Nuclear Receptor 4A
NSCLC Non-small cell lung cancer
Oct4 Octamer-binding transcription factor 4
OxPhos Oxidative phosphorylation
p53 Tumor protein p53
PARP Poly-Adenosine triphosphate (ADP) ribose polymerase
PD-1/PD-L1 Programmed cell death protein 1/programmed death ligand 1
PD-1H Programmed death-1 homolog
PI3K Phosphoinositide 3-kinase
PK Protein kinase
PRAME Preferentially expressed antigen of melanoma
RANKL Receptor activator of nuclear kappa-B ligand
Ras Renin-Angiotensin System
RCC Renal cell carcinoma
RhoA Ras homolog family member A
ROR1 Tyrosine-protein kinase transmembrane receptor
ROS Reactive oxygen species

SNAIL/SNAI1 Snail Family Transcriptional Repressor 1
SNHG Small nucleolar host gene
SLUG/SNAI2 Snail Family Transcriptional Repressor 2
Sox2 Sex-determining region Y gene (SRY)-Box Transcription Factor 2 **Src** Steroid Receptor Coactivator
TAA Tumor-associated antigen
TAG-72 Tumor-associated glycoprotein-72
TAMs Tumor-associated macrophages
TANs Tumor-associated neutrophils
TAP Transporter associated with antigen processing
TCA Tricarboxylic acid
TCR T-cell receptor
tDCs Tolerogenic DCs
TDO2 Tryptophan-2, 3-dioxygenase
TGF-β Transforming growth factor-beta
Th T helper cells
TIGIT T-cell immunoreceptor with immunoglobulin and ITIM domains
TIM3 T-cell immunoglobulin and mucin domain 3
TINKs Tumor-infiltrating natural killer cells
TJP1 Tight junction protein 1
TLE1 Transducin-like enhancer of split 1
TME Tumor microenvironment
Trp Tryptophan
TRUCKs T-cells redirected for antigen-unrestricted cytokine-initiated killing
TOX Thymocyte selection-associated high mobility group box protein
TRAIL Tumor necrosis factor-related apoptosis-inducing ligand
Tregs Regulatory T-cells
TSA Tumor specific antigen
TSP1 Thrombospondin-1
TWIST1 Twist family basic helix-loop-helix transcription factor 1
UC Uterine carcinoma
VCAM1 Vascular cell adhesion protein 1
VEGF Vascular endothelial growth factor
VISTA V-domain immunoglobulin (Ig) suppressor of T cell activation
VTCN1 V-Set Domain Containing T Cell Activation Inhibitor 1
Wnt Wingless/Integrated
WT1 Wilms' tumor protein 1
Zeb Zinc Finger E-Box Binding Homeobox

1.1. MHC molecules

The antigen processing machinery (APM) plays a vital role in initiating an efficient anti-tumor immune response by mediating the processing and presentation of antigens to the immune system [14]. The APM comprises various steps, including uptake, processing, and presentation of antigens. Antigen-processing cells (APCs) can present antigen-derived peptides, in the form of complexes with MHC molecules, to Tcells [15]. The MHC classes I and II molecules are membrane-bound glycoproteins involved in the adaptive immune response by presenting peptide antigens on the cell surface to $CD8^+$ and $CD4^+$ Tcells, respectively [16]. MHC class I molecules are expressed on the surface of almost all nucleated cells, while MHC class II molecules are mainly present on the surface of professional APCs such as dendritic cells, macrophages, and B cells. The MHC-I molecule comprises of three domains: the alpha chain, beta-2-microglobulin (β2M), and the peptide antigen. The alpha chain is further made up of three main domains: the α1, α2, and α3; while the α1 and α2 domains regulate the binding of the MHC-I molecule to the peptide antigen, the α3 domain plays a role in the interaction of the MHC-I molecule with the CD8 Tcell receptor [17]. The β2M subunit is essential for the proper folding and stability of the MHC-I molecule. The peptide antigen (8–10 amino acids long) binds to the groove formed by the α1 and α2 domains of the MHC-I molecule [18]. On the other hand, the MHC-II molecule is made up of two polypeptide chains, an alpha chain (α) and a beta chain (β) [19]. The α and β chains each consists of two extracellular domains: α1, α2 and, β1 and β2, respectively [19]. The α and β chains form a peptide-binding groove that allows binding of peptide antigens of up to 13–25 amino acids in length [20].

A critical mechanism by which tumors evade the immune mechanism is by the suboptimal expression of MHC molecules and the APM, including latent membrane protein (LMP) 2 and LMP7, transporter associated with antigen processing (TAP) protein, and tapasin [21–23]. The optimal expression of these molecules mediates and regulate the efficient antigen processing and presentation, and the subsequent eliciting of T-cell responses. T-cells can recognize MHC/peptide complexes and engage stimulatory and co-stimulatory signaling, leading to their activation and proliferation [24]. Studies have demonstrated that the downregulation of MHC-I molecules and APM can occur in tumors such as colorectal cancer (CRC), breast cancer, and melanoma [25–27]. Defects at genetic, epigenetic, transcriptional, or post-transcriptional levels could deregulate MHC and APM molecules [28]. The mechanisms by which the expression of MHC molecules is modulated by tumor cells can be classified into two types: reversible or irreversible. Irreversible MHC defects arise from mutations in the genes of human leukocyte antigen (HLA) or APM components such as β2M, LMP2, LMP9, tapasin, ERp57, calnexin, and calreticulin [29–31]. Loss of heterozygosity (LOH) of the HLA-ABC genes of chromosome locus 6p21 is the most reported genetic change in CRC, non-small cell lung carcinoma, and cervical cancer [25, 32].

One of the key mechanisms involved in the defective and unstable expression on the surface of the cells of HLA molecules is represented by mutations in the β2M genes [33]. IFN-γ is known to modulate the expression of HLA molecules. Mutations in the IFN-pathway genes, such as JAK/STAT or IRF1, have been associated with loss of responsiveness of tumor cells to IFN-γ [34–36]. Mutations in the HLA genes are associated with the upregulation of IFN-γ, which can lead to the up-regulation of the inhibitory molecules programmed cell death-1 ligand 1 (PD-L1), PD-L2, indoleamine 2,3-dioxygenase 1 (IDO1), inducible nitric oxide synthase (iNOS), FAS and FAS ligand (FASL) [30]. These are all molecules that can inhibit the effector functions of the immune cells.

Reversible or non-structural HLA defects, mediated by transcriptional or post-translational mechanisms, are the most common cause of the downregulation of MHC expression in most cancer types [14]. The expression of HLA molecules can be restored by the exposure of tumor cells to some cytokines, epigenetic agents, such as methyltransferase inhibitors, transcriptional regulators and autophagy inhibitors [28]. Histone deacetylase (HDAC) and DNA methyltransferase (DNMT) inhibit the expression of MHC Class I and APM proteins by covalent modifications of histone proteins that regulate chromatin and gene expression [37,38]. Reduced STAT1 expression in head and neck squamous cell carcinoma (HNSCC) was linked with methylation of the promoter region, and the treatment of HNSCC cell lines with DNMT inhibitor, 5-azacytidine could restore the expression of this molecule and, subsequently, of MHC molecules [39].

HLA-I expression is also regulated by RNA-binding proteins through a post-transcriptional mechanism. A study conducted by Huang et al. found that in patients with CRC, the abnormal expression of the RNA-binding protein MEX3B resulted in reduced HLA-A expression and resistance to immunotherapy [40]. The conditions that persist in the tumor microenvironment, mainly hypoxia, acidosis, glucose deprivation, and excess immunosuppressive cytokines also dysregulate antigen presentation and HLA-I expression [41]. IL-10, the commonly

overexpressed cytokine that exhibits significant immunosuppressive effects, has been observed to decrease the expression of HLA class-I molecules, restrict antigen presentation, and induce HLA-G expression in cancer cells [42–44]. Post-translational silencing was described by Yamamoto et al. [45] where the levels of surface MHC molecules could be considerably decreased by inducing lysosomal degradation of these molecules through mechanisms dependent on autophagy. Cell surface MHC expression was restored, and the anti-tumor Tcell response was enhanced in animal models in response to chloroquine.

1.2. Tumor-associated antigens (TAAs)

Tumor-Associated antigens (TAAs) are molecules, including those bound to the membrane, located in the cytoplasm or nucleus, and can even be secreted by the tumor cells, that can be recognized in the form of MHC/peptide complexes by T lymphocytes. These antigens can also be expressed by normal cells. Tumor antigens can be categorized into different types, as shown in Table 1 [46].

Immunogenicity is the ability of an antigen to trigger an immune response. TAAs play an important role in the immunogenicity of tumors by several mechanisms [47]. TAAs stimulate different immune cells including T and NK cells, and induce an immune response against the tumor cells [48]. In addition, TAAs are processed and presented by APCs, which break TAAs into small peptide fragments and present them on their cell surface *via* MHC molecules allowing the activation of Tcells [49]. CTLs recognize and eliminate tumor cells displaying TAAs [49]. On the other hand, TAAs generate adaptive immune responses and stimulate the production of tumor-specific antibodies by Bcells [49]. The produced antibodies bind to TAAs to eliminate tumor cells. Immunological memory also helps to trigger an augmented immune response upon re-encountering a specific TAA [50]. Identification and molecular characterization of TAAs have led to the development of TAA-based cancer vaccines to stimulate TAA-specific TCR [51,52]. However, TAAs can have low immunogenicity, which can be attributed to the host's immunotolerance, the tumor's immunosuppressive microenvironment, and the low levels of costimulatory molecules expressed by the tumor [53]. In certain conditions, TAAs are self-antigens and are presented in normal healthy cells. Hence the TAAs are not recognized as foreign bodies by the immune system and, hence, low immune response is triggered [50]. Similarly, low or heterogeneous expression of TAAs on tumor cells can lack co-stimulatory signals produced by APCs and does not trigger a strong immune reaction [50]. Moreover, tumor cells transform TAAs expression by producing immunosuppressive molecules or creating an immunosuppressive environment [54]. In addition, prolonged exposure to TAAs present on tumor cells can lead to immune tolerance or exhaustion [50]. These mechanisms can lead to low immunogenicity of TAAs and strategies including ICP blockade or combination immunotherapies are necessary to improve TAAs immunogenicity and promote effective anti-tumor immune responses.

Table 1
Types of tumor-associated antigens.

Category	Description	Examples
Oncofetal antigens	Antigens found in fetal tissues and cancerous somatic cells	Carcinoembryonic antigen (CEA), Immature laminin receptor, Tumor-associated glycoprotein 72 (TAG-72)
Oncoviral antigens	Antigens that are encoded by viruses with tumorigenic transforming properties	Human Papilloma Virus (HPV) E6, E7
Overexpressed/ accumulated antigens	Antigens found in both normal and cancerous tissues, but highly elevated in cancer	BING-4, Calcium-activated chloride channel 2, EpCAM, EphA3, Her2/neu
Cancer-testis antigens	These antigens are found only in cancer cells and reproductive tissues	BAGE family, CAGE family, MAGE family, PRAME
Lineage-restricted antigens	Antigens found mostly in a single cancer histo-type	Melan-A/MART-I, Tyrosinase, Prostrate-specific antigen
Mutated antigens	Antigens resulting from genetic mutation or transcription alteration	β-catenin, Fibronectin, p53, Ras, patient's specific neoantigens
Post-translationally altered antigen	Modified by tumor-associated changes in glycosylation, acetylation, phosphorylation	Mucin (MUC)-1
Idiotypic antigens	Antigens arising from highly variable genes resulting in a specific "clonotype" expressed by tumor cells, as in B or T cell lymphomas/ leukemias with clonal aberrancies	Immunoglobulins, TCR

BAGE: B Melanoma antigen; EpCAM: Epithelial cellular adhesion molecule; EphA3: ephrin type-A receptor 3; MAGE: Melanoma Antigen gene; MART1: Melanoma-associated antigen recognized by T cells; PRAME: Preferentially expressed antigen of melanoma; TCR: Tcell receptor.

Neo-antigens are tumor-specific antigens, generated either by somatic mutations occurring in tumor cells and are associated with high immunogenic properties [55]. Post-translational modifications such as acetylation, phosphorylation, glycosylation, and SUMOylation have been associated with several TAAs in different cancer types [56]. Hypermethylation of genes encoding neoantigens has been associated with the ability of lung cancer cells to evade the immune system [57]. There are two types of neoantigens: shared and patient's specific [58]. Shared neoantigens are mutated antigens found in multiple cancer patients but not in normal cells. Highly immunogenic shared neoantigens can potentially be used to create broad-spectrum cancer vaccines for patients with the same gene mutation. The second category is composed by neoantigens which are unique for each patient. Therefore, personalized therapy is necessary for the preparation of therapeutic interventions that lead to the induction of immune responses toward these neoantigens. Since neoantigens are not present in normal cells, they are candidate targets for immunotherapeutic strategies for cancer treatment [59]. During the initial steps of neoantigen identification, the patient's tumor and normal DNA are sequenced [59]. Algorithmic calculations are used to recognize candidate neoantigens based on the binding of neoantigens to MHC molecules. Once identified, the candidate neoantigens are validated through functional assays to verify their ability to provoke a Tcell response [60] to be used to develop personalized cancer vaccines and adoptive cell therapies (ACT) [61,62]. A trial with 13 melanoma patients utilized an individualized RNA-based vaccine treatment approach [63]. The treatment strategy involved the identification of the specific mutated antigen in each patient-derived tumor genome and the production of an antigen-based vaccine. Genocea Biosciences's GEN-009 vaccine trial (NCT03633110), utilizing neoantigens as a personalized therapy, has shown promising efficacy at targeting a broad range of solid tumors, with zero percent of relapse among treated patients [61]. An improved Tcell response with no adverse side effects was observed in a trial using personalized neoantigen vaccine NEO-PV-01 combined with PD-1 blockade in patients with advanced melanoma, non-small cell lung cancer, or bladder cancer [64]. Neoantigen vaccines exhibit a noticeable impact on tumor treatment and are anticipated to emerge as a promising immunotherapy intervention in the future for reducing the rising morbidity and mortality rates associated with tumors, however, certain factors such as rarity of neoantigens, lack of effective screening methods and the long time taken for the development of vaccines may hinder the process [55].

2. Immune checkpoints (ICPs)

Immune checkpoints (ICPs) are essential cell surface molecules that exert immunoregulatory functions, limiting autoimmunity and uncontrolled immune responses by mediating intercellular communications [65,66]. ICPs act in ligand-receptor pairs as gatekeepers to control the

interaction between antigen-presenting cells and cells of the innate and adaptive immune system, mainly Tcells [67]. Based on their impact on immune responses, ICPs are classified as inhibitory and stimulatory immune checkpoints. It has been observed that inhibitory ICPs or their ligands are often overexpressed by tumor cells or the tumor microenvironment (TME), effectively suppressing the immune reactivity towards tumor cells [67]. ICP molecules expressed on cancer cells also potentiate several malignant features such as self-renewal, metastasis, therapeutic resistance, evasion of apoptosis, and angiogenesis [68–72]. Fig. 1 depicts the main immune checkpoint molecules involved in regulating anti-tumor immune responses, which are described below.

