Japanese Dental Science Review 55 (2019) 113–120

Contents lists available at ScienceDirect

Japanese Dental Science Review

journal homepage: www.elsevier.com/locate/jdsr

Review Article

Immunomodulatory aspects in the progression and treatment of oral malignancy

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ARTICLE INFO

Article history:
Received 23 May 2019
Received in revised form
13 September 2019
Accepted 17 September 2019

Keywords:
Immune suppression
Tumor microenvironment (TME)
IL-1α
IFN-γ
Programmed death (PD)1
Programmed death ligand (PD-L)1
Tumor associated macrophage (TAM)
Cancer-associated fibroblast (CAF)

ABSTRACT

Inflammation substantially affects the risk of oral malignancy. Pro-inflammatory cytokine, interferon (IFN)-γ, confers anti-tumor activity using several different mechanisms. Conversely, higher expression of interleukin (IL)-17 is associated with worse prognosis. Monocyte chemotactic protein (MCP)-1 correlates positively with poor long-term survival of head and neck squamous cell carcinoma (HNSCC) patients. IL-1α affects cancer associated fibroblasts and macrophages, and promote several malignant phenotypes including immune suppression. Some anti-inflammatory cytokines, including IL-10 and transforming growth factor (TGF)-β, relate to pro-tumoral activities.

Among immune checkpoint modulators, programmed death (PD-)1 and PD-ligand (L)1 facilitate oral squamous cell carcinoma (OSCC) cell evasion from immune surveillance, and the expression status of these has a prognostic value.

OSCCs contain tumor associated macrophages (TAMs) as major stromal cells of their tumor microenvironment. Among the two distinctive states, M2 macrophages support tumor invasion, metastasis and immune suppression. Crosstalk between TAMs and OSCC or cancer-associated fibroblasts (CAF) plays an important role in the progression of OSCC.

Clinical trials with blocking antibodies against IL-1α or melanoma-associated antigens have been reported as therapeutic approaches against OSCCs. The most promising approach activating antitumor immunity is the blockade of PD-1/PD-L1 axis. Manipulating the polarization of pro-tumorigenic macrophages has been reported as a novel therapeutic approach.

1. Introduction

Immunomodulatory aspects of cancer tissues include several cancer cell-intrinsic and extrinsic mechanisms controlled in the tumor micro environment (TME), which promote progression and often confer resistance to their therapy [1]. The progression from premalignant lesions to OSCC is a complicated multi step process. Chronic inflammation can cause tissue damage and changes in the inflammatory cells and cytokines present in the TME. OSCCs could also be promoted by chronic inflammation occurred in the periodontitis. Chronic infection of resident microbiota *P. gingivalis* activates enzymatic cascades enhancing cellular invasion of OSCCs [2]. These changes promote the eventual development of tumors toward highly malignant phenotypes. The anti-inflammatory cytokines, such as IL-10 and TGF-β1, pro-inflammatory cytokines, including IFN-γ and some others, are specifically regulated under extrinsic and intrinsic mechanisms in tumor milieu [3]. Higher expression of IL-17 is associated with worse prognosis [4]. MCP-1 correlates positively with poor long-

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https://doi.org/10.1016/j.jdsr.2019.09.001

term survival of head and neck squamous cell carcinoma patients [5]. IL-1α from tumor cells specifically enhances the immune suppressive activity of mesenchymal cells [6].

On the other hand, the axis of immune check point inhibitors, represented by PD1/PD-L1, plays an important role in regulation of immune tolerance [7]. One of the main elements of the stromal cells, and contributing to the extracellular environment of solid tumors, is the TAMs, mostly polarizing to an M2 phenotype, that involve immune regulatory mechanisms leading to malignant metastatic distribution of OSCC [8].

Clinical trials with blocking antibodies against IL-1α, or vaccination against tumor-specific melanoma-associated antigens have been reported [9,10]. The most promising approach activating antitumor immunity is the blockade of the PD-1/PD-L1 axis. As novel therapeutic approaches manipulating the polarization of pro-tumorigenic macrophages using specific ligand to TLR3, bisphosphonate, and blockings of specific cytokines have been reported [11–14].

