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REVIEW

Cervical Cancer: Emerging Immune Landscape and Treatment

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Abstract: Immune cells are essential for defending the body's balance and have increasingly been implicated in controlling tumor growth. In cervical cancer (CC), the immune landscape is extensively connected with human papillomavirus (HPV) status. Recent insights from studies have revealed that as a result of infection with HPV, immune cell populations such as lymphocytes or monocytes change during carcinogenesis. Immune therapy, in particular checkpoint inhibitors, those targeting PD-1 or PD-L1, has shown promising efficacy. This article reviews the immune landscape and immunotherapy of CC.

Keywords: immune, TIL, macrophage, immune therapy, checkpoint blockade

Introduction

Cervical cancer (CC) is one of the most common gynecological malignancies worldwide, with nearly 570,000 new CC cases and more than 311,000 deaths every year.[1] In 2019, there were 13,170 new CC cases and 4250 new deaths in America according to cancer statistics. In fact, CC is the second leading cause of cancer death in women aged 20–39 years, causing 9 deaths per week in this age group.[2] Although vaccines and CC screenings, including human papillomavirus (HPV) test, cytologic test and colposcopy, have developed rapidly in recent years, effectively decreasing CC mortality,[3,4] there is also an increasing need for cervical precancer screening and early-stage cervical cancer fertility preservation treatment, as well as chemotherapies such as paclitaxel.[5]

Hausen first postulated a possible role of HPV in CC in the 1970s and later put forward the structure of viral genes (such as E6 and E7) that were closely connected with CC.[6] In fact, there are five genera of HPV, α, β, γ, μ and ν, including high-risk 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 and low-risk 6, 11, 42 and 44. HPV prevalence is different according to genotype differences. Currently, it is known that HPVs lead to more than 90% of cervical lesions, especially HPV 16 and 18.[7] In general, HPV is associated with approximately 70% of vaginal and vulvar cancers, 60% of penile cancers, 70% of oropharyngeal cancers and 10% of oral cavity cancers.[8] In a worldwide study, HPV genotype prevalence rates with invasive cervical cancer were HPV16 (61%), HPV18 (10%), HPV31 (4%), HPV33 (4%), HPV35 (2%), HPV39 (2%), HPV45 (6%), HPV52 (3%), and HPV58 (2%), respectively.[9,10] Then, HPV integrates into the host genome and mutates Retinoblastoma (Rb) or p53, which suppresses apoptosis and immortalizes epithelial cells, resulting in the development of low/high squamous intraepithelial lesions (LSIL/HSIL) or carcinogenesis.[11,12]

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As HPV infection can be divided into transient and persistent infections, and 61% of LSIL cases regress spontaneously within 1 year and 91% regress within 2 years, there must exist an imbalance of the immune system in the context of persistent infection.[13] Moreover, the immunosuppressed nature of the tumor microenvironment has long been appreciated, and CC evolution is well influenced by it.[14,15] Therefore, this review attempts to focus on insights into the immune landscape and therapy of HPV-positive CC.

Cervical Cancer Genomics

A large number of studies have revealed that chromosome aberrations, DNA copies alterations, somatic mutations and methylations are related to the occurrence and development of CC. For instance, PIK3CA, TP53, KRAS and PTEN are all commonly mutated genes in CC patients. A recent study in Japan also showed that approximately one-third of Japanese women with CC developed a mutation of STK 11.[16] In 2015, a team of academicians identified frequent HPV integrations in CC: POU5F1B, FHIT, KLF12, KLF5, LRP1B and LEPREL1, as well as HMGA2, DLG2 and SEMA3D, by conducting genome-wide sequencing and high-throughput viral integration detection.[17] Recently, a group found that BRM270 could suppresses CC stem cells proliferation.[18] Additionally, academicians found that host gene MYC disorder may also be the integration site of HPV.[12] Researchers have begun to pay attention to the gene alterations in the tumor immune microenvironment, trying to predict the prognosis of patients. Researchers have also discovered 384 integrated gene sites related to T cell activation in the KEGG (gene ontology and Kyoto encyclopedia of genes and genomes) database.[19] Therefore, this discovery elicits a comprehensive consideration for the study of immune genes in the tumor microenvironment and the prognosis of CC. As the majority of CCs are caused by HPV infection, the integration of E6 and E7 viral genes into the host genome causes excessive cell proliferation and ultimately leads to cancer. However, the mechanism of viral gene integration still needs further study.

