The pathogenic response of cytotoxic T-lymphocytes, a common therapeutic target for cancer, has a direct impact on treatment outcomes (Review)

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Abstract. Cytotoxic T lymphocytes (CTLs), also known as $CD8^+$ T cells, participate in immune function by secreting various cytokines after recognizing specific antigens and class I major histocompatibility complex molecules associated with tumor cells, and thus have a key role in antitumor immunity. However, certain $CD8^+$ T cells show low reactivity and thus cannot effectively remove tumor cells or viral antigens. Due to this heterogeneity, effective biomarkers representing these differences in $CD8^+$ cells are needed. The identification of suitable biomarkers will also enhance the management of cancer treatment. Recent research has improved the understanding of $CD8^+$ T lymphocytes in the tumor microenvironment and circulatory system. Treatment efficacy is impacted directly by the pathogenic response of CTLs, and thus, the use of adjuvant therapies to address these pathological changes, e.g., stimulating the increase in the proportion of reactive T cells or suppressing the proportion of terminally exhausted T cells, would be advantageous.

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1. Introduction

Tumor-related antigen-specific $CD8^+$ T cells severely restrict tumor growth (1). Following exposure to tumor antigen-derived peptides, the T-cell antigen receptor (TCR)-CD3 complex interacts directly with major histocompatibility complex (MHC) I molecules to activate dormant $CD8^+$ T cells. Concurrently, further $CD8^+$ T-cell activation is induced by CD8 and CD28 molecules (2). $CD8^+$ T cells can also be transformed into cytotoxic T lymphocytes (CTLs) by exposure to CD137 (4-1BB), CD80, CD70 and cytokines released by other immune cells (such as IL-2, IL-4, IL-12 and IL-15) (3).

Upon activation, effector $CD8^+$ T lymphocytes that express the C-X-C motif chemokine receptor 3 (CXCR3) migrate from the circulatory and lymphatic systems to tumors, where they interact with the type 1 T-helper cell-type chemokines, C-X-C motif chemokine ligand 9 (CXCL9), CXCL10 and CXCL11 (4). The cells then release granzymes and perforin, which, in turn, induce the death of tumor cells. $CD8^+$ T cells also express death-associated ligands, namely Fas ligand and tumor necrosis factor (TNF)-related apoptosis-inducing ligands, which promote the apoptosis of tumor cells (2). In addition, activated $CD8^+$ T cells secrete cytokines, including TNF-α, TNF-β and interferon-γ (IFN-γ), which regulate and augment the overall antitumor response via activation of both the innate and adaptive immune systems (5).

Of note, cytotoxic $CD8^+$ T cells do not respond to cancer cells. Mechanistically, there is a marked loss of human leukocyte antigen (HLA) class I expression within tumor cells, as well as mutations in JAK1/2 elevated programmed cell death 1 (PD-1) expression in tumor-infiltrating $CD8^+$ T lymphocytes (TILs) (6,7). Furthermore, emerging evidence suggests a significant link between $CD8^+$ TILs and overall survival (OS) in cancer patients (8). However, the $CD8^+$ TIL-mediated tumor response remains insufficient for tumor regression, despite large numbers of available $CD8^+$ TILs, and is closely associated with patient prognosis in various human malignancies. This discrepancy is likely due to a strongly immunosuppressive tumor microenvironment (TME) (9). The current immunotherapeutic strategies primarily focus on reducing T-cell suppression (10).

2. Role of CD8+ T cells in the antitumor response during tumor immunotherapy

In tumor immunotherapy, immune checkpoint blockers (ICBs) targeting CTL-associated protein 4 (CTLA-4) or the PD-1-programmed cell death ligand 1 (PDL1) axis, specifically, PD-1 blocking therapy, CTLA-4 blocking therapy and their combinations, as well as novel ICB therapies, modulate neoantigen-specific T-cell activity, thereby restoring T-cell responses through the targeting of inhibitory receptors that are overexpressed in dysfunctional TILs (11). However, due to the marked heterogeneity within the immune TME and TIL phenotypes associated with specific tumor types and in different patients, tumors and patients show a highly varied response to immunotherapy (12). Furthermore, these checkpoints induce T-cell fatigue in the TME and enhance the immune evasion of cancer cells (13).