In this review, we attempt to report immune suppressive mechanisms in the OSCC tissues, and also refer to effective or potential therapeutics against oral malignancy.

2. Function of inflammatory modulator

Epidemiological and molecular biological studies have revealed that inflammation substantially increases the risk of oral malignancy [2]. In fact, chronic inflammation can induce continuous tissue damage and can also induce specific inflammatory cytokines. Sun et al., have demonstrated that the expression of anti-inflammatory or pro-inflammatory cytokines (TGF-β1, IL-10, IL-4, or IFN-γ, MCP-1) are specifically regulated during development from premalignant lesions to OSCC tissues [3]. Helper T (Th) cells mainly participating in tumor immunology are functionally classified into Th1, Th2, and Th17 cells, according to secretory cytokines and immunological roles [15]. Th2 cytokines (IL-4, IL-5, and IL-10) are classified as anti-inflammatory ones, and are often related to pro-tumoral activities, whereas most Th1 cytokines, represented by IFN-γ, are classified as pro-inflammatory cytokines, and are associated with, in general, good prognosis [16]. Serum levels of IL-17A, TGF-β1, IL-4 and IL-10 were significantly higher in OSCC patients while IL-2 and IFN-γ were relatively low in OSCC patients when compared to controls [17]. Increased expression of IL-10 and TGF-β1, and decreased IFN-γ are associated with negative regulation of natural killer (NK) cells in OSCC patients [18]. Representative cytokines affecting inflammatory modification and tumor phenotypes are as follows.

2.1. Anti-inflammatory and pro-tumoral cytokines

IL-10 and TGF-β are representative anti-inflammatory and immunosuppressive cytokines that promote immune escape of neoplastic cells [19–23]. In fact, overexpression of IL-10 and TGF-β2 is associated with poorer prognosis of OSCCs [24]. IL-10 inhibits antigen depiction of antigen presenting cells (APCs), i.e. macrophages and dendritic cells [21], regulating differentiation of regulatory T cells [22], and conferring resistance to the action of cytotoxic T cell upon tumor cells [23]. Hypoxic stress induces several immune suppressive molecules including IL-10 and TGF-β that could induce the differentiation of tumor-associated macrophage into M2 type suppressing anti-tumor immunity [24]. Another anti-inflammatory cytokine, IL-4, is also considered to be pro-tumoral [3,16,17], however, this function may vary depending on the tumor's diplotype [25].

2.2. IFN-γ

As a representative pro-inflammatory cytokine conferring anti-tumor activity, IFN-γ is mainly secreted by activated T cells and natural killer cells. It enhances macrophage activation, Th1/Th2 balance, cellular proliferation and apoptosis [26,27]. Hyper methylation of IFN-γ promoter has been denoted as an intrinsic mechanism for the down regulation of IFN-γ expression in macrophages infiltrating malignant OSCC tissues, rather than in benign and normal tissues. [28]. Interestingly, IFN-γ inhibits viability and migration of OSCC cells, and induces apoptosis, possibly by regulating ER stress and unfolded protein response (UPR) mechanisms [29]. The apoptosis induced by IFN-γ in head and neck SCC cell lines seems to be mediated by the activation of indoleamine 2,3 protein [30]. IFN-γ treatment of OSCC cells has also been revealed to downregulate heat shock protein 27, which is a proposed anti-apoptotic molecule [31]. Dentin sialophosphoprotein (DSPP) is expressed in the cytoplasm and perinuclear perimeter of OSCC cells, and the expression of this product is significantly elevated in poorly differentiated OSCC cells [32]. DSPP affects ER stress, the UPR and Ca homeostasis [29]. Treatment of OSCC cells with IFN-γ downregulates DSPP and matrix metalloproteinase (MMP-20), leading to disturbances in endoplasmic reticulum (ER) homeostasis, which may cause decreased cell viability, migration and increased apoptosis of OSCC cells [33]. Hypoxia-dependent pathways demonstrating HIF-1α play a key role in the development of OSCCs [34,35]. HIF-1α regulates CD4+ and CD8+ T cells survival, since in HIF-1-knockdown mice, activation of CD4+ and CD8+ T cells together with higher levels of IFN-γ production is observed [36].