Cervical Cancer and the Immune Landscape

On the one hand, the development of CC is directly linked to HPV infection. On the other hand, immune system defects play a significant role in cancer progress. It is believed that HPV infection triggers a primarily cell-mediated immune response, and there is evidence for T helper cell involvement in regressing lesions.[20] One study suggested that Langerhans cells were increased in women who cleared HPV.[21] Low- and high-risk HPV are stratified into different groups due to their oncogenic potential. Even though they stimulate a similar cellular environment and immune defense, it is interesting that they developed respective pathologies and cellular targets. One explanation is that low-risk HPV E7 protein has lower binding affinity, but the mechanism is not known.[22] Tumors are recognized by the immune system and they may be attacked or prevented through a process called immunosurveillance. In the human body, mucosal immunity represents the first line of defense; cellular and humoral immunity also exert essential functions during carcinogenesis and disease progression. The peripheral blood of patients and the tumor microenvironment inspire us to explore cervical carcinoma's connection with immunology.[23]

The Immune Cell Subpopulation in Cervical Cancer

As mentioned above, the characteristics of precancer LSIL and HSIL progression are also tightly correlated with the immune system. Thus, we discuss immune alteration with cervical lesions and cervical cancer below. An abundance of various types of immune cells comprise the tumor microenvironment, including T cells, B cells, dendritic cells, NK (nature killing) cells and macrophages. Immune cells can be divided into immunoactive and immunosuppressive types according to their function (Table 1). Moreover, the presence of many tumor-infiltrating lymphocytes (TIL) is generally associated with CC disease progression.[24]

Tumor-Infiltrating Lymphocyte (TIL) T Cells

Analysis of tumor-infiltrating lymphocytes (TILs) is one of the cornerstones for the research of the tumor microenvironment. The interactions between tumors and the immune system are critical for tumor initiation, and TILs have attracted extensive attention in anti-tumor immunity. However, their functions during the tumor immunoediting processes are ambiguous. The cytotoxic immune response is characterized by CD4, CD8, antigen-presenting cells, and the infiltration of other lymphoid elements.[25] CD4+ T cells are appointed to assist CD8+ T cells in exerting their effects. CD4+ T cells are subdivided into four major subsets: Th1, Th2, Th17 and regulatory T cells (Tregs).

Table 1 Differences in Immunophenotype Between Active and Suppressive Cells for Cervical Cancer

	Immune Active Cell	Immune Suppressive Cell
T cell	Th1 secretes anti-tumor factors IL-2, IFN-γ; CTL increases.	Th2 via IL-10, Th17 via IL-17, Tregs via IL-12, IL-21, abundant immunosuppressive cytokines infiltrate.
B cell	Unknown	B cells may promote tumor progression.
NK cell	CD56 NK cells increase IFN- γ, TNF-α.	/
DC	DCs Elicit Th1 and CTL response	/
Macrophage	M1 secretes TNF-α, kills pathogens and promotes Th1 response.	TAM refers to M2, higher immune infiltrates including TGF-ß, VEGF and PD-L1 to elicit tumor promotion and Th2 response.
EOS	/	Increased EOS are regulated by cytokines as IL-3, IL-5 and GM-CSF, correlated with prognosis.
MDSC	/	MDSC and IL-10 attenuate tumor growth and inhibit IL-6.

