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REVIEW

Personalized Targeted Therapeutic Strategies against Oral Squamous Cell Carcinoma. An Evidence-Based Review of Literature

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Abstract: Oral squamous cell carcinoma (OSCC) is the most common type of malignant tumor in the head and neck, with a poor prognosis mainly due to recurrence and metastasis. Classical treatment modalities for OSCC like surgery and radiotherapy have difficulties in dealing with metastatic tumors, and together with chemotherapy, they have major problems related to non-specific cell death. Molecular targeted therapies offer solutions to these problems through not only potentially maximizing the anticancer efficacy but also minimizing the treatment-related toxicity. Among them, the receptor-mediated targeted delivery of anticancer therapeutics remains the most promising one. As OSCC exhibits a heterogeneous nature, selecting the appropriate receptors for targeting is the prerequisite. Hence, we reviewed the OSCC-associated receptors previously used in targeted therapy, focused on their biochemical characteristics and expression patterns, and discussed the application potential in personalized targeted therapy of OSCC. We hope that a better comprehension of this subject will help to provide the fundamental information for OSCC personalized therapeutic planning.

Keywords: oral squamous cell carcinoma, receptors, targeted therapy, active targeting, drug delivery

Introduction

Oral squamous cell carcinoma (OSCC), originating from the mucosa of the tongue, buccal, palate, floor of the mouth, alveolar ridge, and other parts of the oral cavity, is the most common malignant tumor in the head and neck. The newest global cancer statistics reported that OSCC accounted for over 370,000 new cancers and 170,000 cases of death.[1] Despite lots of efforts having been put on treatment of OSCC, its five-year survival rate is still no more than 50%. The leading causes for poor prognosis might be correlated to recurrence and metastasis, which could be due to incomplete resection of tumor and neglected metastases.[2,3] Developing more efficient therapeutics is essential for improving prognosis of OSCC.

The principal strategies for OSCC treatment are surgery, chemotherapy, radiotherapy, or a combination of these modalities based on the severity of disease.[4,5] Surgery remains the most efficient treatment for OSCC, while it inevitably damages the functions and aesthetics of the orofacial region.[6] Moreover, together with radiotherapy, they have difficulties in dealing with metastatic tumors.[7] Chemotherapy could inhibit rapidly growing cells including those in metastatic sites via inhibiting cell growth and division.[8,9] However, its selective toxicity is relatively low, and normal cells with enhanced proliferation rates such as the hair follicles, bone marrow and gastrointestinal tract could also be harmed.[10] To alleviate toxicities to normal cells, chemotherapeutics is often used at suboptimal doses, which might lead to the final failure of

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treatment, and even drug resistance and metastatic disease. Therefore, there has been a great pursuit for development of targeted anticancer drugs to increase the selective toxicity in cancer therapy.

At present, two targeted approaches are being explored for improving the selective toxicity. One is developing newer drugs that alter specific signaling pathways of cancer cells.[11,12] For example, bevacizumab, a monoclonal antibody that directly targets vascular endothelial growth factor receptor (VEGFR), suppresses functions of all VEGF-A isoforms and blocks correlated downstream signaling, leading to cell-cycle arrest, apoptosis and anti-angiogenesis.[13] However, researches for these molecular targeted therapies will not be pressed ahead further, as these may cause a series of adverse effects in normal cells that usually distinct from classical cytotoxic chemotherapy.[14] The other emerging one is targeted delivery of anticancer drugs to cancer region, increasing the drug dosages that reach the malignant tissue and avoiding the undesirable side effects to the normal tissue through specific receptors targeting.[15,16] A paradigmatic example is trastuzumab emtansine, an antibody-drug conjugate targeting HER2-positive breast cancer cells and functioning via transporting cytotoxic compound emtansine, which was approved by the US Food and Drug Administration (FDA) in 2013.[17] Thus, in the first place, it is essential to select the appropriate receptors for targeting, especially in OSCC which remains a heterogeneous nature.

Where Do We Stand in Oral Squamous Cell Carcinoma Treatment?