CD8+ T-cell exhaustion. T cells that are heavily immunosuppressed enter a dysfunctional state called T-cell exhaustion (14). During this state, T cells show reduced cell division, cytokine production and cellular killing abilities, together with increased expression of inhibitory receptors on the T-cell surface. One major feature of T-cell exhaustion is prolonged T-cell exposure to antigens and elevated antigen loading. Emerging evidence suggests that these 'exhausted' $CD8^+$ T cells express multiple co-inhibitory receptors, namely, PD-1, T-cell immunoglobulin mucin family member 3 (TIM-3), lymphocyte activating 3 (LAG-3) and CTLA-4, which function synergistically to abrogate the functions of active effector T cells (15). Furthermore, these receptors cooperate, implying that the distinct functions of the coinhibitory receptors combine to regulate T-cell responses (16). Transcription factor 1 $(TCF1)^+$ stem cell-like $CD8^+$ T cells and their progeny, a clonally linked terminally differentiated population that shows increased expression of checkpoints, are two functionally independent subsets of TILs. The conventional concept of 'exhausted' $CD8^+$ T cells applies to these terminally differentiated cells (17). A recent report suggested that $CD8^+$ T cells represent a developmental continuum wherein the lineage ranges from stem cell-like $PD\text{-}1^{Lo}$ $CD8^+$ T precursor progenitors to terminally defective $PD\text{-}1^{Hi}$ $CD8^+$ T cells. These $CD8^+$ T subsets respond differently to ICBs and their distribution varies between normal and tumor tissues in cancer patients (18).

Immunosuppression in the TME. The expression of inhibitory ligands, production of immunosuppressive cytokines and competition for resources are among the strategies used by tumors to develop a tolerant microenvironment. Together, these events synergistically suppress immune-cell activity, particularly that of $CD8^+$ T cells, which is critical for tumor eradication (19). TILs are typically associated with improvements in patient survival and positive treatment outcomes in a wide number of tumor types (20). Increased $CD8^+$ T-cell infiltration is common in certain tumors, but not in others. The reasons for this are still unclear. On the other hand, regulatory T cells (Tregs) represent the most challenging obstacles to anti-tumor immunity and effective anti-tumor immunotherapy (21). Immune checkpoints (ICs) generally minimize excessive immune responses by adjusting the status of immune activation (22). IC overexpression, seen in multiple malignancies and immune populations, facilitates enhanced inhibitory signaling and immune evasion (23). For example, diminished cytokine and perforin synthesis is closely related to $CD8^+$ $PD\text{-}1^+$ T-cell presence in the TME (24). Furthermore, increased expression of TIM-3 strongly suppresses T-cell responses. Patients with colorectal cancer exhibit abundant circulating and tumor-infiltrating $CD8^+$ $PD\text{-}1^+$ $TIM\text{-}3^+$ cells, which produce substantially less IFN compared to $CD8^+$ $PD\text{-}1^-$ $TIM\text{-}3^-$ cells (25). Taken together, despite a reported link between enhanced ICs expression in the TME and disease prognosis in various cancers, additional explorations are warranted to further analyze the influence of imbalances in the various IC-expressing T-cell subsets on disease outcomes (26).

Emerging evidence suggests that defective T-cell infiltration of tumors is also closely associated with resistance to cancer immunotherapy (27). In general, phosphorylation of hepatocyte growth factor-regulated tyrosine kinase substrate promotes the production of immunosuppressive exosomes, which, in turn, reduces $CD8^+$ T-cell infiltration into tumors (28). To coordinate and enhance PD-1 activity, neuropilin-1 (Nrp1) can be recruited to the cytolytic synapses of $PD1^+$ $CD8^+$ T cells. One study reported that Nrp1 deficiency in murine $CD8^+$ T cells strongly upregulated the anti-tumor immune response of anti-PD1 antibodies. Likewise, in patients receiving anti-PD1 therapy for metastatic melanoma, the Nrp1 levels in $CD8^+$ TILs indicate poor patient prognosis (29). In another report, T-cell immunoglobulin and ITIM domain (TIGIT) was identified as a co-inhibitory receptor that significantly restricts antitumor and other chronic immune responses reliant on $CD8^+$ T cells. Tumor-infiltrating T cells in both humans and mice exhibit relatively enhanced TIGIT expression. In models of cancer and chronic viral infection, TIGIT and PD-L1 antibodies synergistically induce co-blockade and specifically augment $CD8^+$ T-cell effector activity, thereby accelerating tumor and viral clearance, respectively. This suggests that TIGIT is a major $CD8^+$ T-cell modulator that can significantly regulate both antitumor and antiviral activities (30).