Notes: In this review, immune cells are divided into immune active and suppressive cells to better demonstrate CC's immune microenvironment. That is to say, immune active cells tend to fight against cancer development while immune suppressive cells exert pro-inflammatory or cancer progression role.

Th1, Th2, Th17 and Tregs produce positive or negative effects in the maintenance of normal immune function by secreting various cytokines: interleukin-2 (IL-2) and interferon-γ (IFN-γ), the principal cytokines delivered by Th1cells, IL-12, a key cytokine involved in inducing and maintaining Th1cells and the IFN-γ responses, and IL-10, a potent modulator of cell-mediated immune responses secreted by Th2.[26] IL-17 is a recently identified pro-inflammatory cytokine secreted by Th17 cells. According to a previous report, IL-17 promotes angiogenesis and cell proliferation and invasion in CC.[27] Specifically, Th17 can modulate CC cell growth and apoptosis by the effect of miR-146a or miR155.[28,29] A Th17/Treg imbalance often leads to infection, inflammatory response and autoimmune disorders.[30] Th9 is a newly discovered T cell subset that is suspected to hamper tumor growth in several cancers, and it has been proved that Th9 can inhibit CC progression and immune evasion.[31]

Most importantly, Tregs and the production of TGF-ß are essential for immune homeostasis, and increasing evidence indicates that Tregs are present in human tumors and locally suppress antitumor T-cell responses.[32] Moreover, Tregs express the transcription factor forkhead box protein 3 (Foxp3), which is important for maintaining self-tolerance and immune homeostasis, together with CD25.[33] Additionally, Foxp3 Tregs' prognostic value in different types of cancer is related to the tumor site.[34] Studies also proved that elevated Foxp3 expression was associated with high-grade cervical disease and predicted poor overall survival (OS).[35,36] Therefore, Foxp3 might be a useful biomarker for risk stratification in CC patients.[37] Specifically, HLADRhi Tregs, a subset of Tregs, were associated with unfavorable outcomes in cervical squamous cell carcinoma. That is to say, HLADRhi Tregs were highly enriched in the tumor microenvironment and exhibited potent suppressive activity.[38] In addition, IL-12 and IL-21 are both well-known agents, and a combination of them could fight against CC cells effectively by down-regulating Tregs and Th17.[39]

CD8+ cytotoxic T lymphocytes (CTLs) are the major effector cells that kill tumors.[40] One study observed that CD8+ cells predominantly infiltrated the epithelial layer in HPV+ normal cervical tissue, and the trend decreased with increasing cervical lesion size.[41] Another report obtained the same result, showing that CD8+ cells increased after cisplatin treatment.[42] Ultimately, CD8+ T cells downregulated macrophages or CD4+ cells and mainly exerted cytotoxic responses.[43]

B Cells

B cells are conventionally generated in germinal centers, which exert a strong and swift response to stimulation by secreting antibodies and cytokines. Recently, several teams discovered that B cells associated with tertiary lymphoid structures may influence the development of cancer progression.[44–46] In 1984, a gynecologist reported that both T and B lymphocyte counts decreased in peripheral blood.[47] Recently, a group of scientists discovered that B cells promoted HPV-mediated CC progression in a mouse model with the immunosuppressive cytokine IL-10.[48] At the same time, another group found that B cells and IL-10 were increased in human CC samples, which may be significant in cancer

progression.[49] Most recently, B cells were proved to improve HPV-associated squamous CC, which may be activated by radiation and PD-1 blockade. Following data collection from over 800 head and neck squamous cell carcinoma (HNSCC) and CC patients, single-cell RNA-sequencing revealed dramatic increases in B-cell germinal center formation after PD-1 blockade and enhanced IgG and IgM antibody responses.[50] However, the studies focusing on B cells in cervical cancer microenvironment are limited and might be a very much promising research direction. More reports are needed to support B cells' role in CC.[51]

Dendritic Cells (DCs)