2.1. CTLA4

Cytotoxic Tlymphocyte antigen-4 (CTLA4), also known as CD152, was the first discovered immune checkpoint and is considered as one of the main inhibitory regulators of Tcell activation [73]. CTLA-4 is a member of the immunoglobulin superfamily and is expressed in T regulatory cells (Tregs) and activated cytotoxic Tcells [74,75]. CTLA-4 is highly homologous with CD28 receptor, with which it shares the same ligands, namely B7.1 (CD80) and B7.2 (CD86), expressed on APCs [76] (Fig. 1). Despite their ability to bind identical ligands, CD28 and CTLA-4 mediate opposing effects on Tcell function. CD28 provides a costimulatory signal for Tcell activation and survival, while CTLA-4 suppresses Tcell activation, proliferation, and differentiation [77–79]. CTLA-4 exerts a competitive binding to CD80/CD86 proteins, with 10-100-fold higher affinity than CD28 [80,81]. CTLA-4 has been reported to further dampen Tcell responses *via trans*-endocytosis and degradation of B7 proteins from the surface of APCs as well as interference with Tcell receptor (TCR) function [82]. CTLA-4 has been shown to act also through cell-intrinsic mechanisms through the recruitment of phosphatases, which results in the dephosphorylation of key signaling molecules downstream of TCR and CD28 [79,83,84]. Clinically, dysregulation of CTLA-4 expression has been linked to many autoimmune diseases, such as type 1 diabetes [85] and rheumatoid arthritis [86]. In cancer, elevated CTLA-4 expression within the tumor microenvironment has been found to play a critical role in immune evasion. Notably, high expression of CTLA-4 in breast [87,88], thymus [89], esophageal [90], and nasopharyngeal [91] cancers have been correlated with poor patient prognosis. Accordingly, immunotherapies targeting CTLA-4 have been developed to unleash anti-tumor immune responses. These medications opened a new scenario for the clinical management of cancer patients, even in advanced stages. Ipilimumab, an anti-CTLA-4 monoclonal antibody, was the first approved immune checkpoint inhibitor based on the improved overall survival as well as progression-free survival of patients with metastatic melanoma [92,93]. Currently, ipilimumab is used as monotherapy in melanoma and in combination with anti-PD-1 (nivolumab) in various cancers, including colorectal, renal and lung cancer [94,95]. Nevertheless, the clinical efficacy of anti-CTLA-4 therapies is limited and restricted to a subset of cancer patients. Therefore, there is a need to better understand the mechanisms controlling CTLA-4-mediated immune evasion and identify biomarkers of responsiveness to improve the efficacy of these therapies.

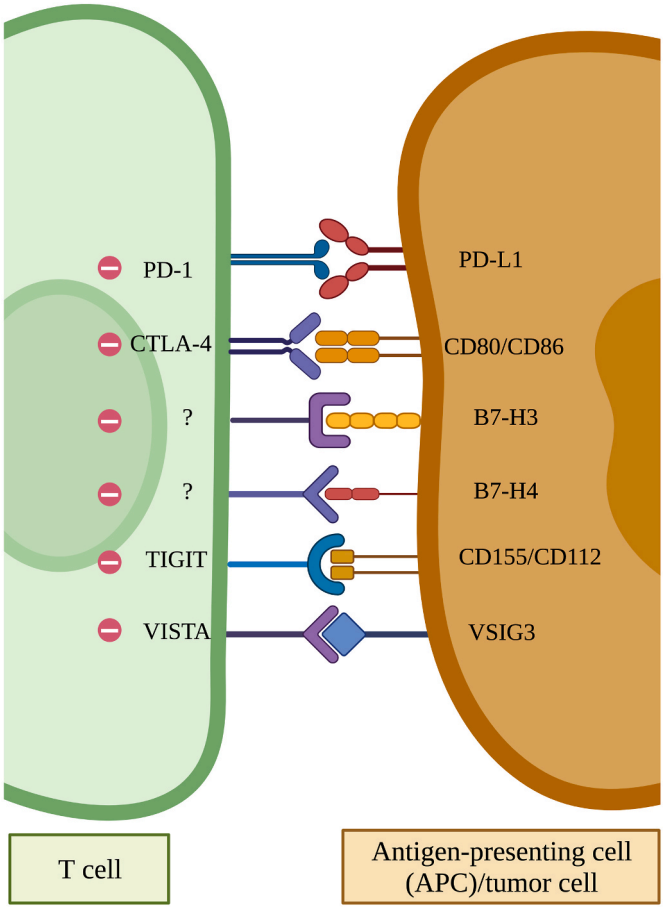

Fig. 1. ***Immune checkpoint (ICP) receptors and their corresponding ligands.*** Immune checkpoint molecules expressed on Tcells are shown with their respective ligands. Immune checkpoints such as programmed cell death protein 1 (PD-1), cytotoxic Tlymphocyte antigen-4 (CTLA4), Tcell immunoreceptor with immunoglobulin and ITIM domains (TIGIT), V-domain immunoglobulin (Ig) suppressor of Tcell activation (VISTA) bound to their respective ligands on antigen presenting cells (APCs) and/or tumor cells, triggering a negative or positive signal to Tcell response. Figure created with Biorender.com.

2.2. PD-1/PD-L1

The programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1) pathway has received extensive research attention due to the groundbreaking success of its inhibitors in clinical settings and their revolutionary role in cancer immunotherapy. PD-1 (PDCD1, CD279) is a type I transmembrane protein that belongs to the B7-CD28 receptor superfamily and is expressed on activated Tcells and, to a lesser extent, on APC, B and NK cells [96–98] (Fig. 1). PD-1 interacts with two ligands from the B7-CD28 family, namely PD-L1 (B7–H1, CD274) and PD-L2 (B7-DC, CD273), which play a critical role in regulating anti-tumor immune responses [67]. PD-L1 is expressed on various cell types, including macrophages, dendritic cells, activated T and B cells, as well as non-immune cells such as tumor cells, vascular endothelial cells, and epithelial cells (11, 34). On the other hand, PD-L2 expression is more restricted and is primarily detected on APCs [75,99]. The interaction between PD-1 and PD-L1 leads to phosphorylation of the intracellular domain of PD-1, which triggers the recruitment of Src homology region 2 domain-containing phosphatase 1 (SHP-1) and SHP-2 [100,101]. These molecules dephosphorylate key proteins in the TCR signaling pathway, suppressing downstream signaling pathways, such as PI3K, Akt, mTOR, RAS, MAPK, and ERK, and inhibiting the transcription of targeted genes [102,103]. Consequently, it arrests the cell cycle of Tcells, downregulates cell survival proteins, such as Bcl-xl, and inhibits the production of cytokines and the proliferation and differentiation of T-cells [102–104]. Collectively, these effects induce an immunosuppressive effect, impair T-cell activation, and suppress immune responses against surrounding tissues. This effect is important for maintaining homeostatic peripheral tolerance, as evidenced by the autoimmune diseases that arise upon deletion of Pdcd1, the gene that encodes the PD-1 protein, in mouse models [105–107]. In the tumor microenvironment, PD-1 acts in the secondary immune response, where its expression gets upregulated upon activation of Tcells, which in turn promotes the expression of PD-L1 in surrounding tissues by inducing the release of cytokines such as IFN-γ, interleukins and TNFα [75,103,108]. In turn, the interaction between PD-1 and PDL-1 induces Tcell exhaustion,

leading to anergy [109]. Tcell exhaustion is a hyporesponsive phenotype of Tcells, where cells lose their function as a result of prolonged antigen stimulation, such as in the tumor microenvironment [110]. It is now accepted that the majority of cancer cells upregulate the expression of PD-L1 as a means to evade immune surveillance [111]. Therefore, the blockade of PD-1/PDL-1 signaling has shown great success in reversing immunosuppressive conditions and enhancing the eradication of tumor cells. Today, immune checkpoint inhibitors targeting this axis, such as atezolizumab, durvalumab, nivolumab, cemiplimab, and pembrolizumab become an important cornerstone in the management of various malignancies [112].

2.3. B7–H3 (CD276)

B7–H3, also referred to as CD276, belongs to the B7 protein superfamily, which plays a critical role in regulating the responses of activated T-cells [70,113]. Similar to other B7 proteins, B7–H3 was initially identified as an immune checkpoint expressed in antigen-presenting cells or macrophages [113,114] (Fig. 1). B7–H3 is detected at low levels in normal tissues but shows a significantly high expression in a broad spectrum of cancers [68,98]. Additionally, a soluble form of B7–H3 was detected in high levels in the serum of non-small cell lung carcinoma (NSCLC) patients as compared to healthy controls and was associated with a higher tumor burden [115]. This soluble form is thought to be released as a result of cleavage of B7–H3 cell surface receptor by MMPs from tumor and immune cells. Although the ligand for B7–H3 has not been identified yet, it is postulated that the ligand is expressed on activated Tcells, which is supported by its inhibitory effect on Tcell mediated tumor immunity [98,115]. Recently, B7–H3 was also found to possess non-immunological pro-tumorigenic roles such as augmenting metastasis, invasion, anti-apoptotic activity, therapy resistance, and stemness [98,114].

2.4. B7–H4 (VTCN1)

B7–H4, encoded by the V-Set Domain Containing Tcell Activation Inhibitor 1 (VTCN1) gene, is another type I cell surface transmembrane protein of the B7 family [71,98,116]. B7–H4 is highly expressed on the surface of a wide variety of tumor cells and tumor-associated macrophages, where the expression is correlated with tumor aggressiveness and poor survival [71,98,116–118] (Fig. 1). Although the receptor for B7–H4 has yet to be identified, it appears to be expressed on activated Tlymphocytes [98]. Functionally, B7–H4 is thought to deliver negative signals to Tcells, abrogating the activation, proliferation, and cytokine production of $CD4^+$ and $CD8^+$ T-cells [116,117]. Additionally, B7–H4 appears to be involved in the expansion of myeloid-derived suppressor cells (MDSCs), an immature myeloid cell with a strong immunosuppressive activity [119]. Like B7–H3, soluble B7–H4 is detected in the blood of cancer patients, where its high expression has been associated with a worse prognosis [117]. Moreover, overexpression of B7–H4 significantly increased anti-apoptotic effects, tumor formation, and invasion, suggesting additional tumor-specific functions other than its immune suppression role through modulation of EMT and JAK2-STAT3 signaling [117]. On the other hand, it has been reported that knockdown of B7–H4 inhibited tumor proliferation, colony formation, migration, and invasion; and increased apoptosis and cell cycle arrest at G0/G1 phase [120].

2.5. TIGIT

Tcell immunoreceptor with immunoglobulin and ITIM domains (TIGIT), also known as WUCAM, Vstm3, or VSIG9, is a transmembrane glycoprotein containing an extracellular Ig-like V-type domain and an immunoreceptor tyrosine-based inhibitory motif (ITIM) in its cytoplasmic tail [121,122]. TIGIT belongs to the immunoglobulin superfamily and is mainly expressed in activated and memory T, regulatory T (Tregs) and NK cells [121] (Fig. 1). Accumulating evidence has shown that TIGIT plays a critical role in regulating immune responses and mediating cancer immune evasion [123]. TIGIT binds to two main ligands, CD155 and CD112, that are expressed on antigen-presenting cells or tumor cells [124]. Engagement of TIGIT with its ligands exerts various immunosuppressive effects, including inhibition of CD8 T-cell initiation and differentiation, blocking T and NK cell-mediated tumor killing, and suppressing the production of proinflammatory cytokines (e.g., interferon-γ, IL-17) while increasing the release of immunosuppressive cytokines (e.g., IL-10) [125–128]. TIGIT has been found to be upregulated in several malignancies, such as lung cancer [110], melanoma [129], gastric cancer [130], and acute myelogenous leukemia [131,132]. Clinically, studies have shown that increased TIGIT expression is associated with poor clinical outcomes in different cancers [133]. For instance, the expression of TIGIT on tumor-infiltrating lymphocytes of melanoma patients or on the peripheral blood of gastric cancer patients has been correlated with increased metastasis and poor survival [109,134,135]. Similarly, the TIGIT ligand, CD155, was found to be broadly overexpressed in several types of human malignancies compared to normal tissues and was recognized as an unfavorable prognostic marker in multiple cancers [136–138]. Given that TIGIT expression is higher within the tumor microenvironment as compared to the periphery, highlights the potential utility of this molecule as a target for cancer therapy with fewer systemic autoimmune-related side effects [127]. Currently, various antagonistic monoclonal antibodies targeting TIGIT, such as tiragolumab, vibostolimab, M − 6223, BGB-A1217, domvanalimab, and etigilimab, are being tested in clinical trials as new therapies for different tumor types [123]. To date, these therapies have not shown dramatic anticancer activity as monotherapy [121]. Nevertheless, the use of anti-TIGIT mAbs along with other therapies, such as anti-PDL-1 or anti-TIM3, has demonstrated synergistic activity in different preclinical models [139,140]. Taken together, TIGIT is a recently discovered immune checkpoint that plays a crucial role in tumor immune evasion, and its inhibition by monoclonal antibodies represents a potentially attractive therapeutic strategy for cancer.

2.6. VISTA

V-domain immunoglobulin (Ig) suppressor of Tcell activation (VISTA), also known as programmed death-1 homolog (PD-1H), Dies1, c10orf54, VSIR, Gi24, B7–H5, SISP1, and DD1α, is an immune checkpoint that is expressed on a variety of hematopoietic cells including myeloid cells, T and NK cells, with no expression on B cells [141,142] (Fig. 1). Besides, VISTA expression was detected to varying degrees in different tumors [143,144]. It has been found that VISTA possesses a dual functionality where it acts as both a ligand as well as a receptor [141,145]. The role of VISTA in regulating anticancer immune responses is complicated, in which contradictory roles have been reported [75,127]. The majority of studies have reported that VISTA acts as a negative regulatory ligand for Tcells, suppressing their activation, proliferation, and cytokine release, thereby promoting immune evasion and tumor growth [146–148]. On the contrary, some studies have found that VISTA may also act as a stimulatory ligand for antigen-presenting cells leading to immune activation [67,141,149]. Owing to its role in regulating immune responses, VISTA is currently being evaluated as a target for cancer immunotherapy [75]. To date, monoclonal antibodies directed against VISTA and small molecules inhibiting VISTA are being investigated in phase-1 clinical trials (e.g., NCT02812875 and NCT02671955) and so far, have shown acceptable tolerability and anti-tumor activity [127,142]. Particularly, VISTA blockade enhanced tumor-infiltrating lymphocyte activation and promoted tumor-specific T-cell responses even in the presence of high PD-L1 expression [148]. Thus, PD-L1 and VISTA pathways are considered independent, and their simultaneous dual blockade induces synergistic anti-tumor responses as supported by preclinical studies [73,127,150]. Notably, VISTA blockade was shown to be effective despite the lack of detectable VISTA expression within

tumor cells, offering the advantage of broader clinical utility; however, it presents a challenge in identifying biomarkers to predict the response [148,151]. VISTA has recently been investigated as a potential biomarker for different types of cancer. Remarkably, a systematic review and meta-analysis of 10 studies found that high VISTA expression within the tumor microenvironment was associated with improved overall survival compared to low VISTA expression [152]. Taken together, the regulatory role of VISTA in mediating anti-tumor immune responses remains unclear, and its precise function requires further characterization as it may act in a tissue-specific manner. The complexity of the VISTA pathway, along with controversies in the literature, limit its clinical utility as a therapeutic target for cancer. Therefore, a deeper characterization is warranted to facilitate the clinical applicability of this checkpoint.