Side effects of CD8+ T-cells in tumor therapy. Although certain cancer patients respond well to ICB vs. traditional chemotherapy, numerous patients experience multiple side effects, appropriately termed immune-related adverse events (irAEs). IrAEs can target any organ; however, the most common targets are the skin, endocrine organs, lungs and liver (31). Despite the rare occurrence of serious irAEs, those patients who do develop severe irAEs are often diagnosed at a later stage, when treatments become ineffective, and the outcome is potentially fatal (32). In clinical trials, the baseline peripheral $CD8^+$ T-lymphocyte content was reported to be a potent stand-alone risk factor for irAE development.

3. Association between the CD8+ T-cell status and tumor prognosis

Cancer prognosis is heavily dependent on the cytotoxic T-cell response. However, there is still controversy on whether the number of $CD8^+$ TILs is positively associated with improved cancer prognosis. This is likely due to the diversity of invading $CD8^+$ T cells, differences in tumor origins or the

TME. Furthermore, microanatomical TIL localizations in various tumor tissues may have different effects on the clinical outcomes of patients.

$CD8^+$ T cells and melanoma. Patients with melanoma with relatively upregulated $CD8^+$ T-cell infiltration potentially experience better clinical outcomes. Researchers have been able to construct a risk score for patients, which can serve as an indicator for predicting the sensitivity of patients with melanoma to immunotherapy. They discovered a six-gene signature (CD274, CLEC4E, GBP4, PMSE1, KIR2DL4 and KLRD1) that directly influenced $CD8^+$ T-cell infiltration in the melanoma TME. These genes were found to be robustly indicative of immunotherapeutic success among patients with melanoma (33).

Relative to normal tissues and the peripheral blood, a larger percentage of metastatic melanoma-invading $CD8^+$ lymphocytes express PD-1. In addition, these $CD8^+$ $PD\text{-}1^+$ TILs exhibit signs of exhaustion reminiscent of reduced effector activity (34). In addition, $CD8^+$ $PD\text{-}1^+$ T cells possess enhanced oligoclonal expansion of specific TCRβ clonotypes, compared to $CD8^+$ $PD\text{-}1^-$ TILs. The $CD8^+$ and $CD8^+PD\text{-}1^+$ populations are the largest TCR clonotypes within autologous tumors and they contain clonotypes that target altered antigens. PD-1 expression on $CD8^+$ TILs accurately recognizes the repertoire of clonally enhanced tumor-reactive cells, along with the well-documented negative modulatory role of PD-1 in T cells. This demonstrates the dual relevance of PD-1 expression in the TME (35).

In addition to PD-1, scientists also discovered other inhibitory molecules, namely, LAG-3, CD137 and TIM-3, which show variable levels of expression on $CD8^+$ TILs in melanoma. The wide-ranging tumor-reactive cells in melanoma are accurately defined by PD-1, rather than CD137, expression (35). Patients with melanoma typically have minimal to no CD39-expressing $CD8^+$ T cells in the peripheral blood and non-invaded lymph nodes. However, these cells were present in tumors and invaded or metastatic lymph nodes. This indicates that CD39 serves an immune regulatory role on $CD8^+$ T cells. Thus, it can be used as a promising biomarker of T-cell dysfunction, as well as a target for immunotherapeutic intervention (36).