Targeted anticancer therapy generates the concept of personalized cancer therapy, which can be explained as conducting the specific targeted therapy on patients according to their specific molecular characterization of cancer cells and cancer microenvironment, thus promoting clinical outcome. In brief, that is performing the right therapeutics on the right patient at the right time, and has become an irresistible trend in the field of anticancer research.[18,19] A simplified example is that patients with non-small-cell lung cancer (NSCLC) usually respond to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors erlotinib and gefitinib well when they have specific EGFR mutations.[20] During the personalized cancer therapy, the urgent need is to identify biomarkers uniquely expressed or overexpressed in cancer compared to normal tissues, and use them for early detection, prognosis prediction, clinical outcome evaluation, or personalized diagnostic and therapeutic planning.[21–23]

Till now, two kinds of molecular targeted treatment have been approved by FDA for OSCC therapeutics. The first one is EGFR targeted therapy. EGFR is the member of ErbB family of receptor tyrosine kinase. Activated by either its ligands EGF or transforming growth factor-α (TGF-α), EGFR becomes phosphorylated and subsequently activates signal transduction pathways, such as mitogen-activated protein kinase (MAPK), phosphatidylinositol 3 kinase (PI3K)/ Akt pathway, and Src pathway. These processes play crucial roles in a variety of cellular behaviors especially growth and migration, in both normal and neoplastic cells.[24] Studies have reported that EGFR activity is increased in a large majority of cancers, such as NSCLC, breast, colorectal, pancreatic and head and neck cancer,[25] and almost all premalignant and malignant lesions of oral cavity are witnessed with EGFR overexpression.[26,27] In 2006, a chimeric monoclonal antibody cetuximab which competitively inhibits binding of EGFR to its ligands was approved by FDA for the treatment of OSCC under certain conditions.[28,29] However, the clinical outcome has not been remarkably improved as the median survival time of those administered with cetuximab plus chemotherapy increased marginally from 7.4 to 10.1 months compared to those with chemotherapy alone.[30]

Another recently approved targeted therapeutics for OSCC is the immune checkpoint blockade-based anti-PD1 therapy. In cancer immune microenvironment, the immune checkpoint programmed cell death 1 (PD1) expressed on the surface of $CD8^+$ T cells and its ligand programmed cell death ligand 1 (PDL1) expressed on the surface of cancer cells and associated stromal cells, act as accomplices to blunt the anticancer effects of $CD8^+$ T cells. Anti-PD1 therapy blocks the interaction of PD1/PDL1, thus abolishing the inhibition of $CD8^+$ T cells and promoting the immune normalization.[31–33] In OSCC, anti-PD1 therapy using pembrolizumab and nivolumab was approved by FDA in 2016.[34,35] Although there was a statistically significant improvement in overall survival in patients with metastatic and recurrent head and neck squamous cell carcinoma (HNSCC) when administered with pembrolizumab plus chemotherapy, compared to those administered with cetuximab plus chemotherapy as reported by a recent clinical trial, only a fraction of patients responded to anti-PD1 therapy and toxicities existed in organs like lung, which also express PDL1.[36] Hence, existing targeted therapies remain limited for OSCC patients, and other targeting strategies need to be explored.

How Strategic is Targeting Specific Oral Squamous Cell Carcinoma Cell Receptors?

As introduced before, receptors- or antigens-mediated targeted delivery of anticancer drugs to cancer cells or cancer-associated regions will be a rapidly growing field of research and a source of newer anticancer products for clinical use. Herein, searching for appropriate targeting receptors is regarded as the key factor to this targeted anticancer therapy, except for selecting cytotoxic drugs, drug carriers, etc.[37] OSCC, as well as other types of cancer, exhibits various surface receptors. These receptors might have unique expressions indicating that they are only expressed or functional in tumor regions, or have evidently higher expressions in tumor regions compared to those in normal sites, thus exhibiting the possibility of being utilized for mediating drug delivery. Next, we will review the OSCC cell receptors that have been previously targeted in published researches concerning targeted delivery of anticancer therapeutics to OSCC region, focusing on their biochemical characteristics, expression patterns, and targeting strategies (Figure 1, Table 1).

Targeting Receptors with Cancer Specific Expression

Urokinase-Type Plasminogen Activator Receptor (uPAR)

uPAR is a cell membrane protein important for cancer invasion, angiogenesis and metastasis of various cancers, including OSCC.[38–40] The main mechanism underlying these functions is uPAR's binding to its ligand urokinase-type plasminogen activator (uPA) in cell membrane of migrating cells, thus mediating the extracellular matrix remodeling.[41] Additionally, uPAR activates many intracellular pathways through interaction with transmembrane receptors, and thus induces malignant behaviors of cancer cells.[42] uPAR expression is usually cancer specific, and in most cases, its high expression correlates with increased aggressiveness, thus conferring it the ability of being as a promising diagnostic, therapeutic and prognostic biomarker.[43,44] For example, in breast cancer, bladder cancer, and prostate cancer, a uPAR-targeting peptide was used for tumor imaging in a Phase I clinical trial.[45]