2.7. Inducing Tcell exhaustion

Tcell exhaustion is a state of Tcell dysfunction arising from persistent activation in response to chronic antigen exposure, such as during chronic viral infections or cancer [153]. Exhausted Tcells exhibit decreased effector functions, including decreased cytokine production and cytotoxic activity, as well as increased expression of inhibitory receptors such as PD-1, TIM-3, CTLA-4, and LAG-3 [154]. The process of exhausted Tcell development is typically regarded as a gradual differentiation involving specific transcriptional mechanisms, alterations in gene expression patterns, changes in metabolism, and modifications in the epigenetic landscape [155]. Exhaustion can occur in both $CD8^+$ and $CD4^+$ Tcells. Exhausted $CD8^+$ cells lack the strong killing ability and secrete low amounts of effector cytokines such as IFN-γ. In hepatocellular carcinoma, the interaction between Kupffer cells and Tcells mediated *via* PD-L1 and PD-1 expressed on these cells, respectively, led to Tcell exhaustion [156]. NR4a, a family of nuclear receptors, overexpressed in exhausted Tcells, is associated with Tcell anergy by up-regulating the inhibitory receptors PD-1 and TIM3 and repressing the IFN-γ and TNF-α expression [157]. TOX, a transcription factor that regulates NR4a, regulates the transcriptional program of exhausted Tcells by controlling the expression of various genes, such as inhibitory receptors, cytokines, and metabolic regulators [158]. Reversing Tcell exhaustion by immune checkpoint blockade therapy or a combination of immune checkpoint and cytokine blockade therapies can be promising in restoring the effective immune functions of Tcells.

3. Metabolic pathways

Metabolism consists of a group of biochemical reactions responsible for the production of metabolites from nutrients [159] which help cells to produce energy essential for their survival [160]. In normal cells, absorbed nutrients are broken down through glycolysis followed by mitochondrial tricarboxylic acid (TCA) cycle coupled to oxidative phosphorylation (OxPhos), generating adenosine 5′-triphosphate (ATP) that provides the required energy to the cells. However, cancer cells modulate the metabolic pathways to generate the energy required to meet their enhanced needs for cell proliferation and migration. Metabolic reprogramming and the capacity of cancer cells to evade the immune surveillance are hallmarks of cancer [161]. In the following sections we will discuss the different metabolic programs and how metabolic reprogramming of cancer and immune cells lead to antitumor immune response to induce immune evasion by cancer cells.

3.1. Glycolysis

Cancer cells exhibit significant changes in metabolism, as demonstrated by the Warburg effect, a principal feature of cancer cells displaying increased aerobic glycolysis [162]. While oncogenes are primarily responsible for the shift from glycolysis to the Warburg effect, tumor suppressor genes hinder this transition [163]. Glycolytic cancer cells consume and oxidize glucose at an enhanced rate and convert glucose into pyruvate along with lactate production. The produced acidic lactate is expelled by the monocarboxylate transporter 4 (MCT4) which leads to the formation of an acidic microenvironment and thus helps in providing therapeutic resistance to cancer cells [164]. In hepatocellular carcinoma, CD147 stimulates the Warburg effect through the PI3K/Akt/mTOR axis, leading to Tcell immunosuppression [165]. In contrast, in non-small cell lung carcinoma, PD-L1 triggered HK2 to promote the Warburg effect resulting in low expression of $CD8^+$ T-cell function-associated genes [166]. The glycolysis inhibitor 2-deoxyglucose (2DG) has been identified as a potent anti-cancer agent that can be used in immunotherapy [167]. On the other hand, the non-glycolytic (OxPhos) cancer cells produce lactate in the tumor microenvironment due to oxidative stress induced by molecules secreted by cancer-associated fibroblasts. The produced lactate is further broken down by non-glycolytic cancer cells through the TCA cycle, a process known as “reverse Warburg effect” [168] and is plausibly involved in inhibiting the acidic environment formation. This metabolic interdependence where the glycolytic cells release lactate, and the non-glycolytic cells import the lactate allows the sustenance of tumor cells with varying metabolic phenotypes and enhances the formation of the tumor microenvironment. Since activated immune cells, including Tcells, macrophages produce lactate, immune cells are used to exposure to lactate; however, several mechanisms enhance lactate-induced immune evasion by tumor cells [169,170]. Aerobic glycolysis is known to restrict Tcell-mediated tumoricidal effector functions. Elevated levels of lactate in the tumor microenvironment inhibit the release of lactate by glycolytic-T-cells and affect the growth and functional activation of Tcells [171]. Likewise, high lactic acid modulates antigen expression on tumor-associated dendritic cells and is a key factor in altering the dendritic cells phenotype in the tumor environment, thus contributing in immune evasion [172]. Nevertheless, the intake of lactate by macrophages increases expression of arginase-1 and blocks T-cell activation and proliferation [173]. Similarly, natural killer cells are also modified by lactate production [174]; aerobic glycolysis decreases reactive oxygen species production, thus inhibiting the expression of major histocompatibility complex class I chain-related protein A or B (MIC-A/B). MIC-A/B shedding correlates with tumor progression and immune evasion [175].

3.2. Indoleamine 2, 3-dioxygenase

Indoleamine 2,3-dioxygenase (IDO), a catabolic enzyme of tryptophan (Trp), can trigger kynurenine acid (KYN) biosynthesis *via* dioxygenases IDO1 and TDO2 (tryptophan-2, 3-dioxygenase) in tumor cells and dendritic cells, suppressing Tcell proliferative growth and promoting an immunosuppressive tumor microenvironment, thereby providing a mechanism of immune escape [176]. IDO can also shew the immune effector functions towards the differentiation into regulatory Tcells [177]. IDO is overexpressed in several malignancies, including brain, breast cancers and CRC [178]. IDO and TDO-stimulated tryptophan metabolism enhance inflammatory response [179] and their overexpression is associated with tumor progression and poor prognosis [180]. In addition, IDO and TDO are present in several cells of the tumor microenvironment; the presence of IDO and TDO in tumor cells decreases Trp levels in the tumor microenvironment and stimulates immune escape of tumor cells [181]. Moreover, KYN activates and stimulates aryl hydrocarbon receptor (Ahr), a transcription factor that mediates the toxicity of most environmental toxins, which further induce PD-1 levels in Tcells [182]. Increase in the levels of KYN and quinolinic acid triggers β-catenin leading to colon cancer cells growth and proliferation [183]. Presence of IDO1 led to an increase in the recruitment of immunosuppressive regulatory Tcells leading to cancer progression [184,185]. Palucka and colleagues [186], demonstrated an increase in IDO levels along with an inhibition of Bin1, that enhances immune escape by tumor cells to promote tumorigenesis. A possible

treatment option to undo the effects of IDO includes the use of a combination of IDO inhibitors, such as 1-methyl tryptophan (1-MT), along with chemotherapeutic agents, such as doxorubicin [187].

In addition to the above-mentioned immune and metabolite pathways, cancer cells create their environment, the tumor microenvironment to aid the onset and development of cancer hallmarks [188].

4. Tumor microenvironment (TME)

The TME is a heterogeneous and dynamic environment surrounding a tumor made up of the extracellular matrix (ECM), signaling molecules as well as various molecules formed and released by stromal, tumor as well as immune cells [189,190]. The cells within the TME comprise not only cancer cells, but also immune cells, such as T, B NK and myeloid cells, including tumor-associated macrophages (TAMs), DCs, tumor-associated neutrophils (TANs), MDSCs, cancer-associated fibroblasts (CAFs), endothelial cells, and pericytes [191] (Fig. 2). The components of the TME have a complex interaction affecting the fate of tumor cells and regulating their differentiation, dissemination, and susceptibility to immune responses [188,189,192].

Tumor-infiltrating lymphocytes (TILs) are a diverse group of lymphocytes that penetrate the TME in response to the presence of cancer cells [193]. Penetration of TILs in tumor cells is evoked by chemokines, integrins and selectins to affect immune cell infiltration, tumor cell differentiation and metastasis [194,195]. In the TME, Tregs are recruited to the site of the tumor and inhibit the function of effector Tcells through the secretion of immunosuppressive cytokines and the expression of inhibitory receptors on their cell surface [196]. Tregs undergo OxPhos *via* Foxp3-induced inhibition of myc and glycolysis which further enhances NADH oxidation NADH and promotes immune evasion [197]. Treg cells also regulate the production of immunological checkpoint modulators (PD-1/PD-L1, CTLA4) [198–200]. On the other hand, elevated levels of GLUT1 enhances glucose uptake, increases glucose consumption of $CD4^+$ Tcells, and increases the differentiation of effector Tcells, thus further increasing the secretion of IL-2 and IFN-γ by effector Tcells [201]. Likewise, presence of lactate suppresses effector Tcells proliferation and function by inhibiting IFN-γ production, and thus disrupts the innate immune response and stimulates IL-17 or IL-23-induced tumor development and progression [202]. Similar to glycolysis, lack of Trp and overexpression of KYN lead to the proliferation of Tregs and enhance tumor growth [203].

Although the role of Bcells in the TME is nascent, Bcells are involved in triggering tumor growth and is reported in several carcinomas including breast, ovarian, prostate, and pancreatic cancers [204–208]. Bcells induce tumor growth by suppressing the immune response through transforming growth factor-beta (TGF-β) and IL-10 secretion [209,210]. In addition, B-cells also regulate angiogenesis and chronic inflammation by the accumulation of immunoglobulins in the TME which further activate myeloid cells [211]. Like CTLs, NK cells are innate immune cells that have effective cytolytic activity on combat with transformed cells [212]. NK cells have a wide array of inhibitory and stimulatory receptors on their cell surface that are used for immune surveillance [188]. NK cells eliminate tumor cells by secreting cytolytic granules upon natural killer group 2 D (NKG2D) receptor-ligand binding [213]. However, tumor cells inhibit their surface ligands to impede the anti-tumor recognition to escape NK cell-mediated immune surveillance [214]. Nonetheless, the TME alters the tumor-infiltrating NK cells (TINKs) and present a dysregulated phenotype with altered cytotoxic ability in addition to upregulated vascular endothelial growth factor (VEGF) and reduced IFN-γ, CD16, NKG2D, and DNAM-1 expression [215]. Nevertheless, TGF-β-releasing cancer cells convert NK cells into cytotoxic innate lymphoid cells (ILCs) in the TME as an immune escape mechanism [216].

MDSCs, a heterogeneous population of immature myeloid cells are produced in the bone marrow in response to several factors, including inflammation and cancer [217]. In the TME, CCL2-CCR2 signaling recruits MDSCs by cancer cells to primary and metastatic tumor locations through the secretion of chemokines (CCL2, CXCL5, and CXCL12) and

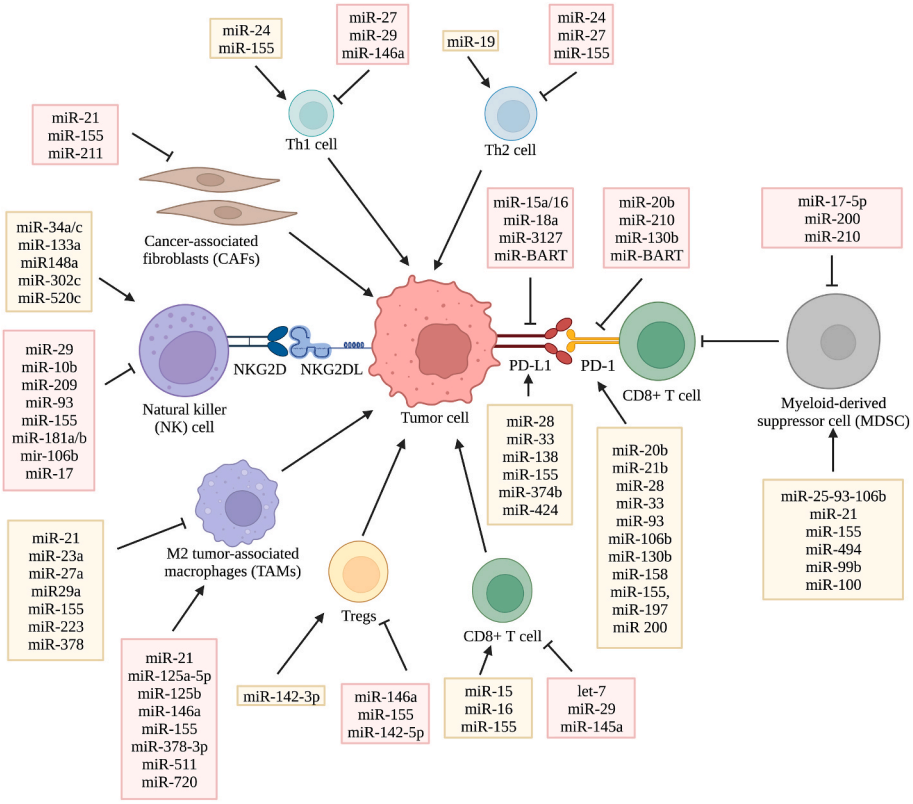

Fig. 2. ***Immunomodulatory responses by cells in the tumor microenvironment (TME) and roles of miRs in immune evasion.*** The TME comprises of complex interactions between immune and stromal cells that can either contribute to the direct killing of tumor cells or promote the proliferation of tumor cells by immunosuppressive mechanisms. While the immunostimulatory TME is made up of $CD8^+$ Tcells, dendritic cells (DCs) natural killer (NK) cells, and M1 macrophages, the immunosuppressive TME is mainly constituted of M2 macrophages, cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs) and T-regulatory cells (Tregs). miRs regulate the immunosuppressive as well as the immunoreactive functions of the immune cells in the tumor microenvironment. Figure created with Biorender.com.

other factors to suppress antitumor immune responses [218,219]. Additionally, tumor-infiltrating monocytic MDSCs increase levels of Treg cells and produce high levels of CCL3, CCL4, and CCL5 which are involved in the migration of MDSCs [220,221]. Similarly, ILs −18 and −33 promoted expansion of MDSCs population resulting in a significant inhibition of $CD4^+$ T-cell proliferation and IFN-γ secretion along with an increase in differentiation of Treg cells [222,223]. Additionally, MDSCs release TGF-β and IL-10 which can also induce the differentiation of Treg cells, which further suppress the immune response against cancer [224]. MDSCs create an immunosuppressive environment by enhancing expression of PD-L1 [225]. Like the MDSCs, the TAMs and TANs in the TME also possess immunosuppressive properties and can trigger immunological checkpoints and their receptors promoting tumor formation [226]. TAMs are further classified into M1-like (classically activated macrophages) and M2-like TAMs (alternatively activated macrophages); while M1-like TAMs depend on glycolysis, M2-like TAMs are dependent on the TCA cycle and utilize the Krebs cycle [227,228]. TAMs are known to trigger aerobic glycolysis, tumor hypoxia and suppress apoptosis [229]. TAMs significantly inactivate Tcell expression [230], while TANs express PD-1 and enhance cytokine expression to induce resistance to PD-1 inhibition [231]. Within the TME, immature DCs initiate immune response by processing tumor antigens. Mature DCs move to the lymph nodes where they present antigens on MHC class I and II molecules to stimulate $CD8^+$ and $CD4^+$ T-cells, respectively [232]. Moreover, in the TME, regulatory or tolerogenic DCs (tDCs) are triggered by VEGF, cytokines as well as pathogens and express several immunomodulatory (PD-L1, TNF-related apoptosis-inducing ligand (TRAIL)) and immunosuppressive (TGF-β, IL-10) molecules [233]. On the other hand, tumor-associated pericytes regulate immunomodulation of the TME by increasing MHC class II and PD-L1 levels [234], indicating a role of TAP in promoting tumor progression by altering anti-tumor Tcell responses.