$CD8^+$ T cells and nasopharyngeal carcinoma (NPC). Patients with Epstein-Barr virus-positive NPC typically have more TILs, which, in turn, results in a better prognosis compared to less TILs. Elevated $CD8^+$ TIL infiltration in the intra-tumoral site is strongly correlated with favorable OS (37). Furthermore, PD-L1-expressing tumor cells recruit more CD8-positive TILs. Mechanistically, exosomes derived from NPC cells carry PD-L1, which interacts with PD-1 on $CD8^+$ T-cell surfaces to effectively reduce its activity. This, in turn, encourages NPC cells to evade the immune system, thereby accelerating NPC development (38). Given this evidence, both PD-L1 expression on tumor cells, as well as the $CD8^+$ TIL population, can serve as potent biomarkers for prognosis prediction for patients with NPC (39).

In another report, it was suggested that the forkhead box (Fox)$P3^+$ TILs, rather than $CD8^+$ TILs, have essential functions in NPC anti-tumor immunity. Patients with NPC have dysregulated CTLs. Alternately, FoxP3 is a favorable prognostic indicator for patients with NPC, and it is strongly linked to enhanced OS and progression-free survival in all patients with NPC (40).

$CD8^+$ T cells and lung cancer

Small cell lung cancer (SCLC). The findings that patients with SCLC experience immune escape and cannot benefit from ICB therapy in the long term are strongly associated with their relatively low TIL numbers (41) and PD-L1 expression (42). Suppression of lysine-specific demethylase 1 (LSD1) enhances ICB antitumor activity by increasing $CD8^+$ T-cell infiltration into SCLC tumors, as well as augmenting MHC class I expression and the ability to kill tumor cells. This is supported by a new clinical trial that integrates LSD1 inhibition with ICB to treat SCLC (43).

Lung squamous carcinoma (LSC). $CD8^+$ T-cell deficiency within tumors is strongly associated with poor clinical outcomes and low lymphocyte motility in human LSC. Endogenous $CD8^+$ T cells physically bind to tumor-associated macrophages (TAMs) in the tumor stroma to render it inactive. Using colony-stimulating factor 1 receptor blockade to deplete TAMs strongly enhances the quantity of tumor-infiltrating $CD8^+$ T cells and enhances $CD8^+$ T-cell migration and infiltration into tumor sites in mice. Thus, combining anti-PD-1 and macrophage depletion therapies can vastly increase $CD8^+$ T-cell concentrations in the malignancy, thereby slowing its growth (44). Therefore, this can be a promising adjuvant approach to the therapeutic modulation of macrophage behavior.

Non-SCLC (NSCLC). PD-1/PD-L1 immunotherapy is a first-line treatment for NSCLC. In these tumors, TIL activity is closely linked to PD-L1 expression (45). Chemotherapy is known to significantly alter PD-L1 expression and $CD8^+$ TILs infiltration, both of which can strongly regulate patient outcomes (46). Upregulated lymphocytic infiltration in tumors is a strong indicator of positive outcome for patients with NSCLC after surgery (47). In addition, following chimeric antigen receptor T-cell therapy, increased $CD8^+$ TIL levels are a significant prognostic indicator (43). Enriched $CD8^+$ T subsets were identified in tumors vs. non-tumor tissues and blood. Furthermore, single-cell transcriptome sequencing revealed that *in vitro* $CXCR5^+$ $TIM\text{-}3^-$ $CD8^+$ T cells were more adaptive to self-renewal and pluripotency than more differentiated subpopulations, and they exhibited stronger versatility (48).

$CD8^+$ T cells and breast cancer. Cancer immunotherapy is highly successful in a large number of tumor types. However, patient response rates are substantially lower in breast cancer. One reason for this may be $CD8^+$ T-cell exhaustion. A majority of $CD8^+$ TILs that express PD-1 and CD39 display a terminally exhausted phenotype (49). Using tumor-derived extracellular vesicles, malignant breast cancer cells often transmit active transforming growth factor (TGF)-type II receptors to promote TGF signaling in target cells. In a xenograft model, extracellular vesicle-TGFβ receptor type-2 (EV-TβRII) was found to be absorbed by low-grade tumor cells, thereby accelerating the epithelial-mesenchymal transition. This, in turn, enhanced tumor stemness and, eventually, metastasis. EV-T-βRII deployment as cargo to $CD8^+$ T cells often stimulates Smad3

activation. Smad3 physically interacts in tandem with the TCF1 transcription factor, which, in turn, contributes to $CD8^+$ T-cell exhaustion and immunotherapy failure (50).