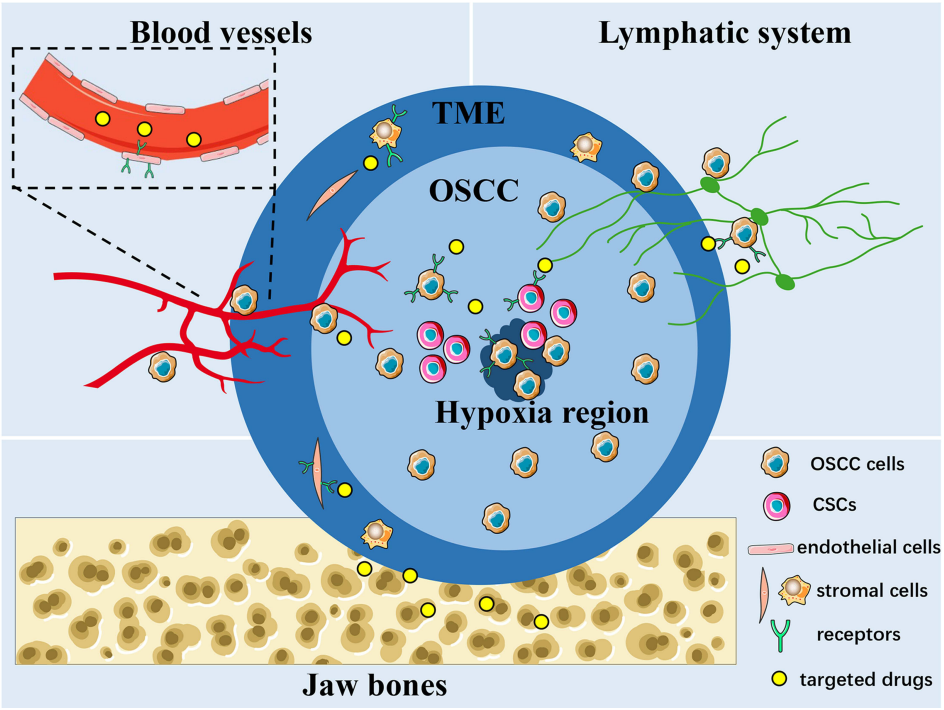

Figure 1 Schematic illustration of target receptors in OSCC and OSCC-associated regions for anticancer drugs delivery.
Notes: Except for targeting receptors expressed on OSCC cells, biomarkers of OSCC-associated regions can also be targeted for anticancer drugs delivery, such as CSCs, cancer cells in hypoxia regions, stromal cells, blood endothelial cells, metastatic lymph nodes, and jaw bones adjacent to oral malignancies.
Abbreviations: CSCs, cancer stem cells; OSCC, oral squamous cell carcinoma; TME, tumor microenvironment.

Table 1 OSCC-Associated Receptors That Have Been Used in Targeted Therapy

Classification	Receptors	Representative Ligands in OSCC Therapy	Representative Targets	Ref
Cancer specific expression	uPAR	AE105	Cancer cells and cancer-associated stroma cells	[50, 51]
	αvβ6	RGD, anti-αvβ6 mAb	Epithelial cancer cells	[57, 58]
	Folate receptors	Folic acid	Cancer cells	[62–65]
Cancer overexpression	EGFR	Cetuximab	Cancer cells and cells from dysplasia, normal epithelium and normal salivary gland	[66–70]
	PDL1	Anti-PDL1 Ab	Cancer cells	[72]
	c-Met	cMBP	Solid cancer cells especially OSCC cells	[78, 79]
	GRPR	Bombesin, TM1	Cancer cells	[85, 86]
	PDPN	Anti-PDPN Ab	Cancer cells and lymphatic endothelial cells	[92]
	Sigma receptors	Anisamide	Cancer cells	[97, 98]
	TfR1	Ferritin heavy chain	Cancer cells and activating lymphocytes and osteoclasts	[101, 102]
	αvβ3	RGD	Cancer cells, osteoclasts and vascular endothelial cells	[109–111]
	SPARC	HSA	Cancer cells and CAFs in some cancers including OSCC	[114]
	LDLR	Anti-LDLR Ab	OSCC cells in hypoxia regions	[116]
	CD44	Anti-CD44 Ab, hyaluronic acid	Cancer stem cells	[118, 119]
	P-selectin	Fucoidan	Vascular endothelial cells of various cancers	[121]
	CXCR4	SDF-1	Metastatic lymph nodes	[122]