CD4+ and CD8+ T lymphocytes can be activated by specific antigen-presenting cells (APCs). Dendritic cells (DCs) are highly potent APCs and play an important role in the CC immune response, though the response is less focused on CC. Once DCs present antigen signals to elicit Th1 and CTL responses, anti-tumor immunity starts, inspiring us a novel immune therapeutic strategy.[52,53] However, DCs tend to tolerate CC cells via RANKL secretion, a receptor activator of nuclear factor kappa-B ligand, a TNF family member. RANKL is a promising candidate for immune evasion together with Tregs in human CC.[54] Furthermore, low DCs and high Tregs might be significantly associated with hrHPV persistence, suggesting that DCs gradually lose antigen-presenting ability gradually.[55]

Eosinophils

Eosinophils (EOSs) have long been known to infiltrate human tumors, such as gastric, colorectal, nasopharyngeal, oral, laryngeal and breast cancers. The cytokines IL-3, IL-5 and GM-CSF are critical in regulating EOS development. Several studies now focus on eosinophils' function in CC.[56] Researchers have proved that EOS infiltration increased with the progression of the CC. Thymic stromal lymphopoietin (TSLP) is a cytokine that can regulate EOS. Moreover, TSLP secreted by CC cells is able to promote tumor proliferation and invasion and may be correlated with a decline in microRNA-132 expression decline.[57,58]

Scientists have begun to focus their attention on eosinophils as a new CC prognostic biomarker. Recently, a new pre-treatment biomarker, the eosinophil-to-lymphocytes ratio (ELR), has been used to predict prognosis in CC patients. Studies have found out that higher values of ELR in peripheral blood are suspected to predict better overall survival (OS), while the ELR value in tumor is unclear.[59] However, another report disagreed with the former retrospective study and concluded that higher eosinophil number are correlated with worse outcomes of cervical squamous cell cancer.[60]

NK Cells

NK cells play an important role in cancer immunity through secreting various cytokines. In the tumor environment, NK cells are stimulated by IL-2. Likewise, NK cells release interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) to fight against CC tumor proliferation.[61] In other words, NK cells are the primary effector to recognize abnormal cells without an antigen presentation process. NKG2D, a type Ⅱ C-type lectin-like family of transmembrane proteins that is different from the NK cell biomarker CD56, works as a stimulatory receptor. Several studies have revealed its association with cancer immunosurveillance and HPV-induced cancers, indicating that the NKG2D gene may influence NK cell cytotoxicity and susceptibility to CC.[62,63] While NKG2D, NKp46, and NKp30 are activating receptors, CD158a, CD158b, and NKG2A are inhibitory NK receptors. One study detected the upregulation of inhibitory NK receptors in CC, suggesting that Tregs may suppress NK function by the inhibition of TGF-ß[64] In addition, recent studies have reported that NK cells could not only mediate immune clearance but also predict disease prognosis. One clinical trial indicated that after 4 cycles of chemotherapy on cervical squamous cell carcinoma at stages Ⅱb-ⅲb, NK cells increased and tumor size reduced.[65] Another study added evidence to this discovery, reporting that NK cells were significantly associated with improved prognosis.[66]

Tumor Associated Macrophage

Macrophages are derived from bone marrow, and their role is particularly prominent. At the same time the function of tumor-associated macrophage (TAMs) has long been discussed. Macrophages can be divided into two groups, namely the classical M1 and the alternative M2, which promote inflammation and tumor progression. First, M1 macrophages are activated by IFN-γ, lipopolysaccharides (LPS) through Toll-like receptors and granulocyte-monocyte colony-stimulating factor (GM-CSF). M1 macrophages highly express major histocompatibility complex class Ⅱ and co-stimulatory molecules such as CD86/CD80, IL-12, IL-13, TNF-α, and reactive nitrogen species. Their major functions are killing pathogens and promoting a Th1 immune response. M2 macrophages are

stimulated by IL-4, IL-10, IL-13, IL-33 and IL-21 and release vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-ß, indoleamine 2.3-dioxygenase, and programmed death ligand 1 (PD-L1) expression. M2 macrophages can take part in tumor promotion and the Th2 response.[67] CD68 is a well-recognized maker of macrophages, while CD163 is regarded as a dominant marker for identifying M2 macrophages. As M2 macrophages mostly promote tumor inflammation, TAMs more likely refer to M2 macrophages.[68]