Of note, the disease-specific survival rates for female patients with estrogen receptor (ER)-positive malignancies were substantially reduced, while the disease-specific survival was increased among ER-negative tumor patients who inherently carry massive numbers of TIL $CD8^+$ T cells (51). Tregs were also reported to be present in excess in the breast TME relative to normal tissue, which were predominantly $FoxP3^+$ $Helios^+$. Furthermore, they also expressed enhanced CTLA-4 and PD-1 levels. The aforementioned findings suggest that breast tumor cells potentially employ Tregs and components of various suppressive pathways, namely PD-1 and CTLA-4 molecules, to generate an immuno-subversive environment to survive. A dual blockade of these immunosuppressive molecules may be considered an effective approach to treating breast cancer (49).

In triple-negative breast cancer (TNBC), patients with high-density TILs have a better prognosis. TILs, such as $CD4^+$, $CD8^+$ and $FoxP3^+$, are significantly predictive of TNBC occurrence (52). Furthermore, studies including outcome prediction after $CD8^+$ TIL endocrine therapy showed that lower $CD8^+$ TIL levels are more beneficial for treatment response than excess $CD8^+$ TIL levels (53).

In human epidermal growth factor receptor (EGFR) 2 $(HER2)^+$ breast cancer, TILs are a strong predictor of neoadjuvant diagnosis and prognosis (54). In ipsilateral breast recurrence, the numbers of $CD8^+$ TILs in true recurrence far exceed those in new primary disease, and there is a clear rising trend (55).

$CD8^+$ T cells and squamous cell carcinoma of the head and neck (HNSCC), mouth and skin. Patients with HNSCC exhibit relatively elevated $CD8^+$ T-cell infiltration and better prognosis (56). Furthermore, CD8+ subsets in TILs strongly predict HNSCC patient prognosis (57). To further elucidate the prognosis of patients with oropharyngeal HNSCC, scientists employed a brightfield quantitative image analysis $CD8^+$ algorithm (58). In oral squamous cell carcinoma, $CD8^+$ $CD103^+$ TILs are abundant in the stromal region, and this is strongly associated with a favorable prognosis (59). In addition, the semi-quantitative Klintrup-Makinen score can also be used as a TIL scoring system for skin invasive squamous cell carcinoma to assist in prognosis evaluation (60). Other indicators, namely, exhaustion and clonally restricted immune signatures within TILs, are useful for prognosis prediction in lymphoma, whereby $CD8^+$ TIL exhaustion is described as having upregulated $TIM\text{-}3^+$, $PD\text{-}1^+$, $CD39^+$, $CD45RO^+$ and $HLA\text{-}DR^+$ marker expression (61).

$CD8^+$ T cells and cancers of the digestive system

Colorectal adenocarcinoma (CA). CA modulates a wide range of bystander $CD8^+$ TIL frequencies and phenotypes. PD-L1 expression is directly associated with $CD8^+$ TIL presence in the stroma of patients with CA (62). In patients with EGFR-wild-type tumors, the $CD39^+CD8^+$ TIL frequency was substantially higher and CD39 was a strong indicator of tumor-specific $CD8^+$ T cells. Using phenotypic identification of $CD3^+$ $CD8^+$ T cells in tumor and normal colon tissues of patients with colorectal cancer and in their blood circulation, FoxP3 expression was shown to be significantly elevated in tumor-infiltrating $CD8^+$ T vs. normal colon cells. Furthermore, this increase was strongly associated with ICs, such as CTLA-4, PD-1, LAG-3 and TIM-3 (63).

In the TME, relative to advanced-stage patients with considerable lympho-vascular invasion (LVI), those in the early stages of the disease with no LVI exhibited significantly elevated TIM-3 expression. Enhancement of the circulating $TIM\text{-}3^+$ $CD8^+$ T-cell subset in patients with colorectal cancer (CRC) is closely linked to extended disease-free survival (DFS) (64), suggesting that TIM-3 expression in CD8+ T cells serves as a potent biomarker for prolonged DFS of patients with CRC.