2.3. IL-17

As a pro-inflammatory cytokine, IL-17 is primarily secreted by T-helper type 17 cells and neutrophils. Increased IL-17 expression has also been observed in OSCC [37]. IL-17 overexpression in tongue cancer is correlated with cancer progression [38]. Expression of IL-17 protein in the OSCC tissue is associated with worse prognosis, i.e. T classification, metastasis, clinical stages and recurrence. Interestingly the IL-17 protein is prominent at tumor invasion fronts (or budding sites) [4].

2.4. MCP-1/CCL2

Monocyte chemotactic protein 1 (MCP-1/ CCL2) is produced by fibroblasts, epithelial cells, monocytes, and various tumor cells. MCP-1 facilitates the recruitment of monocytes and macrophages into the local inflammatory tissues, where it regulates their functions [39] (see below section on tumor associated macrophage). MCP-1 correlates positively with upregulation of pro-survival signaling by Akt, ERK, and/or STAT, and results in poor long-term survival of HNSCC patients [5].

2.5. IL-1α

The IL-1 family consists of 11 molecules which control inflammation and immunity [40]. Several lines of evidence demonstrate pleiotropic roles of IL-1α in immune regulation in tumor milieu surrounding OSCCs. In OSCC tissues, IL-1α affects CAF or fibroblasts to produce C-C motif ligand (CCL) 7, C-X-C motif ligand (CXCL)1, IL-8 and CCL2, which promote motility and invasion of tumor cells as well as macrophages [41–44]. In HNSCC patients, significant correlation between IL-1α expression and development of distant metastasis has been reported [45].

Immunosuppressive function of IL-1α via CAF has been reported in the tumor milieu of melanomas harboring BRAF (V600E) oncogene, by which the expression of IL-1α is specifically activated

Table 1
Effects of cytokines upon inflammation and tumor phenotypes.

Cytokines	Inflammaton	Tumor	References
IL-4	anti-	pro-	3, 16, 17, 25
IL-5	anti-	pro-	3, 16,
IL-10	anti-	pro-	3, 16-20, 22-24
TGF-β1	anti-	pro-	3, 17, 18, 21, 22, 24
IFN-γ	pro-	anti-	3, 17, 18, 26-28, 30, 31
IL-17	pro-	pro-	17, 37, 38
MCP-1/CCL2	pro- (recruitment of monocyte)	pro-	5, 39, 44
IL-1α	pro-	pro-	40-45, 48, 49

Promotive (pro-) and antithetic (anti-) effects are denoted.

[46]. In the prostatic carcinoma tissue, IL-1α upregulates TGF-β secretion from mesenchymal stem cells, that is resulting in the suppression of immune cells, then induces the promotion of tumor cells [6].

As we have already reported, the immunosuppressive efficacy of the OSCC milieu in the early stage is developed without reliance on the induction of myeloid derived suppressor cells (MDSCs) [47]. In the early stage, as represented by mouse OSCC, Sq-1979 cells, IL-1α from OSCC cells can functionally enhance immune suppressive activity of mesenchymal stromal cells which are directly contacted with activated spleen cells [48]. In contrast, MDSCs are strongly induced in mice with metastasized, advanced OSCC cells [47]. In fact, IL-1 may specifically contribute to the development of early-stage OSCCs, since IL-1 receptor antagonist (IL1RN) is markedly downregulated in early OSCCs compared to premalignant lesions and advanced OSCCs [49]. The mechanism by which OSCCs differentially utilize immune modulation involving CAFs, MDSCs and several other factors is not fully understood. Among these aspects, IL-1α could be a promoter of motility, invasion and immune suppression in OSCC tissues. However, the function of IL-1α seems to be pleiotropic depending on the tumor cell types. On the other hand, tumor-derived IL-1β promotes tumor cell proliferation [50], or cancer cell invasion [51] in OSCCs; however, to date few reports note this molecule as an immunological modulator of oral malignancy.

Modification of inflammatory and tumoral phenotype by representative cytokines are summarized in Table 1.