Abbreviations: CAFs, cancer-associated fibroblasts; c-Met, mesenchymal-epithelial transition factor; cMBP, cMet-binding peptide; CXCR4, CXC chemokine receptor 4; EGFR, epidermal growth factor receptor; GRPR, gastrin-releasing peptide receptor; HSA, human serum albumin; LDLR, low-density lipoprotein receptor; mAb, monoclonal antibody; OSCC, oral squamous cell carcinoma; PDPN, podoplanin; PDL1, programmed cell death ligand 1; RGD, Arg-Gly-Asp tripeptide; SDF-1, stromal cell-derived factor-1; SPARC, Secreted Protein Acidic and Rich in Cysteine; TfR1, transferrin receptor 1; uPAR, urokinase-type plasminogen activator receptor.

In OSCC, it has been reported that enhanced uPAR expression was associated with cancer invasion, lymph node metastasis, high recurrence rate and significant reduction in overall survival of OSCC patients. Also, uPAR is highly cancer specific in OSCC, where it is expressed on OSCC cells and stromal cells like fibroblasts and inflammatory cells in the cancer microenvironment, and almost absent in normal cells (Figure 2A). Moreover, uPAR has been found to have strong expressions at the invasive front of OSCC.[46,47] The early investigation for clinical potential of uPAR in OSCC is tumor imaging and intraoperative guidance.[45,48,49] For example, Christensen et al have developed a uPAR-targeting fluorescent agent and a PET agent using conjugates of AE105 (a ligand for uPAR) and fluorophore ICG or radioactive isotope ^{64}Cu, for fluorescence-guided tumor resection or preoperative tumor imaging of OSCC and the metastatic lymph nodes (Figure 2B).[50] In addition, Zuo et al constructed therapeutic drugs-encapsulated dendritic mesoporous silica nanoparticles (NPs) decorated with AE105 targeting uPAR, and applied them for photonic hyperthermal and sonodynamic targeted therapy of OSCC.[51]

Integrin αvβ6

The integrin αvβ6 is composed of an αv subunit and a β6 subunit, both of which contain three domains: the cytoplasmic domain, the extracellular domain, and the transmembrane domain. The extracellular domains recognize and adhere to specific ligand which contains the Arg-Gly-Asp (RGD) motif, while the cytoplasmic domain of β6 subunit transmits