CAFs are activated fibroblasts with alterations in their gene expression, morphology, and function in response to signals from epithelial, endothelial, and mesenchymal cells that transform to the mesenchymal state in the TME [235]. Within the TME, CAFs secrete signaling molecules that promote angiogenesis, cancer cell proliferation, migration, invasion, and inhibition of anti-tumor immune responses [236]. One of the subsets of CAFs, CAF-S1, inhibits immune response by attracting and stimulating $CD4^+CD25^+$ T lymphocytes activation, differentiation, and survival [237]. Moreover, CAFs release high levels of VEGF, collagen, fibronectin, and MMPs leading to ECM remodeling [235,238–240]. CAFs also release lactic acid which tumor cells use as a substitute nutrient source by tumor cells [241].

The extracellular matrix (ECM) present in the basal membrane makes up the non-cellular component of the TME. It is a network of proteins, including collagen, elastin, hyaluronan, integrins, fibronectin, and laminin, that provides structural support for cells and contributes to cell signaling [69]. In the TME, the ECM is often altered into a metastasis-inducing microenvironment [242]. Activated monocarboxylate transporters export lactic acid into the ECM, resulting in an acidic TME which impacts the T-cell mediated antitumor immune responses, inhibits tumor immunity, and promotes tumor progression [243,244]. Moreover, TGF-β-induced CAFs activation results in a significant production of collagen and development of fibrosis, thus leading to tumor stiffening, a characteristic of desmoplastic tumors [245,246]. The tumor cells enhance lactate production and lead to acidification of the TME [247]. Along with tumor cells, CAFs and monocytes release MMPs and ROS which degrade the ECM and enhance tumor cell migration along with immune reprogramming of the TME [248]. Moreover, hypoxia-induced cells (CAFs, TAMs and cancer cells) in the TME stabilize hypoxia-inducible factor (HIF) and modulate cross-linking of collagen and elastin, leading to ECM stiffening, hallmark events for tumor cell migration and cancer progression [249,250].

5. Role of Epithelial-Mesenchymal Transition in evading the immune system

Epithelial–mesenchymal transition (EMT) is described as a pleotropic alteration in cellular phenotypes where the epithelial cells develop mesenchymal characteristics with increased plasticity. EMT is reported in several cancers, including the breast [251,252], CRC [253,254], oral [255], prostate [256], ovarian [257] and thyroid [258] and is considered to play a vital role in tumor development *via* the PI3K/Akt/PKB, MAPK/ERK [251,255], NF-κB [258] and Wnt/β-catenin [254,259] signaling pathways (Fig. 3). The following section will focus on the role of EMT in promoting immune evasion by tumor cells. As mentioned above, the TME comprises endothelial cells, CAFs, $CD4^+$ Tcells, Tregs, MDSCs, and TAMs which secrete cytokines and chemokines to regulate EMT, one of the hallmarks of tumor progression [260]. In addition, cancer-activated immune cells, including Tregs, M2 macrophages, and MDSCs suppress the expression of anti-cancer immune cells, including $CD8^+$ Tcells, NK cells, and activated macrophages (M1), thus, promoting tumor progression [260–262]. On the other hand, EMT-induced tumor cells produce immunosuppressive cytokines and chemokines, leading to an immunosuppressive TME. It was reported that prostate cancer cells generate the chemokine CXCL1, while its downstream receptor CXCR1 releases lipocalin 2 (LCN2) leading to the stimulation of Src signaling, promotion of EMT, and tumor progression [263]. Likewise, CXCL8 were found to promote CXCR1/CXCR2-induced EMT, leading to increased cell invasion and metastasis [264,265]. An *in vivo* study on papillary thyroid carcinomas revealed overexpression of CXCL16 to correlate with angiogenesis, the presence of M2 macrophages and poor prognosis [266]. Likewise, in colorectal cancer, CXCL16 induced EMT characterized by loss of E-cadherin and overexpression of vimentin; CXCL16 was also found to mediate cell growth, invasion, and colorectal cancer-induced liver metastasis [267]. In breast cancer cell lines, CXCL16/CXCR6 axis induces EMT and invasiveness *via* Erk1/2 and F-actin signaling pathways [268,269]. Chung et al. [270], reported CAFs as the primary source of chemokines and reported the role of CXCL12 and CXCL16 in promoting breast cancer induced brain metastasis. On the other hand, in renal cell carcinoma, the cancer cells recruited macrophages through CXCL8 signaling and promoted EMT and the development of stem-cell like populations by stimulating the AKT/mTOR signaling pathway [264]. The classical EMT is characterized by the alteration of the epithelial cells to mesenchymal-like cells due to loss of cell-to-cell adhesion triggered by EMT transcription factors including SNAIL, Twist1, SLUG, Zeb1 and Zeb2. An *in vitro* and *in vivo* study using melanoma cells and murine models, respectively, demonstrated the stimulation of EMT and immunotherapeutic resistance due to overexpression of SNAIL in melanoma cells [271]. The study reported SNAIL-induced melanoma cells to release TGF-β and thrombospondin 1 and trigger Treg activity and deregulated dendritic cells through TSP1 production [271]. Similarly, in breast cancer, an *in vitro* study demonstrated that breast cancer cells (MCF7) when cocultured with T lymphocytes can elicit antigen-specific immune responses, however, SNAIL overexpression in MCF7 reduced the Tcell functions [272]. In addition, hypoxic tumor environment and signaling pathways such as the TGF-β, VEGF, epidermal growth factor (EGF), WNT and NOTCH stimulate the expression of the EMT transcription factors to induce cell proliferation, stemness, metastasis as well as therapy resistance [273,274] (Fig. 3). At the molecular level, the EMT transcription factors can produce or attract immunosuppressive cells such as MDSCs as well as stimulates the expression of immune checkpoint inhibitors (PD-1/PD-L1 and CTLA-4), resulting in a tumor immunosuppressive microenvironment and increase in resistance to immunotherapy, further promoting tumor metastasis [275–278]. Kudo-Saito et al. [279], demonstrated that SNAIL-expressing melanoma cells can release the chemokine CCL2, further leading to LCN2 release. CCL2 and LCN2 were found to increase PD-L1 expression, while MHC-1 expression on T-cells was lost leading to Tcell exhaustion. Vis-à-vis, the immunosuppressive factors trigger EMT

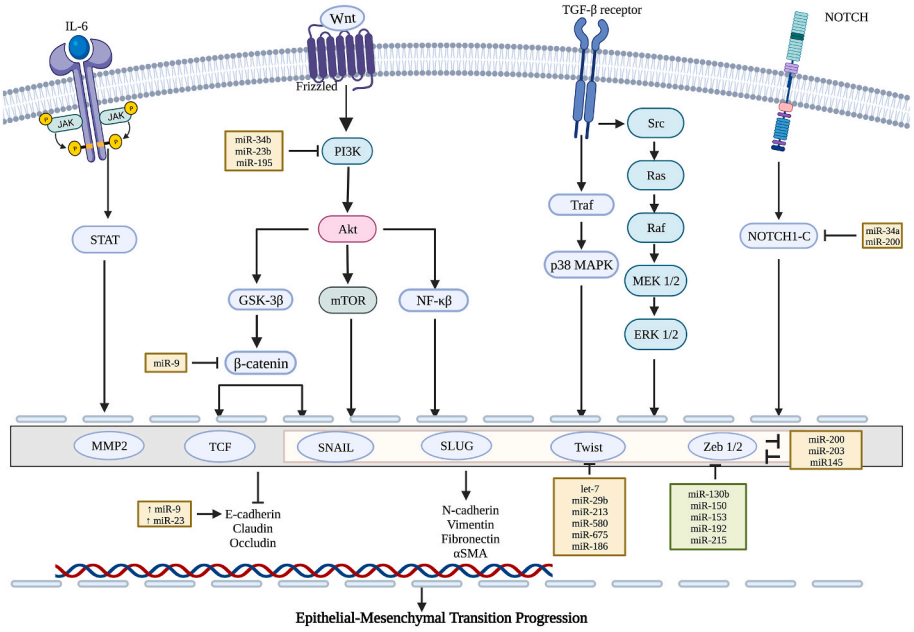

Fig. 3. ***Signaling Pathways regulating Epithelial-Mesenchymal Transition (EMT) in Immune Evasion.*** EMT involves major changes in epithelial cells favoring the development of an invasive phenotype with an increase in motility. The progression of EMT is controlled by multiple signaling pathways. One of the most studied EMT-inducing proteins is the transforming growth factor-beta (TGF-β) which acts at various regulatory levels. Interleukin-6 (IL-6) secreted by cancer cells promote EMT *via* STAT-induced SNAI1/Snail expression. Wnt signaling induces EMT *via* the inhibition of GSK3-β and β-catenin stabilization. β-catenin translocate to the nucleus where is interacts with the transcription factors TCF-LEF and activates the EMT program. The other vital signaling pathway is the TGF-β signaling pathway; TGF-β activates SMAD2/3, resulting in SMA2/3/4 complex generation which translocate to the nucleus to interact with transcription factors regulating genes triggering EMT. TGF-β also induces PI3K-AKT, ERK-MAPK, p38-MAPK and JNK signaling for regulating EMT progression. TGF-β receptor complex-TRAF6 interaction triggers p38 MAPK and JNK to stimulate EMT progression. Expression of Slug is activated by the intracellular domain of Notch resulting in the loss of E-cadherin, claudin and occludin along with upregulated N-cadherin, vimentin, and fibronectin. Figure created with Biorender.com.

in tumor cells; this feedback loop enhances tumor progression. In various cancers, EMT has shown to correlate with an immunosuppressive TME. Guo et al. (2019) [280] performed a comprehensive genomic analysis of sarcomatoid carcinoma of the bladder and reported progression of the carcinoma through the epithelial and mesenchymal subsets due to loss of p53, CDH1, TJP1, CLDN1 and miR-200 family members while, TGF-β1, RhoA, SNA12 were upregulated. Moreover, the study reported sarcomatoid carcinoma to be associated with immune infiltration and with increased PD-L1 expression [280]. Another study by Dongre and colleagues [275] reported differential proneness to immune attack in breast epithelial and mesenchymal carcinomas in mouse models. Xenograft tumors derived from the epithelial cell line comprised a significantly high number of infiltrating $CD8^+$ cytotoxic Tcells while tumors from the mesenchymal cell line had increased frequency of $CD25^+$ $FOXP3^+$ Tregs and lower numbers of $CD25^+$ $FOXP3^-$ effector $CD4^+$ Tcells. Furthermore, as compared to the epithelial cell, the stroma of mesenchymal-derived tumors display higher immunosuppressive features and lower levels of cell-surface MHC class I molecules and high levels of PD-L1 [275]. The study indicated that epithelial tumors can be more sensitive to immunotherapy as compared to the mesenchymal tumors [275]. Similar results were reported in the mesenchymal subtype of ovarian cancer, where lower intraepithelial $CD8^+$ tumor-infiltrating T lymphocytes and enhanced EMT markers were found to correlate with worst prognosis [281]. In non-small cell lung cancer as well, the activation of EMT correlated with high numbers of $CD4^+$ $Foxp3^+$ Tregs and an inflammatory TME with upregulated levels of immune checkpoint molecules, including PD-L1, PD-L2, PD-1, TIM-3, B7–H3, BTLA, and CTLA-4 [282]. Moreover, Zhang et al. (2021) [283] developed a novel prognostic classifier based on EMT score. The immune-hot oral squamous cell carcinomas had low infiltration of active immune cells and overexpression of ICPs (B7H3, TIM-3, CD28, CD137, and OX40L), indicating an immunosuppressive TME, which significantly correlated with EMT. These studies indicate a correlation between EMT and immunosuppressive TME.

Cancer cells within a tumor exhibit an extensive genetic and non-genetic heterogenicity, resulting in diverse range of phenotypes. Cancer stem cells (CSCs) or cancer initiating cells (CICs) are a subpopulation of cells within a tumor that can self-renew and differentiate into multiple cell types of a defined tissues. CSCs were first identified in acute myeloid leukemia model based on the ability to initiate tumor using severe combined immunodeficient mice [284,285]. Subsequently, CSCs have been identified in almost all neoplasms, including cancer of prostate, breast, brain, colon, and many others [286]. Some of the potential surface markers for the identification of CSCs include $CD44^+$, $CD22^-$, $CD133^+$, $CD90^+$, $EpCAM^+$, which distinguish them from other cancer cells although they are not exclusive to CSCs [287]. In addition to these surface markers, CSCs can also be identified and isolated based on their ability to efflux certain fluorescent dyes, such as Hoechst 33342 due to the expression of ATP-binding cassette (ABC) transporters, resulting in the formation of a side population that can be enriched *in vitro* and *in vivo* [288,289]. In some cancers, the expression, and activity of aldehyde dehydrogenase (ALDH1) is used to mark CSCs [290]. In addition, expression of stemness-associated master gene regulators such as Oct4, Nanog, and Sox2 are widely used to address the stemness properties of CSCs [291,292].