3. Immune-checkpoint inhibitor

The regulation of T cell activity generally requires two signals. Firstly, mediation by T cell receptors which specifically recognize peptides presented by major histocompatibility complexes (MHCs) on antigen-presenting cells (APCs), and, secondly, CD28 as a receptor for T cell co-stimulatory molecules (also known as B7 family) ligands located on APCs [52]. The aberrant expression of B7 family molecules by tumor or stromal cells is known to contribute to the suppression of anti-tumor immunity. Among immune checkpoint modulators, PD-L1, FKBP51, B7-H4, B7-H6, ALHD1, B7-H3 and IDO1 are associated with poor OSCC patient prognosis, while CTLA-4, TLT-2, VISTA, PD-L2 and PD-1 seem not to have significant prognostic value [53].

3.1. PD-L1 and PD-L2 expression among the progressive malignancies

Immunological evasion of OSCC cells is strongly affected by the interaction between PD-L1/CD274 /B7-H1 and PD-1/CD279. PD-1 is the first identified as a type-I transmembrane receptor found in a murine T-cell hybridoma undergoing activation-induced cell death (AICD) [54]. The expression of PD-1 is prominent in the exhausted T cells. In several human tumors, a larger numbers of tumor infiltrating lymphocytes (TILs) express PD-1 and are well associated with disabled CD8+ T cell activity [55,56]. High levels of PD-1 expression correlate with increased tumor-infiltrating regulatory T (Treg) cells and reduced effector T cells; therefore, blocking PD-1 by specific antibody could effectively enhance anti-tumor immunity [57].

PD-L1 is a transmembrane glycoprotein belonging to the immunoglobulin (Ig) superfamily, and plays an integral role in the regulation of immune tolerance [58]. It is the main ligand of PD-1 and its expression is found not only on activated T cells, B cells, NK cells, macrophages, dendritic cells and mastocytes, but also on other non-immune cell types including several tumors [59,60]. Peripheral blood of lymph node metastasized (N+) OSCC patients shows significantly higher levels of PD-L1 mRNA than in N0 patients [61]. The mRNA of PD-L2, another ligand for PD1 [62] is also up-regulated in OSCC tissues compared to that of normal oral mucosa [63]. In OSCC tissues, a positive correlation was shown between PD-L1 expression and tumor size, lymph node metastasis and other malignant phenotypes [64,65]. However, among OSCC cells of different grades, PD-L1 expression is lower in high-grade invasive cell lines than in low-grade invasive OSCC cells; and inverse correlation is observed between PD-L1 expression and the degree of epithelial-mesenchymal transition (EMT) [65]. Similar observations have been reported in immunohistochemical analyses, revealing that levels of PD-L1 protein in OSCC cells positively correlate with favorable prognostic factors, i.e., elevated TIL levels, longer overall survival, smaller tumor size and lower lymph node metastasis [66]. These paradoxical observations can be accounted for by the fact that PD-L1 is not only expressed in the tumor cells, but also in stromal cells, i.e., tumor-associated macrophages, dendritic cells (DCs), and CAFs [67,68]. Though PD-L1 expression is lower in high-grade invasive OSCC cells, higher levels of PD-L1 expression in high-grade invasive OSCC tissues could be mainly attributable to stromal cells, for example macrophages and DCs [65].

3.2. Regulation of PD-1/PD-L1 in the tumor microenvironment

Expression of PD-L1 is controlled by extrinsic and intrinsic mechanisms. IL-2, IL-7 and IL-15 directly induce the expression of PD-1 on T cells as well as PD-L1 on APCs [69]. Transcription of PD-L1 can be strongly induced by IFN-γ in tumor cells [70]. TGF-β1 signaling is correlated with PD-L1 downregulation. Furthermore, TLR4-inhibitory peptide suppresses PD-L1 induction on macrophages and DCs co-cultured with mesenchymal-phenotype OSCC cells with a concomitant epithelial mesenchymal transition (EMT)-associated gene regulation [65]. These results suggest that the EMT-induced mechanism is critical for PD-L1 induction. The mediators for this cross talk between advanced OSCC cells and macrophages or DCs on PD-L1 expression should be elucidated.