Hepatocellular carcinoma (HCC). The $CD8^+$ T-cell abundance is also associated with HCC outcome (65). However, certain $CD8^+$ T-cell responses displayed significant exhaustion in HCC (66). A considerable rise in the levels of unfavorable co-stimulatory molecules, such as PD-1, LAG-3, fibrogen-like 1 (67), CTLA-4 (68), CD244 (69), TIM-3 (70) and CD160 (71) is strongly associated with the overexpression of certain cognate ligands on antigen-presenting cells, namely PD-L1, which favors a tolerogenic milieu. Therapies that disrupt these harmful signaling networks have great promise as therapeutic approaches (72).

Relative to primary tumors, early-relapse tumors possess scarce regulatory T cells, augmented dendritic cell levels and upregulated infiltrating $CD8^+$ T cells. Interestingly, unlike the usually exhausted status seen in primary HCC, $CD8^+$ T cells in recurrent tumors overexpress CD161 and exhibit an innate-like reduced cytotoxic state with minimal clonal proliferation. Furthermore, patient prognosis is worsened with enrichment in these cells (73).

Gastric and esophageal cancers. In numerous solid tumors, including gastric cancer, the host microbiota is closely associated with tumor growth. Marked correlations are evident between the tumor microbiota and exhausted $CD8^+$ tissue-resident memory T cells in the TME of gastric cancer. Methylobacterium potentially regulates the development of stomach cancer (74). In one investigation, mass spectrometry was employed to conduct in-depth immunological analyses of tumors, adjacent tissues and blood cells in patients with gastric cancer. The analyses revealed reduced $CD8^+$ T lymphocytes in the tumor vs. surrounding tissues. However, there was a substantial increase in the numbers of Tregs and TAMs, suggesting greater immunosuppression in gastric cancer. Patients with early gastric cancer also have strongly elevated PD-1 expression on $CD8^+$ T cells (75).

In terms of treatment, polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) accelerate $CD8^+$ T-cell exhaustion, thereby reinforcing PD-1 immunotherapeutic resistance in various cancers. Mechanistically, PMN-MDSCs modulate immunosuppression via S100A8/A9 regulation (a hallmark of MDSCs) and $CD8^+$ T exhaustion (76). In addition, patients without PD-L1 expression and positive TILs show marked OS enhancement, suggesting that PD-L1 expression and the TIL status are strong indicators of patient prognosis, and clinical trials are currently underway to further test their performance (77).

Cholangiocarcinoma. In cholangiocarcinoma, enhanced numbers of infiltrating $CD8^+$ TILs indicate longer OS and relapse-free survival (RFS). In biliary tract cancers, OS and

RFS are directly associated with the neutrophil-to-lymphocyte ratio (NLR) and $CD8^+$ TILs. The NLR can predict $CD8^+$ TIL abundance in cancer (78). A portion of $CD8^+$ TILs share several characteristics with tumor-specific cells, although they do not express CD39. Patients typically exhibit varying levels of CD39 expression. Those lacking chronic antigen stimulation at the tumor site in certain malignancies also exhibit a marked absence of CD39 in $CD8^+$ TILs. This supports the $CD8^+$ TILs designation as 'bystanders'. Bystander T cells may be easily counted or isolated by measuring CD39 expression (79).