The definitive feature of CSCs is their ability to initiate the tumor. Limiting dilution transplantation assays have shown that as few as 100 breast cancer cells with a $CD44^+/CD24^-$/low phenotype, obtained from tumors enriched for CSCs, are sufficient to form tumors whereas high number of cells (1 million) with other phenotype failed to generate tumors [293]. Similar observations were made for several other cancers such as prostate, brain and colon cancers [294,295]. CSCs play a crucial role in tumor initiation, progression, invasion, and resistance to treatments. Evidence suggest that most conventional anti-cancer therapies can shrink the tumor by eliminating the differentiated cancer cells (non-CSCs), but unable to target the CSCs, leading to their survival in the tumors [296]. Expression of ABC drug transporters that increase drug efflux rate, ability to sustain DNA damage due to enhanced DNA damage repair pathways, elevated expression of anti-apoptotic pathways, epigenetic mechanisms that control proliferation and survival, and cycling between quiescence and proliferation are among the key molecular pathways that act in favor of CSCs to escape the drug-induced cell death [296]. CSCs are frequently found in the TME or niche, which includes various components as discussed in the section above [297]. Conditions within the TME favors the survival of CSCs and their ability to evade traditional cancer treatments like chemotherapy and

radiation. The CSC phenotype is dynamic because it can change in response to various factors, including microenvironmental cues, oncogenic mutations, epigenetic modifications, hypoxia, senescence, and therapeutic interventions. CSCs can regulate several hallmarks of cancer, including angiogenesis, metastasis, chemoresistance as well as suppress immune cell activation and promote immune tolerance by communicating with other cells within the TME and influence their behavior through the secretion of cytokines, growth factors, and extracellular vesicles such as IL-6, VEGF and TGF-β [298,299]. CSCs interact with the immune cells in the TME, which can confer them the ability to avoid recognition and eradication by immune cells. CSCs use a variety of strategies to escape detection and eradication by the immune system, including the insufficient expression of molecules involved in antigen processing, impaired antigen presentation pathways, downregulation of tumor associated antigens, expression of immune checkpoint molecules, secretion of immunosuppressive factors, and the induction of immune cell exhaustion [113]. Immune checkpoint molecules like PD-L1 can bind to receptors on immune cells, such as PD-1, and inhibit their activation, leading to immune cell inactivation and dysfunction [300,301]. Moreover, CSCs have been shown to induce immune cell exhaustion through the expression of the ligand for the immune checkpoint molecule TIM-3, which is expressed on immune cells and has been shown to promote immune cell exhaustion and dysfunction. Thus, immunotherapy-based anti-CSC approaches have attracted much attention, and these approaches show promise in improving cancer treatment outcomes and may offer new options for patients. Immune checkpoint inhibitors such as nivolumab, cemiplimab, and avelumab that target PD1/PD-L1 and CTLA-4; Chimeric Antigen Receptor (CAR)-T-cell therapies targeting CD19, CD33, CD123, and other antigens are currently in various stages of clinical development, with some of them reaching the standard of care for some subtypes of tumors [302,303]. Other immunotherapy-based approaches for targeting CSCs include the use of cancer vaccines, oncolytic viruses, and the use of NK cells.

CSCs also undergo EMT, where cells acquire increased invasiveness and migratory capacity that compel in situ cancer cells to become highly invasive and disseminate to distant sites in the body, leading to metastasis. Recent studies have suggested that EMT plays a substantial role in the generation of CSCs and EMT-inducing signals can promote the acquisition of stem-like properties in cancer cells, including self-renewal, chemoresistance, and immune surveillance [304–308]. It has been shown that ectopic expression of EMT transcription factors Snail or Twist in immortalized human mammary epithelial cells induced EMT, and these resulting cells displayed increased capacity to form tumor spheres as well as upregulation of CSC surface markers, $CD44^{+}/CD24^{-}$/low, suggesting a direct link between EMT onset and gain of stemness phenotype [304]. Survival, self-renewal and drug resistance of CSCs are controlled by multiple signaling mechanisms such as PI3K/Akt, MAPK, NF-κB, JAK/STAT pathways as well as aberrant expression of members of BCL-2 family proteins [309–311]. Despite the activation of these multiple pathways, they ultimately converge on a set of molecules that regulate cell death. Previously, we showed that PI3K/Akt, Raf/MEK/MAPK, cAMP/PKA/CREB pathways are critical for the survival and maintenance of both CSCs and non-CSCs and for the self-renewal of CSCs from breast, prostate, and melanoma [312–314]. In addition, many of the signaling pathways that regulate EMT such as the Wnt/β-catenin, Notch, Hedgehog, PI3K/Akt/mTOR, NF-κB, JAK/STAT pathways are also involved in regulating CSCs [315], and these common set of pathways are shown to be responsible for resistance to anti-cancer therapies [316]. Inhibition of these pathways could trigger anti-proliferative or cell death effects of both CSCs and non-CSCs, and therefore, targeting these shared molecular pathways has emerged as a promising strategy for the treatment of cancer [317]. Various drugs targeting EMT/CSC pathways that are in clinical trials include Napabucasin, Tarextumab, Saracatinib, LY2157299, OMP-59R5, etc. These drugs are tested in diverse range of cancers, including prostate, colorectal, small cell lung, ovarian, and pancreatic, and showed promising results [318]. Additionally, our lab demonstrated these signaling pathways to converge on proapoptotic protein BAD and exert their survival effects by controlling the phosphorylation of BAD, whose expression is significantly enhanced in the $CD44^{+}$ CSCs of most breast cancer tumor biopsies [312]. In the TME, the differentiated cancer cells can dedifferentiate into CSC phenotype and vice versa due to genetic and epigenetic alterations, thus exhibiting enhanced plasticity. This enhanced plasticity restricts use of anti-cancer therapies as one of these phenotypes can result in the regeneration from the other. Thus, a better therapeutic strategy is to target a 'common' pathway that is critical for both CSCs and non-CSCs. Our work showed that BAD is one of such therapeutic targets because it modulated the survival of both CSCs and non-CSCs and inhibition of BAD phosphorylation along with suppression of BCL2/BCLXL activity rendered synergistic apoptotic effects [312]. Several drugs that target the BCL-2 family proteins are in clinical trials or have been approved by FDA for use in multiple cancers. Venetoclax, a small molecule inhibitor that selectively targets BCL-2, has been approved for the treatment of chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML). Venetoclax combination therapy has been shown to target and eliminate leukemia stem cells [319]. Some of the other inhibitors of BCL2 family proteins that are being evaluated in pre-clinical and clinical trials for use in various malignancies, includ AZD0466, ABT-199, Navitoclax, A-1331852 and S63845 [320,321].

Hypoxic conditions can activate signaling pathways that promote EMT and stemness. As mentioned above, hypoxia triggers the activation of HIFs transcription factors which regulate the expression of Snail, Slug, and Twist, culminating in enhanced cell proliferation, survival, invasion, metastasis, and resistance of CSCs to chemotherapy [234,322]. In glioblastoma and medulloblastoma, HIF-1a controls the proliferation of CSCs and activates NF-κB pathway to promote survival and tumorigenesis of CSCs [323]. In addition to the transcription factors and signaling pathways, the non-coding RNAs (miRs and long non-coding RNAs (lncRNAs)) also play a role in promoting EMT [324].

6. Role of miRs and long non-coding RNAs (lncRNAs)

MicroRNAs (miRs) are a class of short non-coding RNAs that regulate gene expression at the post-transcriptional level through complementary binding to mRNA, resulting in translation inhibition or degradation of target mRNA [325,326]. miRs regulate around 60% of protein-coding genes in humans, whereas single miRs can regulate the expression of several genes [327]. miRs play an important role in cell proliferation, differentiation, and signal transduction [328,329]. Over the past decade, altered expression of miRs was repeatedly associated with a wide range of human diseases, including several human malignancies through promoting anti-apoptotic signaling, proliferation, invasion and metastasis [330]. Recent evidence has shown that some miRs can regulate the immunological properties of cells [113,326]. While miRs can protect tumor cells from immune attack, another group of miRs can help tumor cells evade immune attack; these miRs with modulatory roles are called immune-modulatory miRs (im-miRs). im-miRs originate from tumor cells and regulate tumor antigen processing machinery as well as key immune cells within TME, such as macrophages, MDSCs and NK cells [113,331] (Fig. 2). Overexpression of miR-25a-5p and miR −148a-3p were found to inhibit levels of MHC and TAP2 molecules, thereby modifying antigen processing and presentation in cancer cells [332]. Overexpression of hsa-miR-148a and hsa-miR-125 is associated with reduced expression of HLA-ABC and TAP2 respectively in esophageal carcinoma cell lines [332]. On the contrary, loss of miR-152, miR-148a, and miR-148b results in increased HLA-G expression, a phenomenon occurring during immune evasion [333]. As mentioned previously, loss of NKG2DLs led to the evasion of immune system by tumor cells. While miR-93 targets both MICA and MICB, miR-10b was found to target MICB expression [334]. Enhanced levels of miR, inhibits NKG2DLs expression and helps tumor cells to hide from the immune

attack of NK cells and CTLs [335]. miR-155, miR-125a/b, miR146a, and miR-21 were found to mediate a critical role in the differentiation and activation of macrophages [331], whereas miR-150, miR-155 and miR-181 were shown to be involved in regulating NK cells differentiation [336–338]. Moreover, miRs were shown to be involved in controlling Tcell responses, with miR-181 being involved in the differentiation and tuning of antigen specificity by the TCR of T lymphocytes [339,340]. On the other hand, studies have reported tumor-suppressor miRs to be involved in the regulation of anti-tumor immune responses through controlling immune checkpoints such as PD-1, PD-L1, and CTLA-4, such as miR-33 and miR-BART cluster [326] (Fig. 2). Furthermore, such as miR-205, miR-200, miR-9, Let-7, and miR103/107 can also regulate EMT [341] (Fig. 3). The miR-200 family members (miR-200a, miR-200b, miR-200c, miR-429, and miR-141) suppress EMT by targeting and inhibiting expression of Zeb1 and Zeb2 [342] (Fig. 3). In addition, miR-200 regulate the WNT/β-catenin and Notch pathways promoting metastasis and cancer stemness [343,344]. Overexpression of miR-9 inhibits E-cadherin expression and activates β-catenin and VEGF-A expression, promoting tumor invasiveness, motility and angiogenesis [345]. Nonetheless, with advancement in transcriptome sequencing, data have shown that more than 70% of the genome is transcribed and over 58,000 long non-coding RNAs (lncRNAs) are present in the human genome [346]. lncRNAs are >200 nucleotides in length and do not encode proteins [347]. However, they display various functions in gene transcription as well as protein regulation and are now emerging as key regulators of gene expression on the immune system [348]. Recently, lncRNAs were found to interact with tumor-infiltrating innate and adaptive immune cells to regulate the interaction between tumor cells and their TME.

A study by Wang et al., showed that the silencing of lncRNA, LINC01116 altered IL-1β secretion, which led to increased recruitment of TANs, thus producing a large number of cytokinesinducing tumor proliferation [349]. Recently, Shao and colleagues [350] identified a panel of 18 HOX-related lncRNAs located in the HOXA-D clusters and were associated with immune cells as well as with the expression of ICPs (PD-L1 and CTLA-4). HOTTIP, lncRNA present in the HOXA cluster, binds to c-jun and inhibits Tcell activity by inducing IL-6 production and altering neutrophil activity [351], thus aiding in immunological escape. HOTAIR, the lncRNA located in HOXC cluster sponges hsa-miR-30a-5p and increases PD-L1 expression [352]. The small nucleolar host gene 12 (SNHG12) lncRNA promotes tumor evasion by triggering IL-6/hsa-miR-21 interaction between M2 macrophages and cancer cells, increasing PD-L1 levels and impeding T-cell proliferation [353]. lncRNAs C50rf64 and actin filament-associated protein 1 antisense RNA1 (AFAP1-AS1) were positively associated with PD-1/PD-L1 and CTLA4 expression [354,355]. Moreover, the lncRNA, lnc-Tim3 stimulates Bcl-2 and MDM2 transcriptional activation leading to the growth of exhausted $CD8^+$ Tcells [356]. Yan and colleagues [357] demonstrated that overexpression of the lncRNA nuclear-enriched autosomal transcript 1 (NEAT1) in tumor-infiltrating T-cells triggered $CD8^+$ Tcell death *via* the miR-155/Tim-3 pathway leading to increase in tumor growth. Small nucleolar RNA host genes 14 (SNHG14) and 20 (SNHG20) enhance PD-L1 expression [358,359]. The lncRNA, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) can overexpress PD-L1 and CD8 *via* hsa-miRs- 195 and 200a-3 to promote immune escape and cancer progression [360,361]. Recently, Zhou et al. [362], demonstrated that the overexpression of LINC00473 and the inhibition of hsa-miR-195-5p reduced the number of activated $CD8^+$ Tcells and upregulated PD-L1. The study also reported a decrease in Bcl-2 C-related proteins, IFN-γ, and IL-4 while Bcl-2, IL-10 and MMPs −2 and −9 were overexpressed, thus promoting cancer cell growth, invasion, and migration [362]. Another known lncRNA, NKX2-1-AS1 promotes immune system evasion and cancer cell motility by directly regulating CD274/PD-L1 [363]. Nevertheless, the regulatory mechanisms underlying miRs and lncRNAs-mediated immunomodulatory functions have not been fully elucidated and need further investigation.

7. Role of circulating tumor cells (CTCs)

Circulating tumor cells (CTCs) are heterogeneous populations of tumor cells detached from a primary tumor, and present in the bloodstream or lymphatic system. CTCs vary in size from 12 to 25 μm [364]. CTCs are thought to be responsible for cancer metastasis, as they can potentially colonize and form secondary tumors in other parts of the body [365,366]. Although several CTCs are present in a single form, others migrate as multicellular clusters [367]. While single CTCs originate from a single migratory cell lineage, CTC clusters are derived from more than one cell and are frequently detected in solid tumors [366]. As compared to single CTCs, CTC clusters display more mesenchymal markers and hypomethylation of TFs activates transcription of genes involved in proliferation and stemness [366,368,369]. The molecular characterization of CTCs has revealed that they express genes such as EpCAM, cytokeratins, and stem cell-like markers that are associated with stemness, EMT, and invasion [370–372]. The microenvironment plays a crucial role in the survival and dissemination of CTCs. Recent studies have shown that CTCs can modify their microenvironment to facilitate their survival and colonization in distant organs [373]. CTCs can acquire a more mesenchymal phenotype when exposed to the ECM found in the microenvironment of secondary organs. This mesenchymal phenotype allows CTCs to invade and migrate through tissues and evade immune surveillance. Additionally, CTCs promote the formation of a pre-metastatic niche by secreting cytokines and chemokines that attract immune cells and support the recruitment of stromal cells. These stromal cells, in turn, secrete ECM proteins and growth factors that enhance the survival and proliferation of CTCs. Nonetheless, the microenvironment can also modulate the sensitivity of CTCs to chemotherapy and other treatments, leading to the emergence of drug-resistant CTCs [374]. Several studies have indicated a relationship between CTCs and immune cells. CTCs interact with immune cells and can evade and alter the immune response to drive the metastatic progression.