In 2007, a study first described the population of macrophages in cervical intraepithelial neoplasia (CIN) progression and its influence on CIN outcome. Not surprisingly, the macrophage percentage increased linearly with neoplasia progression.[69] Later studies further revealed that M2 TAMs were associated with high-risk HPV infection and were positively correlated with cervical carcinogenesis. More importantly, higher FIGO stage and lymph node metastasis or lymphangiogenesis usually showed larger counts of M2 macrophages.[70–72] M2 macrophages are usually associated with poor prognosis. CC cell lines possibly induce more monocytes toward an M2-like phenotype in TAMs, significantly maintaining a tumor immunosuppressive microenvironment and promoting angiogenesis and metastasis.[67,73] Furthermore, one study suspected that CC cell lines could induces monocytes into M2 macrophages through lactate secretion.[74] Another study reported that CC cell supernatants may shift LPS-induced M1 into M2 macrophages by increasing the production of TLR and nitric oxide (NO).[75] Moreover, the hypoxic tumor microenvironment can modulate the activation of M2 macrophages via neuropilin-1 (Nrp-1), which may serve as a potential therapeutic marker.[76]

MDSCs

Myeloid derived suppressor cells (MDSCs) are closely linked with tumor staging, progression, clinical therapeutic efficacy and prognosis; thus, MDSCs play an immunosuppressive and tumor-promoting role.[77,78] Using an HPV-mediated CC mouse model, researchers proved that MDSCs mediated an immunosuppressive activity via IL-6-JAK-STAT3 (signal transducer and activator of transcription 3) signaling.[15] More specifically, IL-10 might attenuate tumor growth by inhibiting IL-6 release while activating STAT3 signaling in CC.[79] MDSCs impaired CD8+ T cells cytotoxicity, activation of APCs and immune responses to foreign antigens, ultimately destroying the efficacy of immune therapy against HPV-mediated cancer.[15]

Immune Therapy

Immune therapy is the next generation treatment compared with traditional therapies such as tumor surgery, radiotherapy and chemical therapy. Immune therapy aims to evoke the body's immune system and then enhance tumor-killing ability. In general, CC immune therapy can be divided into four groups: immune checkpoint blockade (ICB), adoptive cell transfer therapy, therapeutic vaccines and cytokine treatment.

Immune Checkpoint Blockade

Immune suppression and activation are two poles of the immune system. Cancer cells are able to escape from the immune balance by provoking an immune-suppressive state and tumor growth. Immune checkpoints often educate the tumor microenvironment into immune tolerance.[80] There are eight well known immune checkpoints [programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte antigen-4 (CTLA-4), T-cell immunoglobulin and mucin-domain containing-3 (Tim-3), 2B4, killer cell lectin like receptor G1 (KLRG-1), TIGIT, B- and T-lymphocyte attenuator (BTLA) and CD160], which serve as the inhibitory signals of T cell activation and help maintain self-tolerance.[81] Checkpoint blockades aim to break microenvironment immune suppression. PD-1 and CLTA-4 are the most promising immune checkpoints targeted in CC.