EBV infection promotes latent membrane protein 1 (LMP1) expression on the membrane of tumor cells, then LMP1 stimulates PD-L1 expression through STAT3, AP-1 and NF-KB signaling pathways [71]. This may promote immunotolerance in the infected cells. MicroRNAs (miRNAs) are single-stranded, noncoding short RNAs that inhibit the expression of genes. Some micro RNAs are correlated with progression of OSCC [72]. High miR-197 expression is tightly correlated with lower overall survival and reduced PD-L1 transcription and TIL in OSCC tissues, demonstrating that PD-L1 expression is regulated by miR-197 in OSCC cells [68].

The phosphatidylinositol-3-OH kinase (PI3K) (also known AKT-mTOR) signaling pathway is essential for both cell growth and survival, and is negatively regulated by a tumor suppressor gene product, phosphatase and tensin homolog (PTEN) [73]. Oncogenic activation of the AKT–mTOR pathway promotes immunological evasion by stimulating expression of PD-L1 in non-small cell lung cancer [74]. PD-L1 is post transcriptionally enhanced after loss of PTEN and activation of the PI3K pathway in glioma [75].

The expression level of PTEN was significantly lower in OSCC specimens when compared with adjacent normal tissues [76,77]. Interestingly, down regulations of PTEN in OSCCs are mediated by non-coding micro RNAs, including miR-221/222, miR-21 and miR-1297 [78–81]. Thus, the PTEN/PD-L1 axis may be a potential target for immune-checkpoint therapy against OSCC.

Hypoxic stress induces several immune suppressive molecules. The binding of HIF-1α to the hypoxia-response element of the PD-L1 promoter may lead to resistance to CTL-mediated cell lysis [82]. TAMs in hypoxic regions could upregulate PD-L1 expression via HIF-1α and induce T-cell suppression [83,84]. Interestingly, in progressive OSCCs, both co-localized HIF-1a and PD-L1 are associated with worse prognosis [85].

4. Tumor associated macrophages

4.1. Specific macrophage polarization

It is known that the majority of malignant tumors contain macrophages as major stromal cells of their tumor microenvironment. Unlike macrophages in normal tissue, TAMs are modified in the tumor milieu, with some losing the ability to phagocytize or present tumor antigens to T-cells [86]. TAMs harbor two distinct phenotypes: one is the conventionally activated (M1) state and the other is the differently activated (M2) state, with these two states representing the extreme polarized phenotypes [87,88]. The M1 polarization state depends on microbial stimulus, represents T helper type 1 (TH1) cytokine profiles and possesses antitumor activity [89]. Interestingly, M1 macrophages were observed to select CD47 negative OSCC cells for phagocytosis, although M2 did not, indicating that the expression of CD47 on OSCC cells could be a marker for evasion from M1 phagocytosis [90]. On the other hand, immune suppressive M2 polarization depends on T helper type 2 (TH2) cytokine profiles [88]. M2 macrophages harbor heterogeneous phenotypes that support tumor progression including invasion, metastasis and immune suppression [91]. Larger numbers of M2 macrophages were closely related to shorter survival times [90]. CD68 is considered to be a pan-macrophage marker, CD163 is an M2 marker and CD11c is an M1 marker [92]. Higher concentrations of CD163 and CD68 in OSCC tissues, were markedly correlated with worse survival rates [92]. Tumor immunology is strongly associated with lymph node metastasis. Immune tolerance in local lymph nodes is a prerequisite for lymph node metastasis. In higher grade OSCC patients, a shift of macrophage polarization from M1 to M2 occurs even in the sinuses of unmetastasized lymph nodes [93,94]. This immunological tolerance is associated with high galectin 3 expression in tumor-free lymph nodes [95]. In higher grade OSCCs, TAMs are further subdivided; CD163+CD204+ TAMs strongly produce IL-10 and PD-L1 and also reduce CD3+ T cells in comparison with CD163+CD204- and CD163-CD204+ TAMs. CD163+CD204+ TAMs negatively correlate with the population of activated (CD25+) T cells and 5-year progression-free survival [96].