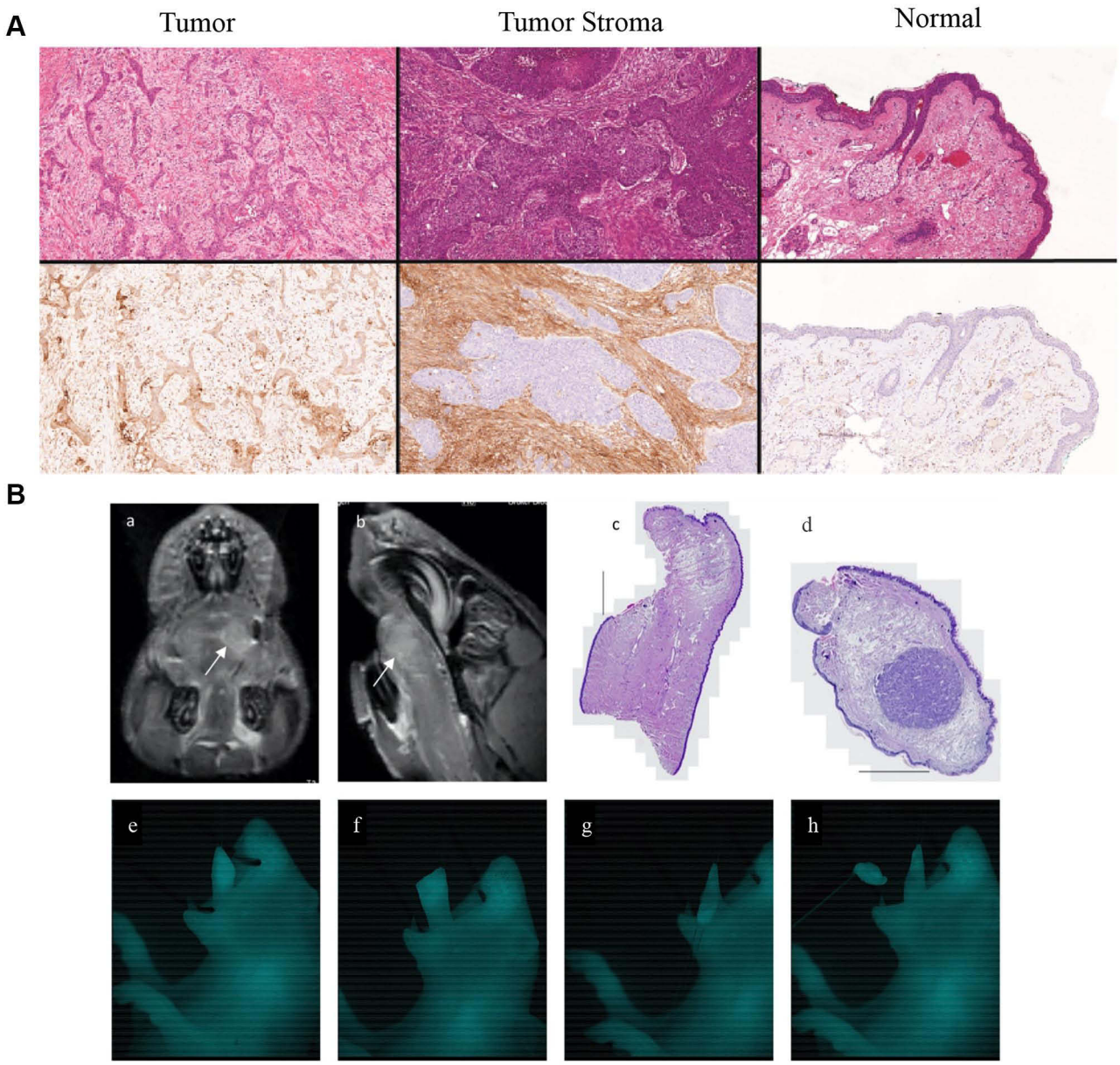

Figure 2 The expression pattern and targeting efficiency of uPAR in OSCC.
Notes: (**A**) Images of H&E and uPAR immunohistochemical staining showing the results of uPAR expression in tumor (left), tumor stroma (middle) and normal squamous epithelium. Reproduced from Baart VM, van Duijn C, van Egmond SL et al. EGFR and αvβ6 as promising targets for molecular imaging of cutaneous and mucosal squamous cell carcinoma of the head and neck region. *Cancers*. 2020;12(6):1474. Creative Commons Attribution License.[46] (**B**) Fluorescence-guided tumor resection using fluorescence agent ICG-Glu-Glu-AE105 targeting uPAR. Mice with a tumor in the left anterior tongue as shown on preoperative MRI (**a, b**, white arrow indicates tumor). A time sequence fluorescence imaging showing that the tongue was fixed with a suture in the tip of the tongue, and tumor resection was performed guided by real-time optical imaging (**e-h**). H&E staining showing the tongue specimen had a clear resection margin (**c**), and the resection specimen showed a localized tumor, indicating radicality of tumor resection (**d**). Reproduced from Christensen A, Juhl K, Persson M et al uPAR-targeted optical near-infrared (NIR) fluorescence imaging and PET for image-guided surgery in head and neck cancer: proof-of-concept in orthotopic xenograft model. *Oncotarget*. 2017;8(9):15,407–15,419. Creative Commons Attribution License.[50]

various extracellular stimulus to cytoskeleton and vast intracellular signaling pathways.[52,53] As the β6 subunit only binds to αv, it is the β6 subunit that contributes to its epithelial specific expression, and many unique functions of αvβ6 especially in cancer invasion and metastasis.[54] αvβ6 is almost undetectable in normal epithelial cells, while highly expressed in malignant epithelial cancers including OSCC,[55] in which its high expression correlates with invasion and poor prognosis,[56] providing the possibility of using αvβ6 as a promising biomarker for OSCC therapeutics. For example, a study conjugated peptides containing RGD to the surface of NPs and exerted the OSCC-targeting effects by

αvβ6-mediated endocytosis.[57] In addition, Legge and teamworkers constructed an anti-αvβ6 monoclonal antibody-conjugated functional NPs for OSCC targeting, and for further therapy.[58]