$CD8^+$ T cells and kidney and prostate cancers. Following checkpoint therapy in patients with renal cancer, only a small proportion of circulating $CD4^+$ and $CD8^+$ T lymphocytes are active, as is shown by the evaluation of activation markers CD38 and HLA-DR, as well as the proliferation marker Ki-67. Furthermore, $CD38^+$ $HLA\text{-}DR^+$ $CD8^+$ T cells increase in numbers following treatment. The optimal antitumor immune response is observed in patients with the largest post-treatment rise in $CD38^+$ $HLADR^+$ $CD8^+$ T cells (80). Furthermore, a mutual restriction exists between $CD8^+$ T cells and neutrophils. In the TME, low-density neutrophils suppress $CD8^+$ T-cell proliferation in peripheral blood mononuclear cells (78) and promote the apoptosis of inactive $CD8^+$ T cells (81). Alternately, using RANK signaling, $CD8^+$ T cells also modulate neutrophil-induced immunosuppression (82). Neutrophils tend to form extracellular traps that drive $CD8^+$ T cells to a metabolically exhausted phenotype (83). $CD8^+$ T cells are also reported to potentially influence neutrophil metabolism in chronic renal cell carcinoma (RCC). $CD8^+$ T cell-derived Sin3-associated protein 18 is inversely associated with E1-like ubiquitin-activating enzyme autophagy-related gene 7^+ neutrophils in RCC, indicating a significant reduction of neutrophil metabolic function in autophagy, thus explaining the role of $CD8^+$ T cells in RCC (84). Furthermore, a descriptive and retrospective investigation examined the effects of androgen deprivation therapy (ADT) on PD-L1 expression, as well as $CD8^+$ T-cell tumor infiltration and activity in primary prostate cancer tissue. The study revealed that a limited number of prostate cancer tissues exhibit $CD8^+$ T-cell infiltration and PD-L1 expression. Furthermore, a hypofunctional $CD8^+$ T cell-containing TME is generated when PD-L1 expression on tumor cells or infiltrating immune cells is >5%. In addition, ADT was found to boost the presence of hypofunctional $CD8^+$ T cells in the TME, creating an ideal tumor immune milieu for immunotherapy targeting (85).

$CD8^+$ T cells and ovarian cancer. In most malignancies, $CD8^+$ TILs are strongly associated with OS. However, this is poorly characterized in ovarian cancer. $CD8^+$ TILs that co-express CD39, CD103 and PD-1 (forming a 'triple-positive' phenotype) exhibit less TCR diversity and express both cytolytic- and humoral immunity-related genes. Uniquely, triple-positive $CD8^+$ effector cells display enhanced TIGIT expression. Given this evidence, PD-1, CD103, CD39 and TIGIT are highly promising immunotherapy combination targets (86).

TILs strongly regulate the immune system of patients with epithelial ovarian cancer. However, there is limited information on the predictive patterns of $CD8^+$ TILs in terms of histotype and in relation to other clinical variables. $CD8^+$ TILs in high-grade serous ovarian carcinomas (HGSCs) are strongly associated with enhanced OS. Among HGSCs, regardless of the remaining malignancy status following cytoreduction, a known standard treatment, and hereditary BRCA1 DNA repair associated (BRCA1) pathogenic mutation, $CD8^+$ TILs are beneficial, but not predictive, for BRCA2-mutant carriers. Furthermore, analysis of uncategorized $CD8^+$ TIL counts revealed a nearly log-linear functional shape. Based on these findings, there is a significant dose-response relationship between $CD8^+$ TILs and HGSC survival, as well as the histotype-specific nature of immune invasion. Furthermore, one can predict not only the presence or absence of infiltration, but also its extent (87). Enhanced treatment efficacies are typically dependent on small subpopulations of $CD8^+$ T cells that transform to active and cytotoxic states in ovarian cancer. Indeed, a specific anti-PD-1/PD-L1 antibody is employed in HGSCs, which activates a small, previously unknown, $CD8^+$ T-cell population to respond to ICB in HGSCs, and they become cytotoxic progenitor-exhausted phenotypes post-treatment (88).