4.2. Crosstalk among cancer and stromal cells

Crosstalk between TAMs and tumor cells is thought to play an important role in OSCC. Increasing expression of kinesin family member 4A (Kif4A) and high infiltration of M2 macrophages in both OSCC and macrophages, causing the overproduction of chemokine C—C motif ligand 2 (CCL2/ MCP-1) and CCR, have been correlated with greater tumor size and poor prognosis [97]. Notably, CCL2 promotes chemotaxis of M0 or M2 macrophages and induces M2 phenotype polarization [98]. Therefore, the Kif4A-CCL2 /CCR2-macrophage axis could be accounted as a novel therapeutic target. MCP-1 mediates osteoclastogenesis of mononuclear cells, and promotes osteoclast development in cancers [99]. Furthermore, a deletion mutant of MCP-1 inhibits osteoclast differentiation of stromal monocytes and reduces bone invasion of OSCC cells [14]. Overexpression of leukocyte-associated immunoglobulin-like receptor (LAIR)-1 in OSCC cells is associated with advanced pathological grade and correlates with immune suppressive features of the tumor tissue; in fact, the expression is tightly associated with immune suppressive markers of TAM and MDSC, i.e., CD11b, CD163, CD33, CD68, two immune checkpoints (B7-H3 and VISTA) and indoleamine 2,3-dioxygenase (IDO) [100]. OSCC suppresses antitumor immunity by the induction of PD-L1 on M2 type TAMs; the IL-10 concentration in the tumor microenvironment directly correlates with the PD-L1 level on the TAMs [101]. Interestingly, TLR4-inhibitory peptide successfully suppressed PD-L1 upregulation on TAMs co-cultured with OSCC cells, suggesting that some EMT-inducing tumor antigen(s) is critical for PD-L1 induction via TLR4 on the cells [65].

Crosstalk with CAFs is also essential to develop TAMs. CAFs are classified into 3 grades depending on the expression of alpha smooth muscle actin, and the CAFs in the higher grade promote the development of CD163 positive macrophages, and promote poor prognosis in OSCC tissues [102]. CAFs educate macrophage progenitor cells via TGF-β1, IL-10 and ARG1, then induce the protumoral TAMs in the tumor immunosuppressive milieu [103].

5. Therapeutic approaches

In the development and progression of OSCCs, immune system plays very important roles. Here we report potential cancer immunotherapies targeting the molecules in the tumor microenvironment including tumor-specific molecules, immune check point inhibitor or TAMs.

5.1. Targeting tumor-specific molecules

Clinical trials with an IL-1α-blocking monoclonal antibody has shown promising outcomes in patients with advanced cancers [9,104]. MABp1 (XBiotech Inc.) is a naturally occurring human IL-1α neutralizing antibody. Monotherapy with MABp1 improved survival rate and other clinical improvements in patients with advanced non-small cell lung cancer, ovarian cancer and other refractory cancers [9,105].

Melanoma-associated antigen (MAGE) genes are expressed in a variety of neoplastic lesions including breast, lung and oral cancers, and are considered to be potential targets of vaccination for treatment [106–108]. This gene family is classified into acidic subgroups, MAGE-A, -B, -C, and a basic MAGE-D [109]. The expression of MAGED4B is elevated in more than 50% of OSCC tissues. Interestingly, the overexpression of this molecule promotes cell migration, cell growth, and conferred resistance to apoptosis [110]. Synthetic peptides of MAGED4B have binding affinity against the MHC-Class I molecules and enhacned IFN-γ and Granzyme-B production in blood cells from OSCC patients, demonstrating that they are immunogenic; furthermore the peptide-pulsed dendritic cells enhance T-cell cytotoxicity against MAGED4B-overexpressing OSCC cell lines, demonstrating that they could be promising candidates of vaccination for OSCC treatment [10]. In OSCCs, the expression of MAGE A subfamilies A1-A12 is significantly associated with their malignancy and could be potential targets for cancer immunotherapy [111].