At present, PD-1/PD-L1 (PD-Ligand1) and CTLA-4 checkpoint inhibitors for CC being tested for clinical use (Table 2). Though immune checkpoint inhibitors have durable response rates, side effects such as autoimmune diseases and low response rates are still unavoidable challenges.[82] The expression levels of PD-1/PD-L1 and CTLA-4 are high in CC, and DCs and T cells express high levels of PD-1 and PD-L1 in CIN samples.[83,84] At the same time, the costimulatory molecules CD80 and CD86 and the anti-inflammatory cytokines IL-12 and IFN-γ are decreased with the increased expression of the immune-suppressive cytokine IL-10.[85] This phenomenon suggests that the upregulation of the immune checkpoint contributes to immune evasion and tumor progression. One study observed that PD-1/PD-L1 blockade interrupted immune suppression in CC; they determined that a subset of T cells, CD8+FoxP3+CD25+T cells increased and immune-suppressive Tregs decreased.[86] Therefore, ICB therapy intends to enhance the body's immune defense and lessen immune surveillance. The application of ICB has rapidly become a promising treatment approach in this decade. In addition, the combination of PD-1/PD-L1 and CTLA-4 may enhance the therapeutic efficiency. Studies in animal models

Table 2 Studies of Immune Checkpoint Inhibitor PD-1/PD-L1 and CTLA4 from Clinicaltrials.gov (Accessed 15th April 2020)

Clinical Trial Identifier	Agent	Immune Target	Primary Endpoint	Sample Size	Status[a]	Phase[b]
NCT01693783	Ipilimumab	CTLA-4	response rate	n=44	ongoing	2
NCT01711515	Ipilimumab	CTLA-4	Toxicity	n=34	ongoing	1
NCT01975831	Tremelimumab, Durvalumab (MEDI4736)	CTLA-4, PD-L1	Adverse event	n=106 (include other cancers)	ongoing	1
NCT02257528	Nivolumab	PD-1	response rate	n=26	ongoing	2
NCT02725489	Durvalumab VS Vigil	PD-L1	Adverse event	n=13 (include other cancers)	ongoing	2
NCT02914470	Atezoluzumab	PD-L1	Toxicity	n=12 (include other cancers)	ongoing	1
NCT02921269	Atezoluzumab	PD-L1	Response rate	n=22	ongoing	2
NCT03073525	Atezoluzumab VS Vigil	PD-L1	Adverse event	n=25 (include other cancers)	ongoing	2
NCT03104699	AGEN2034	PD-1	Response rate	n=150	ongoing	1, 2
NCT03635567	Pembrolizumab (MK-3475) VS chemotherapy	PD-1	Overall survival	n=600	ongoing	3

Notes: [a]Status can be divided into recruit, ongoing, terminated, completed. [b]Clinical phase can be divided into 1, 2, 3, 4.

have determined that this combination prolonged the survival rate with fewer side effects.[32,87] Several clinical trials have investigated the PD-1 checkpoint inhibitors nivolumab and pembrolizumab, the PD-L1 checkpoint inhibitors atezolizumab and durvalumab, or the CTLA-4 inhibitor ipilimumab; some trials are still ongoing, while others have come to their conclusion. These clinical trials proved the safety of ICB, even though many tolerable side effects occurred. However, we still need to pave the way to confirm ICB's antitumor activity in CC.[88–91]

Among gynecological malignancies, besides CC, blockading the PD-1/PD-L1 pathway may also be beneficial in ovarian cancer and vulvar cancer.[92,93] Both ovarian cancer and vulvar cancer express high levels of PD-1/PD-L1, and in tumor cells and mouse models, their antitumor immunities were detected via CD8+ T cells and Tregs regulation.[94,95] However, more clinical trials are needed to explore the effects of PD-1/PD-L1 ICB.