4. Summary

Despite marked advances in ICB treatment, only a limited number of patients show satisfactory clinical improvements (89,90), while most, particularly those with solid tumors, do not show the anticipated effective response (91,92). This demonstrates the serious need for continued research to improve the efficacy of immunotherapy. Fortunately, in recent years, a large number of studies have laid a solid foundation in this field. In 1998, the concept of 'immune cell exhaustion' was proposed (93). In 2006, overexpressed PD-1 was identified on the surface of exhausted $CD8^+$ T cells. Simultaneously, PD-1 blocking therapy was confirmed to effectively stimulate $CD8^+$ T-cellular response (94). In 2008, $CD8^+$ T cells were stratified into two categories: Intermediate PD-1 expression ($PD\text{-}1^{int}$) and high PD-1 expression ($PD\text{-}1^{high}$), which strongly guided subsequent PD-1 blocking therapy (95). In 2010, the $PD\text{-}1^{high}$ subgroup was shown to express TIM3, 2B4, CTLA4 and other immunosuppressive factors (96). In 2016, a stem-like $CD8^+$ T-cell subset was coined as $PD\text{-}1^{int}$ TCF^+, and this group of cells exhibited self-renewal and proliferation potential, which led to a positive response to PD-1 blockade therapy. Furthermore, this subset of cells is closely associated with tumor immunotherapy prognosis (97). In 2019, transitory $CD8^+$ T cells, which were of the $CX3CR1^+$ $CD101^-$ phenotype, were identified. These cells were distinct from stem cell-like $CD8^+$ T cells and possessed enhanced cytotoxicity. Concurrently, a terminally depleted $PD\text{-}1^{high}$ $CX3CR1^-$ $CD101^+$ cell subset was also discovered. In 2020, a stem cell-like $CD8^+$ T-cell subset named $PD\text{-}1^{int}$ TCF^+ was subcategorized into $PD\text{-}1^{int}$ TCF^+ $CD69^+$ (resting-like stem cells) and $PD\text{-}1^{int}$ TCF^+ $CD69^-$ (circulating stem cells). Furthermore, the $PD\text{-}1^{high}$ $CX3CR1^-$ $CD101^+$ cell subpopulation was separated into a $PD\text{-}1^{high}$ $CX3CR1^+$ $CD101^-$ $CD69^-$ (transitory CD8 T cells) and a $PD\text{-}1^{high}$ $CX3CR1^-$ $CD101^+$ $CD69^+$ subpopulation (ultimately exhausted $CD8^+$ T cells) (98,99).

With increasing fine-grained separation of the $CD8^+$ T-cell subsets involved in their pathological response, our understanding of the process of $CD8^+$ T-cell exhaustion has grown.

Simultaneously, our comprehension of the highly complex heterogeneity of immune cells within the human body has also increased (93-99). This complexity may surpass our capacity to comprehend. Naturally, we have access to excellent research techniques today, including the most recent developments in flow mass spectrometry technology and single-cell sequencing in conjunction with spatiotemporal transcriptome technology. To get as close as possible to and observe the most accurate appearance of the immune world, it is advisable that when studying a particular type of immune cells in isolation, their high degree of heterogeneity must be taken into account. Dynamic thinking should be employed. It is suggested to try to apply the above-mentioned novel study methodologies and use as many markers as possible to get as close to the most accurate understanding of the immunological environment. The concept of 'immune senescence' should be mentioned here, and it may be more appropriate to refer to the process of $CD8^+$ T-cell exhaustion as $CD8^+$ T-cell immune senescence. Immune senescence is fundamentally different from the conventional understanding of aging, and it is possible that the development of organismal lesions, such as inflammatory disorders, tumors and autoimmune diseases, occurs before aging. Of course, this is an open topic and further investigation is needed to determine the truth of this stance.

In conclusion, therapy results are directly impacted by the pathogenic response of CTLs, a common therapeutic target for cancer. Adopting certain adjuvant therapeutic options to address such pathological changes-e.g., by stimulating the increase in the proportion of reactive T cells or by suppressing the proportion of terminally exhausted T cells-would be a good way to approach the treatment of tumors while putting treatment plans for various tumors into action.

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Availability of data and materials

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Authors' contributions

The conception and design of the study were primarily the responsibility of JL and NG, who provided the initial framework and theoretical underpinnings for the research. JL, MC, XG and YL were actively involved in the literature search and selection process. The manuscript was written by JL, MC, XG, and YL, with each author focusing on specific areas of expertise and ensuring that the content was well-integrated and coherent. The critical revision of the manuscript for important intellectual content was carried out by NG and JL, who also provided guidance on the overall structure and flow of the paper. All authors have read and approved the final manuscript, demonstrating their commitment to the accuracy and integrity of the research findings. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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