The initial step in the metastatic cascade, intravasation involves the detaching of the cancer cells from the primary or metastatic site to enter the bloodstream, thus forming CTCs. During intravasation, CTCs interact with the neutrophils, NK cells, monocytes, macrophages, and T-lymphocytes. Likewise, while in circulation, CTCs interact with neutrophils, NK cells, monocytes, macrophages, and lymphocytes [375]. Neutrophils interact with CTCs within the primary TME and enhance tumor intravasation by forming CTC-neutrophil clusters through vascular cell adhesion protein 1 (VCAM-1) and intracellular adhesion molecule 1 receptor (ICAM-1) [376–379]. Neutrophils are generally drawn to CTCs producing G-CSF and stimulating cytokines [376,380]. Upon initiation, neutrophils release neutrophil extracellular traps (NETs) which enhance ECM degradation and stimulate CTC proliferation, migration, and invasion as well as protects CTCs from immune cytotoxicity in the blood [381,382]. Neutrophil-CTC interaction triggers the release of cytokines, including IL-6 and IL-1β from neutrophils and activates several proliferative pathways [380]. The presence of TGF-β1 in the TME enhances CTC survival and EMT [383,384]. Moreover, dysregulated expression of TLE1 gene triggers NF-κB-induced cancer progression *via* CTC-induced resistance to neutrophil-mediated apoptosis [385]. On the other hand, CTCs also interact with NK cells to induce metastasis in different human cancers; NK cells with a high number of CTCs have significantly reduced cytotoxicity along with increased metastasis [386]. NK cells have the capacity to control tumor growth and metastasis by detecting and eliminating CTCs [387]. Nonetheless, NK cells exhibit a limited ability to infiltrate and eliminate large solid tumors [388]. NK cells can control tumor progression by recognizing tumor cells that exhibit a lack or a low expression level of major histocompatibility complex (MHC) class I molecules [389]. Interaction between the lectin-like type-2 transmembrane stimulatory immunoreceptor NKG2D and MICA/MICB on NK cells and CTCs, respectively, inhibit CTCs recognition and removal [390]. NK cells can recognize and kill cancer cells through various mechanisms. When NK cells recognize and interact with CTCs, they

release cytotoxic lytic granules containing perforin and granzymes to induce tumor cell death [391]. This interaction can also lead to the engagement of death receptors on the cancer cell surface. Therefore, NK cells can present CD95L or TRAIL on their surface, which activate their respective death receptors CD95/Fas and TRAIL-R1-R2 on the CTCs' surface [391]. However, cancer cells can evade NK cell-mediated killing through various mechanisms, such as downregulation of NK cell ligands or expression of inhibitory ligands that engage NK cell inhibitory receptors. CTCs evade NK cells mediated killing by inhibiting the expression of death receptor 5 (DR5) on their cell surface [392]. Moreover, reduction in the secretion of granzyme and perforin from NK cells as well as lack of binding of TRAIL to apoptotic receptors on tumor cells promotes CTCs survival and progression [393,394]. Moreover, CTCs can express NK cell inhibitory receptor ligands, such as HLA-G and PD-L1 on their surface and can interact with NK cells and provide inhibitory signals and induce NK cell cytotoxicity inhibition [395]. Additionally, CTCs express less the cell death receptor FAS, which leads to escape from NK-cell related apoptosis [396]. More recent *in-vitro* and *in-vivo* studies showed that CTCs and NK cells interact *via* the immune checkpoint molecule pair HLA-E:CD94-NKG2A. However, the disruption of this interaction enhances the capacity of NK cells to eliminate CTCs and, thus, prevent tumor metastasis [397].

The other set of immune cells found in CTC clusters include monocytes and macrophages. A recent study demonstrated tissue-repair-promoting Ym1+Ly6Chi monocytes significantly expressed MMP-9 and CXCR4 to induce CTCs-mediated metastasis [398]. Monocytes develop into macrophages which can differentiate foreign cells from self-cells through CD47; however, CTCs express elevated CD47 levels, indicating a better survival mode in blood by escaping immunological surveillance [399]. Macrophages are involved in promoting CTCs' survival and dissemination. Several mechanisms have been identified to promote the interaction between CTCs and macrophages. In some cases, macrophages can promote the survival and migration of CTCs by releasing cytokines and growth factors, such as CCL2 and VEGF, to support the tumor cells' growth and proliferation [400]. In other cases, macrophages can directly phagocytose CTCs and prevent their dissemination to distant sites [401]. Both macrophages and CTCs express CHI3L1, an important regulator which lacks chitinase enzyme activity [402]. The interaction between macrophages and CTCs, including CHI3L1, induces invasion and tumor progression. High CHI3L1 expression level in CTCs is independently associated with poor overall survival in cancer patients [403]. The interaction of CTCs and MDSCs forms a cluster and promotes CTC metastasis *via* the Notch-Nodal signaling pathway [377]. In addition, CTCs promote M2-like polarization of TAMs *via* canonical Wnt/β-catenin signaling, which results in tumor growth, metastasis, and immunosuppression [404]. TAMs promote CTCs-mediated metastasis by regulating the JAK2/STAT3/miR-506-3p/FoxQ1 axis, which in turn triggers the CCL2 production and macrophage recruitment [405].

CTCs escape tumor surveillance by $CD4^+$ helper Tcells and $CD8^+$ cytotoxic Tcells. A study in breast cancer found that the receptor activator of nuclear kappa-B ligand (RANKL) present on tumor-infiltrating $CD4^+$ Tcells trigger RANK on CTCs to stimulate intravasation. Moreover, lack of $CD4^+$ Tcells mitigates immune response, thus promoting cancer cell intravasation [406]. On the other hand, Tregs also play a vital role in CTC migration and metastasis [407]. CTCs selectively recruit circulating Tregs *via* production of chemokines, including CCL5-CCL17, CCL22, CXCL9 and CXCL10. In addition, IL-10 and TGF-β1 activate circulating Tregs and promote CTC survival [408]. In several human cancers, the number of CTCs is directly associated with the circulating Tregs [409]; CTC-positive patients showed an increase in $CD4^+$ Tregs along with a stem-like CTC phenotype. A study in breast cancer patients reported reduced expression in mTOR, Poly-Adenosine triphosphate (ADP) ribose polymerase (PARP) and Myc with FOXO3 overexpression in CTCs played a role in proteolytic degradation of the ECM and EMT [410]. CTCs also evade immune surveillance by the expression of PD-L1. In EMT-induced CTCs, PD-L1 expression was associated with poor prognosis in cancer [411,412]. CTCs are rare and can be difficult to detect due to their small numbers and variability in phenotype. The detection and characterization of CTCs is an active area of research, and several techniques have been developed for their isolation and analysis. These include methods based on size, density, and expression of cell surface markers. Advances in technology, such as the CellSearch system [413] and the use of circulating tumor DNA (ctDNA) [414] have improved the ability to detect and track CTCs. Recent advances in single-cell analysis technologies have enabled the characterization of CTCs and their microenvironment at the molecular level, providing new insights into the mechanisms underlying the metastatic process.

Although several studies have reported the mechanism underpinning immune evasion by tumor cells, designing effective therapeutic strategies remains a formidable task. For therapy directly targeting EMT has been challenging, the elucidation of the interactive regulation of EMT and immunosuppression is desirable for developing new therapeutic approaches in cancer. Moreover, novel therapeutic approaches that target the microenvironment to disrupt the pro-metastatic signals generated by CTCs are currently being investigated. The combination of immune checkpoint inhibitors and immunotherapy targeting immunosuppressive cells could be a promising therapy for improving the clinical outcomes of cancer patients by preventing or delaying the onset of metastasis. The different therapeutic strategies have been discussed in the following sections (Table 2) (Fig. 4).

8. Therapeutic targets

8.1. Immune checkpoint inhibitors

Accumulating evidence suggests that immune checkpoints, including CTLA-4, PD-1 and PD-L1, are critical in regulating both innate and adaptive immune responses. Inhibition of these ICPs can release the breaks on the immune system and potentiate the anti-tumor immune response (Fig. 4) [67,416]. Over the past decade, targeting inhibitory ICPs by monoclonal antibodies has become one of the important pillars of cancer therapy. Notably, anti-PD-1 (nivolumab, pembrolizumab or pidilizumab), anti-PD-L1 (atezolizumab, durvalumab or avelumab) and anti-CTLA-4 (ipilimumab or tremelimumab) therapies are associated with resounding success in achieving long-term durable responses in several types of malignancies (Table 2) [67,416,417]. Nevertheless, a significant number of cancer patients failed to respond to these therapies, or developed resistance, potentially due to heterogeneity in their TME characteristics [67,418]. For instance, tumors like bladder cancer and NSCLC are often considered as "hot" tumors, as they exhibit inflamed TME, increased expression of neo-antigen and enhanced T-cell infiltration as well as expression of PD-L1, resulting in enhanced susceptibility to immune checkpoint inhibitors (ICP-Is) (Table 2) [419]. Nevertheless, other tumor types, such as prostate cancer, are characterized as "cold" as they exhibit minimal Tcell infiltration and are associated with poor response to single-agent ICP-Is [419,420]. However, some miRs can affect the efficacy of ICPs. The circular RNA fibroblast growth factor receptor 1 (circFGFR1) interacts with miR-381-3p and acts as a miR sponge to enhance expression of CXCR4 which promotes therapeutic resistance to anti-PD-1 therapy [421]. On the other hand, an *in vivo* study demonstrated that enhanced expression of miR-155 in lymphoma cells were significantly sensitive to PD-L1 blockade treatment [422]. A panel of miRs (miRs-146a, −155, −125b, −100, −125a, −146b, −99b and let-7e) were significantly associated with MDSCs and poor response to treatment with immune checkpoint inhibitors in melanoma patients [423].

8.2. Therapeutics targeting of cell metabolism

Since glucose metabolism directly regulates Tcells, therapeutic

Table 2
Immunotherapy in cancer treatment [415].

Cancer Immunotherapy	Target	Generic Name	FDA Approval/Phase	Indication(s)
Immune check point inhibitors	PD-1	Nivolumab	2014	Metastatic melanoma; metastatic NSCLC; advanced RCC; HL; HNSCC; advanced or metastatic UC
		Pembrolizumab	2014	Metastatic melanoma; NSCLC; metastatic HNSCC; HL; UC; MSI-H or dMMR CRC
		Cemiplimab-rwlc	2018	cSCC
	PD-L1	Atezolizumab	2016	Locally advanced or metastatic UC; metastatic NSCLC
		Avelumab	2017	MCC; UC
		Durvalumab	2017	BC; NSCLC
	CTLA-4	Ipilimumab	2011	Metastatic melanoma
	LAG-3 & PD-1	Relatlimab-rmbw and nivolumab	2022	Metastatic or unresectable melanoma
	TIM-3	Sym023	Phase I (NCT03489343)	Advanced solid tumors and lymphoma
	B7–H3	Vobramitamab duocarmazine (MGC018)	Phase I (NCT05293496)	Advanced solid tumors
	B7–H4	SGN-B7H4V	Phase I (NCT05194072)	Solid tumors
	TIGIT/ PVRIG	PM1009	Phase I (NCT05607563)	Advanced tumors
	GITR	REGN6569	Phase I (NCT04465487)	Advanced Solid Tumor malignancies
IDO1 Inhibitors	IDO	Epacadostat	Phase II (NCT03322566)	Metastatic NSCLC
CAR T-Cell Therapies	CD19	Tisagenlecleucel	2017	NHL; ALL
		Axicabtagene ciloleucel	2017	NHL; FL

ALL: Acute lymphocytic leukemia; BC: Breast cancer; CRC: Colorectal cancer; cSCC: Cutaneous squamous-cell carcinoma; dMMR: Deficient mismatch repair; FL: Follicular lymphoma; HL: Hodgkin's Lymphoma; HNSCC: Head and neck squamous cell carcinoma; MCC: Merkel cell carcinoma; MSI-H: Microsatellite instability; NHL: Non-Hodgkin's lymphoma; NSCLC: Non-small cell lung cancer; RCC: Renal cell carcinoma; UC: Uterine carcinoma.

strategies are being developed to target the glucose metabolism (Fig. 4). The drug, metformin is being studied in over 100 clinical trials due to its anti-cancer properties [424]. Metformin inhibits cancer cell proliferation by blocking mTOR and cyclin D1 and prevents cancer cell invasion and migration by reducing expression of MMPs. Nevertheless, this agent inhibits Tcell exhaustion, and it is vital to inhibit glycolysis and oxidative phosphorylation. JHU083 hinders glutamine metabolism and induces T effector cells leading to anti-tumor immune activity [425]. Although IDO or IDO1 inhibitors are still not approved for therapeutic treatment, they are still under investigation either as single agent or in combination with other immunotherapy interventions (Table 2) [426, 427]. Due to high grade of toxicities, the combination of IDO inhibitor plus pembrolizumab has been discontinued [428]. Others IDO inhibitors, Indoximod, Linrodostat mesylate, Navoximod, DN1406131, EOS200271, KHK2455, LY01013, MK-7162 and SHR9146, are under clinical investigation either individually or in combinations [429–432]. Moreover, preclinical studies are being carried out to develop single agents [433–439] as well as in combination [433] with immunotherapy to target IDO2 and TDO.

8.3. Cytokines

As mentioned in the sections above, cytokines (interleukins, interferons, and tumor necrosis factors) regulate the immune responses, cellular communication and play a versatile role in several stages of cancer immunity [440]. Owing to the diverse role of cytokines, they have been used in several clinical trials to evaluate their use as potential agents in immunotherapy (Table 2) (Fig. 4).IL-2 was one of the early candidates for immunotherapy. IL-2 administration as well as the adoptive transfer of antitumor T-cells cultured *ex vivo* in the presence of IL-2 represented successful immunotherapies interventions for renal cell carcinoma and melanoma [441]. Autologous dendritic cells loaded with autologous tumor lysates were infused into patients with low doses of IL-2 as adjuvant therapy for patients suffering from advanced colorectal cancer, ovarian cancer, or melanoma [442–444]. On the contrary, while treatment with IL-12 led to increased cytotoxicity of IL-12-treated NK cells, increased production of IFN-γ in cytotoxic $CD8^+$ Tcells, enhanced proliferative activity, and better differentiation of naïve Th cells to Th1 cells [445,446]. However, significant side effects were observed along with the treatment with IL-12 and hindered its use in immunotherapy [447]. IL-21, another member of the family of IL-2 cytokines, has been used to stimulate the proliferation of germinal center B cells [448], as well as to induce the differentiation of CD40L-stimulated B cells in plasma cells. Clinical trials administering recombinant IL-21 have demonstrated its ability to increase the number of $CD3^+CD56^+$ NKT-like cells in patients with stage IV malignant melanoma [449] and activate T and NK cells in patients with stage IV CRC [450].

Interferons, another group of cytokines, are effective in immunotherapy. The first approved interferon treatment of chronic myeloid leukemia with IFN-α2a, showed a significant increase in the number of CD14high $CD16^+$ and MHC class II^+ monocytes [451].

Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) is being actively used for cancer immunotherapy owing to its ability to regulate the maturation of DCs from myeloid progenitors [452]. Neutropenia is one of the most common symptoms of cytokine-based immunotherapy in cancer patients. The ability of GM-CSF to stimulate the proliferation of activated $CD54^+$ neutrophils may help to overcome this problem [453]. However, the effects of GM-CSF on other subsets of the immune system aren't fully studied, which limits the use of this cytokine in immunotherapy, requiring further investigations.

8.3.1. TGF-β inhibitors

Various anti-cancer pharmacological interventions have been reported to target specific mediators of TGF-β signaling pathway and will be discussed below. One of the small-molecule inhibitors, Galunisertib (LY2157299) is orally available and selectively binds to TGF-β type receptor I and impedes its kinase activity. Along with *in vivo* experimental data [454], phase-I clinical trials in hepatocellular carcinoma, pancreatic cancer, glioma and solid tumors showed favorable results [455–457]. However, a phase 2 study involving recurrent glioblastoma patients failed to improve the overall survival [458]. Vactosertib, an oral bioavailable TGF-β type receptor I kinase inhibitor demonstrated antitumor efficiency in both *in vivo* models [459] and phase I clinical trials [460,461]. Phase II trials for vactosertib are ongoing [461–463]. Other

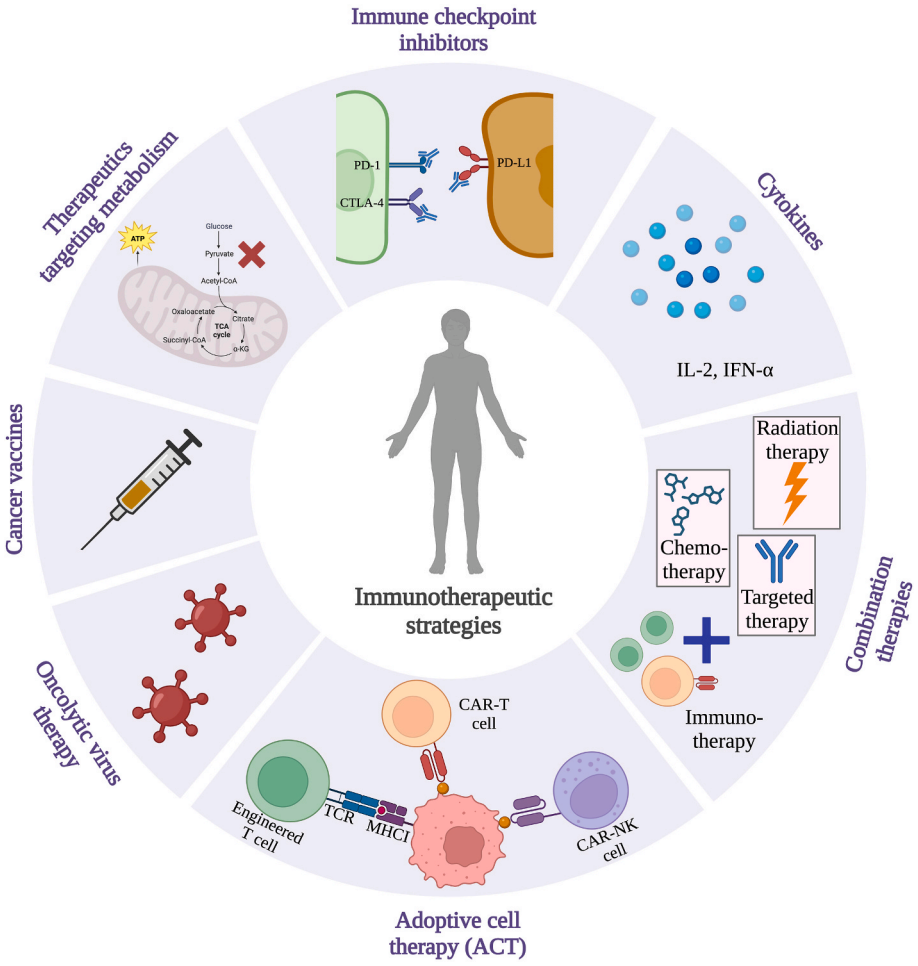

Fig. 4. ***Types of Cancer Immunotherapy.*** Immunotherapeutic strategies employed for anti-tumor response include immune checkpoint inhibitors, cytokine treatment, adoptive cell therapy (ACT), oncolytic viruses, cancer vaccines and metabolic therapies. In certain cases, some of these treatments are used in combination. Figure created with Biorender.com.

inhibitors LY3200882 and PF06952229 are currently under phase I trials [464]. However, treatment with small-molecule inhibitors induced significant side-effects in cancer patients [465] and hence a combination of anti-TGF-β therapy with chemotherapy, radiotherapy, and immunotherapy can plausibly reduce therapeutic resistance.

8.3.2. Combination of anti-TGF-β therapy with chemotherapy, radiotherapy, and immunotherapy

The small molecule inhibitor galunisertib has been combined with several chemotherapeutic regimens such as gemcitabine, paclitaxel and sorafenib to improve therapy response [466–470]. Additionally, the other small molecule inhibitors (LY320082 and vactosertib) are being tested for therapeutic response in combination with capecitabine or paclitaxel, respectively [471]. On the contrary, combination of anti--TGF-β therapy and radiotherapy can enhance treatment response by inducing tumor cell radiosensitivity. A phase II study of the TGF-β-blocking antibody fresolimumab in combination with focal irradiation enhanced the overall survival along with favorable immune responses in metastatic breast cancer, as well as a phase II study for non-small cell lung cancer is ongoing [472,473]. Moreover, LY3200882 in combination with radiotherapy is also currently under clinical development (NCT02937272). Nonetheless, several studies have shown clinical activity of combination treatments with anti-TGF-β. Galunisertib in combination with anti-PD-1/L1 immunotherapy showed effective antitumor immunity with a positive response [474]. The other ICP inhibitor, anti-CTLA4 combined with the TGF-β like receptor II found significant antitumor efficacy as compared to anti-CTLA-4 antibody alone [475]. Combination of vactosertib with anti-PD-L1/PD-1 monoclonal antibody has shown efficient anti-tumor activity [476].

9. ACT

Adoptive cell therapy (ACT) is a highly personalized cancer therapy that is arising as a successful therapeutic strategy in both hematological malignancies and solid tumors (Fig. 4) [477]. It involves isolating cancer-targeting immune cells, such as T or NK cells, expanding or engineering them *ex vivo* to improve their anticancer activity, and then infusing them back into patients to effectively target and eliminate tumor cells. Currently, ACT can be classified into three main modalities, namely TILs, engineered cells with either TCR or CAR [477,478]. The foremost ACT was performed in metastatic melanoma using patients' autologous TILs [479]. [479]. However, TILs can be isolated only from cancer patients undergoing surgical resection, representing only a fraction of patients in the need of immunotherapy [480]. The modification of Tcells with exogenous antigen specific TCR was developed to allow the treatment of larger number of cancer patients [478,481,482]. Peripheral blood Tcells isolated from cancer patients are isolated and genetically modified *in vitro* to express a molecularly characterized antigen specific TCRs and were redirected to tumor cells expressing the specific antigens [483,484]. Clinical evidence for the use of TCRs as a potential therapeutic target was first achieved by Morgan et al., in 2006, who demonstrated that autologous lymphocytes expressing

anti-MART-1 TCR induced metastatic melanoma regression in 2 out of 15 patients [485]. Later, several clinical trials utilizing engineered TCR targeting various antigens have shown clinical activity in different solid tumors. For instance, the use of TCR directed against NY-ESO-1 cancer-testis antigen in synovial cell sarcoma and melanoma patients successfully induced objective clinical responses in more than 50% of treated patients, including a complete regression in a subset of patients [486]. TCR-engineered T-cell ACT targeting other antigens, such as MAGE-A3, Wilms' tumor protein 1 (WT1), PRAME, and Alpha-fetoprotein (AFP), are currently being investigated in clinical trials. However, since TCR-directed therapies require antigen presentation by MHC, the suboptimal expression of MHC molecules by tumor cells can limit the *in vivo* efficacy of this type of therapy [487]. Besides, TCR-based ACT can lead to serious life-threatening toxicities or autoimmune reactions if the TCR cross-reacts with antigens expressed in normal cells. For instance, in a clinical trial assessing the use of anti-MAGE-A3 TCR therapy, several patients developed life-threatening neurological toxicity due to the expression of MAGE-A12 in neurons [488]. Therefore, it is necessary to optimize TCRs to improve their specificity and minimize the serious side effects.

Similar to TCRs, CAR-Tcells are engineered lymphocytes that have been genetically modified to specifically target tumor antigens (Table 2) [478]. Unlike TCRs, CAR-Tcells target antigens expressed on the surface of cancer cells independent of their presentation by HLA molecules [489]. Structurally, CAR-Tcells are composed of a Tcell activation domain that promotes cell proliferation and a single chain variable fragment that offers selectivity for a particular target. In addition to CAR-Tcells, CAR-NK cells are being developed for cancer immunotherapy [490] and are currently under clinical investigation for both hematological and solid malignancies [491]. The development of CAR-T-cells started back in 1989; however, earlier generations of CARs were not capable of maintaining T-cell responses. It has been noted found that suppressive signals produced by cytokines and chemokines in the TME can exhaust the survival and antitumor activity of CAR-Tcells [492]. Subsequently, considerable efforts were directed towards refining the design of CAR constructs to enhance the efficacy and safety of CAR-Tcell therapies. As a result, second and third-generation CARs that incorporated co-stimulatory domains such as CD28 or 4-IBB (CD137) were developed and led to significant enhancement in T-cell activation and proliferation [478,493,494]. More recently, fourth-generation CAR-T-cells, also known as T-cells redirected for antigen-unrestricted cytokine-initiated killing (TRUCKs), have been designed to secrete immune stimulatory cytokines or immune modulators to improve the antitumor activity. These cytokines can modulate the immunosuppressive TME and are under the regulation of the NFA-T-responsive/IL-2 minimal promoter [495]. TRUCKs are currently being evaluated in pre-clinical and early-phase clinical trials.

CAR-Tcell therapy has shown remarkable success in the management of several types of hematological malignancies, such as acute lymphocytic leukemia (ALL) and Non-Hodgkin's lymphoma (NHL) [496]. Strikingly clinical responses were attained for B-cell malignancies using adoptive transfer of anti-CD19-CAR-expressing T-cells [497]. These products have been approved by European Medicines Agency (EMA) and Food and Drug Administration (FDA) for ALL, some subtypes of lymphoma and more recently B cell maturation antigen (BCMA)-CAR for multiple myeloma, for patients who relapse or develop resistance to prior therapies. While several CAR-Tcell therapies have shown remarkable success and were approved for the treatment of blood cancers, none of these therapies was approved for use in solid tumors which represent a more challenging target. Yet, several efforts have been made to specifically target antigens expressed by solid tumors and are currently evaluated in clinical trials, including CARs targeting mesothelin, EGFRvIII, and B7–H3. So far, clinical trials in solid tumors have yielded mixed results. Brown et al. (2016) reported complete regression of glioblastoma for 8 months upon administration of intracranial anti-IL13Rα2 CAR-Tcell therapy [498]. On the other hand, the use of ROR1 targeting CAR-Tcell therapy in breast and lung cancer patients showed mixed responses [499]. To overcome this limitation and enhance the efficacy of CAR-Tcell therapies, clinical trials are undergoing to assess novel combinations of CAR-T-cell therapies along with other immunotherapeutic strategies, including ICB.

Like ICPs, few miRs also affect the efficacy of CAR-Tcells. MiR-153 blocked IDO expression and induced potent anti-tumor CAR-Tcells targeting EGFR in an *in vivo* model of CRC, [500]. Also, miR-143 enhanced specific killing activity of HER2-CAR T-cells against TE-7 cells (esophageal cancer cell line) by blocking glucose uptake and glycolysis [501].

10. Cancer vaccines

Cancer vaccines aim to target specific mutated antigens in the tumor and generate immune responses against cancer cells and are in the form of peptides, DNA or mRNA [502] and can trigger efficient anti-tumor T-cell responses [503,504]. In the 1980s the first cancer vaccine was developed based on tumor cells and tumor lysates [505]. However, discovery of the first human tumor antigen melanoma-associated antigen 1 opened the window for use of tumor antigens in cancer vaccines [506]. Following the years, in 2010, Sipuleucel-T, a dendritic cell-based vaccine displayed efficacy in treating prostate cancer, opening a whole new field in the area of cancer vaccines [507]. Cancer vaccines induce an immune response against TAAs and TSAs or by stimulating cellular immunity and humoral immune response to recognize cancer cells as foreign entities [508]. The overall process of the tumor-immune cycle induced by cancer vaccines involves steps that include immunogenic cell death, APC maturation, activation, and enhancement of T-cell activity. Once administered, the cancer vaccine delivers the selected antigens; the DCs uptake and process the tumor antigens which are presented on MHC I and MHC II molecules to naive $CD4^+$ and $CD8^+$ T cells [509,510]. The presentation of cancer antigens to Tcells activates both the innate and adaptive immune responses leading to the proliferation and differentiation into memory and effector Tcells [511]. Once activated, immune cells including CTLs cells eliminate cancer cells either directly or by triggering apoptosis [512]. In addition, the follicular DCs also promote generation of memory B and plasma cells which on activation induce antibody-dependent cellular cytotoxicity [513]. One of the vital features of cancer vaccines is the initiation of immunological memory. The immune system maintains a memory of the cancer-specific antigens, thus allowing a prompt and targeted response if there is cancer recurrence. At present, several cancer vaccines are in the initial stage of pre-clinical and clinical research [514].

Cancer vaccines can either be prophylactic (preventative) or therapeutic (curative) and will be discussed in the following sections.

10.1. Prophylactic vaccines

Prophylactic vaccines aim to prevent the development of specific cancers by targeting high-risk populations or individuals with precancerous conditions. FDA has approved vaccines against malignancies induced by Hepatitis B virus (HBV) and HPV [7]. The HBV vaccine was the first preventive vaccine to reduce hepatocellular carcinoma (HCC) and three doses are highly effective in providing sustainable immunity against HBV infection [515]. Currently, three FDA-approved HPV prophylactic vaccines are on the market. Cervarix™, a bivalent HPV vaccine protect against two HPV types: 16 and −18 [516]. On the other hand, Gardasil®, a quadrivalent vaccine protects against infection with four HPV types (HPVs −6, −11, −16, and −18) [517], while the nonavalent Gardasil®9 protects against nine HPV types (HPVs −6, −11, −18, −31, −33, −45, −52, and −58) [518]. However, there is no vaccine has been developed for prophylactic immunity against non-viral associated malignancies. Mazumder et al. [519], demonstrated that the anti-Müllerian hormone receptor II (AMHR2-ED) vaccine suppressed tumor growth in murine epithelial ovarian cancer models. The AMHR2-ED-specific antibodies were

induced by $CD4^+$ T helper cells-activated B cells which triggered the Bax/caspase-3 dependent apoptotic signaling cascade [519]. Further research is essential to test the efficiency and safety of prophylactic vaccines in human cancers.