Adoptive Cell Transfer Therapy

Adoptive cell transfer therapy is a highly effective pharmacological option against cancers.[96,97] T cells play an important role in CC immune surveillance; thus, antigen-specific T cell immunotherapy could be used to attack tumor evasion and may have many potential benefits. Scientists have observed that isolated T lymphocytes with HPV E6 and E7 specificity from CC patients expanded stably in vitro.[98] However, the current methods to expand HPV specific T cells from healthy donors have failed to achieve expected results; by optimizing DC maturation and adding appropriate cytokines, it is possible to obtain oncoproteins E6 and E7-specific T cells.[99] If get a good balance in clinical conditions and engineered cell projects is maintained, the potential use of HPV-specific T cells for CC is very promising. Chimeric antigen receptor T cells (CAR-T) have been approved by the Food and Drug Administration (FDA) and are successfully improving outcomes for hematological malignancies.[100] Although the research studies involving CAR-T therapy in CC are rare, one study investigated the killing effect of mesothelin-CAR-T in CC cells and achieved positive results.[101] A clinical trial combined autologous cytokine-induced killer (CIK) cell transfusion and radiochemotherapy in CC patients and showed that the application of CIK cells improved immune function and life quality.[102] Moreover, NK cell transfusion may also improve CC status.[103] In conclusion, adoptive cell transfer therapy should be given more attention in CC.

Therapeutic Vaccines and Cytokines

Virus-like particles (VLPs) of HPV are used as prophylactic vaccines against CC. Though CC is not rare, current treatments involving therapeutic vaccines are deficient. Among preclinical research studies, a therapeutic HPV16 E6/7 vaccines provided a highly effective immune response in murine models, evoking CD8+ and CD4+ T cells via targeting CD40.[40] More Specifically, there is also crosstalk between DCs and innate immune NK cells that assists in the HPV defense effect via CD40 interaction and IL-12p70 secretion, resulting in the production of neutralizing antibodies and cellular immunity.[104] Administration of Fc-fused IL7 could also play a role in modulating vaccines therapy through a CD8+ T cell response.[105] Various therapeutic vaccines are being developed, including DNA, RNA and peptide vaccines. All of these vaccines types exerted antitumor effects through activating the T cell response, especially CD8+ cells.[106–108] In addition, increased level of IFN- γ helped mediate cellular immunity.[109] Scientists prefer to combine therapeutic vaccines and immune checkpoint inhibitors such as PL-L1 and CTLA-4 in trials.[106,110] Several clinical trials have indicated that therapeutic vaccines plus immune checkpoint inhibitors or radiotherapy together induced an immune response in premalignant lesions and CC.[111] Interestingly, another clinical trial even demonstrated that VGX-3100, a therapeutic DNA vaccine targeting HPV16/18, had histopathological regression for CIN.[112] Thus, HPV-associated therapeutic vaccines for CC are a promising research trend that will require further study.[113]

Cytokine therapy has long been an exciting field for cancer treatment since its initial discovery due to its easy accessibility and construction. The release of cytokines has crucial effects in controlling immune responses, educating lymphocytes maturation and exerting biological activities. However, most cytokine-based therapy trials have not performed as expected, with the major obstacle being toxic reaction.[114] In common, TNF-α, IL-6, IL-8, IL-1α are classical pro-inflammatory cytokines, and IL-10, IL-12, TGF-ß are anti-inflammatory cytokines. Their specific functions in CC are not clear. IL-2 and IL-6 confer protection to CC cells against apoptosis.[115–117] In addition, immunoactive TNF- α and immunosuppressive IL-10 are associated with CC susceptibility.[118] More efforts are needed to explore cytokine-based therapies in CC.

Perspective

Even with the recent advances in understanding the genomic and immune landscape of CC, there have been few clinically useful biomarkers developed except for HPV tests and immunohistochemistry (IHC). CC is closely connected with virus infection, which fights against the human immune system. It is commonly known that the tumor microenvironment is very different from normal tissue, and immune-suppressive cells assume a leadership role in immune cell population. Therefore, obtaining a thorough knowledge of tumor immunology will definitely promote CC treatment. Immune therapy is one of the most promising breakthroughs in cancer treatment. Moreover, PD-1/PD-L1 blockade seems to be a potential treatment approach for CC, though the toxicities of current immune therapy will require more effort. Additional research studies bridging the gap between HPV-positive cervical disease and the vaginal metabolome.[119] These discoveries enlightened us of the importance of enhancing CC immune research with metabolism studies.

Author Contributions

All authors contributed to conception and design, drafting and revising the article, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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