5.2. Targeting immune checkpoint inhibitors

Recently, the most promising approach in activating therapeutic antitumor immunity is the blockade of immune checkpoints. In clinical trials, therapeutic antibodies against PD-1 [112], PD-L1

[113], and in combination against both cytotoxic T-lymphocyte-associated protein (CTLA)-4 and PD-L1 [114] have been shown to extend the survival of many cancer patients. A clinical trial in phase I study of OSCC patients using novel anti-PD-1 antibody is also reported [115]. Expression of PD-L1 by tumor cells and immune infiltrates is markedly associated with the expression of PD-1 on lymphocytes, as well as responses to anti-PD-1 therapy [116], or anti-PD-L1 therapy [117]. The PD-1 blockade is accompanied by induction of IFN-γ, STAT-1 activation and the production of the T cell effector granzyme B. This activity prevents the development of carcinogen-induced oral premalignant lesions [118].

As a novel approach, exosomal delivery of miRNA targeting immune checkpoint inhibitor has been reported. γδ T cell-derived extracellular vesicles (γδTDEs) delivering miR-138 efficiently targets PD-1 and CTLA-4 in CD8+ T cells, then activates them to achieve synergistic therapeutic effects on OSCC [119].

5.3. Targeting TAMs

Manipulating polarization of pro-tumorigenic M2 to the anti-tumor M1 macrophage phenotype provides a new therapeutic approach. Stimulation of TLR3/Toll-IL-1 receptor domain-containing adaptor molecule 1 using Poly (I:C) immediately enhances the secretion of several proinflammatory cytokines, including IL-1β, and accelerates M1 macrophage polarization [11]. The TLR3 agonist Poly(I:C) is effective in triggering the cytotoxic activity of tumor conditioned macrophage against cancer cells [120].

Another approach targeting macrophage polarization could be challenged using bisphosphonates. Bisphosphonates have cytotoxic potential on myeloid cells and are useful for the treatment of osteoporosis and prevention of bone metastases. Osteoclast stimulatory transmembrane protein could induce a phenotypic switch in macrophage polarization [121]. Zoledronic acid promotes TLR-4-mediated M1 macrophage polarization [122]. Several strategies aiming at re-education and/or depletion of M2-like protumoral TAM, including drug delivery of bisphosphonates, are reported [12].

Macrophage colony-stimulating factor (CSF-1) is a potential target in preventing macrophage recruitment. In animal models, CSF-1 receptor inhibition strongly reduces tumor-associated macrophages and increase the CD8+/CD4+ T cell ratio [13]. The dominant-negative deletion-mutant of MCP-1 inhibits osteoclast differentiation of monocyte and reduces the bone invasion by OSCC cells *in vivo* [14]. The blockade of MCP-1 could also prevent M2 phenotype polarization of macrophages.

5.4. For improvement of surgical treatment

Surgical treatment is still the most effective method of removing primary and metastasized OSCCs. Anesthetic choice may affect immune regulation and prognostic implications. Lydokine increases NK cell activity. Anesthetics using propofol decrease neuroendocrine response, and may cause less immunosuppression when compared to volatile anesthetics and opioids [123]. In general, anesthetics reduce IL-1, while enhancing IL-10 levels [123]. They may modulate surgical stress by acting on the central nervous system, affecting catecholamines and glucocorticoids [124].

6. Conclusion

There are several immune modulators, including cytokines, immune-check point inhibitors, and cellular components in the TME of OSCC. These molecules and cellular components are regulated by extrinsic and intrinsic mechanisms among the TME. There are several therapeutic approaches targeting these activities using specific antibodies, miRNAs and T cell-derived extracellular vesicles. As a novel therapeutic approach, alternative differentiation of TAM could be induced using bisphosphonates. However, when considering more fine tuning of therapeutic approaches, pro-tumoral immune components are not fully understood. Linking of anesthesiology and immunology may provide new therapeutic advantages. However, the mechanisms by which anesthetic drugs affect the immune system remains unclear.

Further elucidation of the regulatory mechanisms consist of tumor-host interactions could identify important therapeutic targets in OSCC development.

Conflict of interest

None.

Acknowledgements

This work was financially supported in part by the Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (KAKENHI) Grant Number (JP17K11891).

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