10.2. Therapeutic vaccines

Therapeutic vaccines are designed to treat cancers by stimulating immune response against tumor cells [520]. Therapeutic cancer vaccines are categorized into four types based on the preparation methods and include cell-based vaccines, peptide-based vaccines, nucleic-acid based vaccines, and virus-based vaccines [521].

Cell-based cancer vaccines employ whole cells as antigen carriers and are the primary form of primeval cancer vaccines [522]. Tumor cell vaccine and Immune cell vaccines are the two types of cell-based cancer vaccines. While the whole tumor cell vaccine consists of the whole TAAs including $CD4^+$ helper Tcells epitopes and CTLs, immune cell vaccine is based on the role of the cell in the immune system. Clinical trials of cell-based cancer vaccines are ongoing. In the engineered tumor cell vaccine, GVAX, the tumor cell is transfected with the GM-CSF gene; expression of the GM-CSF enhances anti-tumor activity by triggering DCs and NK cells. In RCC, melanoma as well NSCLC the GVAX has shown a series of significant and durable responses [523,524]. Combination of GVAX with CRS-207, PD-1 or Urelumab (NCT03190265, NCT02451982) are ongoing and has shown positive results [525]. On the other hand, AGI-101H, a gene-modified melanoma stem cells-like vaccine has shown significant efficiency against melanoma and contributed to long-term survival [526]. Similarly, DCs vaccines have shown significant efficacy in clinical trials. DC vaccines are made from monocyte-derived DCs [527]. A recent phase IIB trial in melanoma patients using a tumor lysate, particle-loaded, dendritic cell (TLPLDC) vaccine showed a significant increase in disease-free survival in patients who completed the vaccine series [528]. Similar data were obtained in a phase III clinical trial in glioblastoma where the DC vaccine (DCVax-L) enhanced patients' median overall survival [529].

Another possible approach to whole-cell vaccines are peptide-based vaccines which are polypeptides made up of known or predicted tumor antigen epitopes. Peptide-based vaccines are generally less immunogenic and tend to require a combination with adjuvants to stimulate their immunogenicity [530]. Peptide-based cancer vaccines require both $CD8^+$ T epitopes and $CD4^+$ T cell epitopes. While the $CD8^+$ T epitopes activate CTLs tumor immunity *via* the antigens cross-presentation pathway, $CD4^+$ T cells trigger helper T-cells to maintain the function of CTLs [531]. Additionally, the length of the peptide chain mainly determines the peptide vaccine performance; in comparison to short peptides, the long peptides vaccines have a higher potential to trigger a long-term and effective anti-tumor response. Various platforms are used for producing cancer vaccines and include plants, yeasts, mammalian cells and *Escherichia coli* (E.coli) [532]. The initial clinical trial of peptide vaccine was based on MAGE-1 [533]. Peptide-based cancer vaccines are being used to treat several types of human cancers including HNSCC [534], lung, pancreatic and esophageal cancers [535,536]. The polypeptide, IMU-131 is fused to diphtheria toxin by B-cell epitopes in the HER2 extracellular domain and phase I clinical trials demonstrated IMU-131 to trigger HER2-specific antibodies and cellular responses [537]. Another polypeptide cancer vaccine, DSP-7888 consists of peptides that trigger the Wilm tumor gene 1-specific CTLs and helper T-cells and demonstrated efficacy in recurrent or advanced malignancies [538]. SurVaxM was another peptide vaccine which was shown to enhance glioblastoma patient survival [539].

The fourth class of nucleic acid vaccines include DNA and RNA vaccines which are made up of the encoding gene and carrier group of pathogen antigens. DNA cancer vaccines are closed circular DNA plasmids which encode TAAs or immunomodulatory molecules to induce innate and adaptive immune responses [540,541]. DNA vaccines are transcribed in the nucleus and then translated to the encoded antigens in the cytoplasm. The antigen is processed and presented to $CD8^+$ T and $CD4^+$ T cells by MHC I and MHC II molecules to activate specific immune responses. DNA vaccines have been frequently studied in cervical cancer. In phase III trials, VGX-3100 is being tested for safety and efficacy (NCT03185013, NCT03721978). Although DNA vaccines have shown efficiency in preclinical models [542], they have insignificant progress in clinical trials due to poor immunogenicity [543].

On the other hand, mRNA vaccines are processed *invitro* and are encapsulated within nanoparticles. mRNA translation results in the development of a protein antigen which stimulates an immune response [544]. Introduction of exogeneous synthetic mRNA into cells triggers antigen synthesis which are then delivered to the surface of APCs *via* MHC molecules to trigger anti-tumor immune response [545,546]. Recently, mRNA cancer vaccines have shown positive response against solid tumors. An mRNA vaccine, BI1361849 (CV9202) encodes six antigens (NY-ESO-1, MAGE-C1, MAGE-C2, survivin, 5T4, and MUC-1) and was found to be well-tolerated and efficient [547]. Reinhard and colleagues [548] introduced CLDN6 as a CAR target and demonstrated increased efficiency of CLDN6-CAR-T cells against solid tumors. mRNA vaccines are categorized into non-replicating mRNA and self-amplifying RNA (SAM). Cancer mRNA vaccines are generally non-replicating [546, 549]. mRNA vaccines implicit MHC I-induced $CD8^+$ T cell responses. Cancer vaccines based on in-vitro transcribed mRNA have shown effectual results against metastatic solid tumors in clinical trials. There are three classes of the antigens encoded by mRNA and include immunostimulants, TAAs and tumor neoantigens. Immunostimulants are generally used in combination with other vaccines or immunotherapies. The mRNA, TriMix consists of three mRNAs encoding CD70, CD40L and an active form of TLR4, and has shown positive results in several clinical trials [550]. In phase II clinical trials including patients with stage II or IV melanoma, a combination of TriMix and TAA mRNA vaccine triggered $CD8^+$ T cell responses [551,552]. mRNA-2752, a lipid nanoparticle encapsulating mRNAs encoding OX40L, IL-23 and IL-36γ is used to treat lymphoma and is under clinical trial (NCT03739931). On the other hand, BNT111, encodes for TAAs NY-ESO-1, MAGE-A3, tyrosinase, and TPTE) and displayed positive effects against melanoma [553]. However, mRNA vaccines encoding neoantigens are gaining success in personalized vaccines.

Virus-based cancer vaccines utilize viruses as vectors to treat and prevent tumors; the commonly used viral vaccine vectors are derived from adenoviruses, alphaviruses and poxviruses [554]. One of the advantages of using virus-based vaccines is the efficient response of the immune system to the viruses. The three forms of the virus-based vaccine include inactivate, live or subunit vaccines. Two types of virus-based vaccines have been developed: the oncolytic virus vaccine and the virus vector vaccine. Although, inactivated whole virus vaccines have shown efficiency in treating Ebola or COVID-19 [555,556], it demonstrated less efficacy in treating virus-induced malignancies [557]. Oncolytic virus, a novel immunotherapeutic class of drugs, specifically eliminates tumor cells and induces anti-tumor response. On being infected with oncolytic viruses, tumor cells generate ROS and cytokines to trigger immune cells and release of TAAs [558]. Several genetically modified viruses have been developed as oncolytic agents and include herpes simplex virus, adenovirus, reovirus, etc [559]. BT-001, an oncolytic virus vaccine expresses the anti-CTLA4 antibody and GM-CSF and is tested in a clinical trial (NCT04725331) [508]. On the other hand, another oncolytic virus vaccine, Talimogene laherparepvec (T-VEC) was used in a phase II study in unresectable stage IIIB-IV melanoma [560]. The study reported T-VEC to induce systemic immune activity and modify the TME which may enhance the effectiveness of other immunotherapy agents in combination therapy [560]. Adenovirus-based cancer vaccines have also shown positive results in preclinical and clinical trials [561]. VRP-HER2, a viral vector-based vaccine encoding HER2 demonstrated positive results in *in-vivo* models of breast cancer as well as clinical trials [562]. A combination of VRP-HER2 and anti-PD-1-therapy improved overall efficacy and is under clinical trials

(NCT03632941) [563]. Additionally, Nadofaragene firadenovec, a non-replicating adenovirus vector vaccine encoding human IFN-α, showed clinical efficacy against non-muscular-invasive bladder cancer; more than half of the patients had a complete response after the first dose [564].

Moreover, combination of neoantigen vaccines with ICP-Is have shown significant efficiency in eliciting antitumor T-cell response [565].

11. Combination therapy

Combination therapy use multiple therapies and aims to target multiple aspects of the cancer cells, achieving a more significant effect on the cancer cells while minimizing the side effects of each treatment. Most chemotherapy drugs were developed with a primary focus on their direct cytotoxic effects, with little consideration given to their impact on the immune system. The mechanisms of action of chemo-immunotherapies include debulking of tumors, immunogenic cell death, increasing antigenicity of tumor cells, depletion of immunosuppressive cells in the TME, modulation of gene expression and increasing sensitivity of the tumor to chemotherapy [566]. FDA-approved chemo-immunotherapies includes the use of immune checkpoint inhibitors with standard treatment and has shown a significant improvement in the overall survival of the patients with small cell lung, bladder, breast and, head and neck cancers [567–569]. However, in certain cases including urothelial and non-small cell lung cancer, chemo-immunotherapy has not shown promising results.

As compared to chemo-immunotherapy, radiation therapy when used in conjunction with immunotherapy provides various advantages. Radiation induces expression of MHC Class I molecules and ICPs, downregulates CD47 on the surface of cells and, the ROS generated during radiation can modify proteins and DNA leading to increased antigenicity [570–574]. Apart from anti-PD1/PD-L1 antibodies, researchers are also exploring the potential of combining radiotherapy with other immunotherapeutic agents, including cytokines, cell therapy, vaccines, and other immune checkpoint modulators [575]. A Phase II clinical trial involving a small number of participants indicated that the combination of radiotherapy and CAR-Tcell therapy enhanced the overall response rate of diffuse large B-cell lymphoma [576].

Nevertheless, since several targeted therapeutic agents alter the immune cell functions, various clinical trials are being carried out to investigate the efficiency and cytotoxic effects of a combination of targeted therapy with immunotherapy [122–124]. Anti-angiogenesis agents display multifaceted roles in several immune cell subpopulations [125]. Among the six FDA-approved targeted therapy and immunotherapy combinations, Axitinib and Pembrolizumab [577], Cabozantinib and Nivolumab [578], Axitinib and Avelumab [579], Lenvatinib and Pembrolizumab [580] and, Bevacizmab and Atezolizumab [581] combinations directly target angiogenesis. The only combination of targeted therapies that does not directly target angiogenesis is the administration of vemurafenib (BRAF inhibitor) and cobimetinib (MEK inhibitor), along with atezolizumab in patients with BRAF V600 activating mutation-advanced melanoma [582]. At least 10 clinical trials have investigated the combination of immunotherapy with agents that target the PI3K/AKT/mTOR pathway [583]. Interestingly, seven clinical trials are investigating the combination of ibrutinib and acalabrutinib (Bruton's tyrosine kinase/IL-2-inducible T-cell kinase inhibitors) with CAR-T-cell therapy in cancer [566].

Clinical trials combining cytokines with other immunotherapies are underway. Studies have confirmed the use of an anti-IL-1β antibody, especially in combination with an anti-PD1 antibody to significantly increase M1 macrophage and the M1/M2 macrophage ratio in the TME [584]. Both native and genetically modified forms of immunostimulatory cytokines, including IL-2, IL-10, IL-12, and IL-15, have been combined with ICP-Is in various clinical trials. A combination of pegylated long-acting IL-10 with anti-PD-1 antibodies pembrolizumab or nivolumab has shown manageable toxicity profiles and viable potential antitumor activity [585]. On the other hand, for immunosuppressive cytokines like TGF-β, CCL2, and IL-8, neutralizing antibodies or small molecule inhibitors have been tested in clinical settings in combination with ICP-Is and chemotherapy [566].

Several preclinical and clinical trials aimed at combining PD-1/PD-L1 blockade with CAR-T therapy and have shown synergistic antitumor activity [586]. To generate an immunostimulatory environment, CAR-Tcells can be combined with other molecules that stimulate the immune system, including immunostimulatory cytokines, cytokine receptors, and co-stimulatory molecules [587]. Alternatively, CAR-Tcells can be genetically modified to directly express these molecules, which is a feature of the fourth generation of CAR-T-cells. A clinical trial to study the anti-tumor effects of CAR-Tcells expressing IL-12 has been initiated [588]. CD19 CAR-Tcells combined with agents such as ibrutinib, pembrolizumab, atezolizumab and rituximab are being used for the treatment of B-cell malignancies [589–592]. The combination of GD2-CAR-Tcells and oncolytic adenovirus expressing RANTES, and IL-15 demonstrated a synergistic effect in a neuroblastoma xenograft mouse model by increasing CAR-Tcell accumulation at tumor sites and enhancing tumor cell sensitivity to the lytic effects of CAR-Tcells [593]. Reducing adenosine 2A receptor expression using retroviral technology significantly enhanced the function of anti-HER2 CAR-Tcells [594]. The combination treatment of anti-EGFRvIII-CAR-Tcells with the overexpression of miR-153, which suppresses IDO, was evaluated in a xenograft model of CRC, demonstrating effective tumor cell eradication [595].

12. Conclusion

In conclusion, cancer cells have evolved complex mechanisms to evade the detection and eradication by the immune system. These mechanisms include altered tumor antigen expression, enhancing the levels of immune checkpoint receptors, recruiting regulatory immune cells, and producing immunosuppressive factors. Understanding these mechanisms is essential for developing effective cancer therapies. The current direction of investigations focuses on targeting immune checkpoint inhibition, modulating the tumor microenvironment to create a pro-inflammatory environment, and combining immunotherapies with other cancer therapies to enhance anti-tumor immune responses. However, while immunotherapy is a favorable approach for cancer treatment, there are several limitations and challenges, especially in solid tumors as the therapy is dependent on the type of cancer and the individual's immune system. Ongoing research should aim on developing therapeutic strategies based on the tumor and TME characteristics. Therapeutic strategies need to be developed to increase Tcell persistence and proliferation, reduce immunosuppression, and inhibit Tcell exhaustion. In terms of ACT, genetic alteration of Tlymphocytes is essential to enhance their anti-tumor efficacy and to progress towards a new generation of CARs. Furthermore, the use of combination therapies instead of single therapy can lead to a more stable and prolonged treatment for cancer. Further research involved in investigating the genomic make up of patients' tumor cells and their role in shaping the immune responses, can pave the way to develop more effective precision ImmunOncology.

Funding

This has been supported by the QNRF grants: NPRP10-0129-170277) and GSRA8-L-1-0506-21033.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

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.

Data availability

No data was used for the research described in the article.

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