Folate Receptor

Folate receptors (FRs) including FRα, FRβ and FRγ, are cell surface glycoproteins that bind folic acid with high affinity. Usually expressed at low levels in most tissues, FRs, especially FRα, have high expressions in numerous cancers including OSCC, in order to meet the dramatically increasing need of rapidly growing cancer cells for folic acid.[59,60] Interestingly, although FRα expression in cancer cells is not cancer specific, we categorize it into this kind of receptors as it localizes at the luminal surface of polarized epithelial cells and is separated from the circulation in nonmalignant situation. However, in malignant situation, FRα is expressed on the cell surface with high densities, becoming easily targeted for cancer therapy.[61] In OSCC, various folic acid-linked NPs have been designed to improve the OSCC targeting efficiency and for gene therapy, drug delivery or photothermal therapy (PTT).[62–65]

Targeting Receptors with Cancer Overexpression

EGFR and PDL1

As the applications of anti-EGFR therapy and PD1/PDL1 blocking therapy have been described previously, the concept using EGFR or PDL1 as the targeting receptor for OSCC therapeutics has also been put forward. EGFR has been found to be highly expressed in a majority of cancers, and up to 90% of HNSCC exhibits overexpressed EGFR. However, EGFR lacks a cancer specific expression. Specimens containing dysplasia, normal epithelium and normal salivary gland tissues also exhibit regular EGFR expressions.[46,47] Studies have already shown the use of EGFR monoclonal antibody such as cetuximab for targeting EGFR on the surface of OSCC cells, and conjugating with contrast agents for the purpose of imaging-guided therapy.[66–68] However, as reported by a phase I clinical trial, normal epithelium and salivary gland tissues outside the OSCC compartment also showed signals with the use of an EGFR targeting imaging agent.[69] Hence, EGFR targeting needs to be improved further. Recently, Wang et al constructed a kind of NPs which exposed the peptide targeting EGFR of OSCC cells in the acidic cancer environment, while sequestered it in the physiological condition, thus improving the problem of cancer non-specific expression of EGFR.[70]

Also, targeting PDL1 has been utilized for receptor-mediated drug delivery in OSCC therapeutics, as PDL1 was reported to be highly expressed in human OSCC tissues when compared with healthy tissues, and its overexpression in OSCC correlated with disease progression and increased tumor infiltrating $CD8^+$ T cells.[71] In this case, a recent study modified a kind of drug-encapsulated NPs with an anti-PDL1 antibody in OSCC targeted therapy, to improve both drug specificity and immune function.[72]

Mesenchymal-Epithelial Transition Factor (c-Met)

c-Met, a member of the tyrosine protein kinase receptor family, is also called the hepatocyte growth factor (HGF) receptor, as it is the only receptor that binds to HGF. As a key transmembrane protein encoded by the proto-oncogene c-MET, it can promote the growth of hepatocytes, and is overexpressed in a broad range of solid cancers to stimulate proliferation, survival, migration, invasion and angiogenesis.[73,74] When compared with other cancers and normal tissues, OSCC cells exhibit highly expressed c-Met.[75] According to an investigation, 90% of HNSCC cell lines and 84% of patient tissues had upregulated c-Met expression, indicating its potential for targeted therapeutics.[76,77] Recently, the main application of targeting c-Met in OSCC is the field of imaging for early diagnosis, intraoperative navigation and prognosis prediction.[78,79]

Gastrin-Releasing Peptide Receptor (GRPR)

GRPR, which binds to GRP with high affinity, has regulatory roles in various parts of the body, such as the brain, the vascular system, intestinal mucosa and the endocrine system. In physiologically normal organs, GRP/GRPR has low concentrations, while in human cancer, it is highly overexpressed and can stimulate cancer growth.[80] Initially, GRPR was found to be overexpressed in prostate cancer and used as a diagnostic tool. Nowadays, more cancers have been

recognized with increased GRPR, and emerging studies have investigated the possibility of targeted diagnosis and therapy using GRPR, such as in breast cancer, gastrointestinal cancer, colorectal cancer, and so on.[81–83] In OSCC, Lango et al have reported that GRPR expression was six times higher than that in normal tissues, and four times higher than that in adjacent normal epithelial tissues.[84] Furthermore, studies focusing on near-infrared fluorescent imaging of OSCC utilized GRPR targeting, and results showed that it's available in intraoperative surgical margin decision and metastatic lymph node detection.[85,86]

Podoplanin (PDPN)

PDPN is a small mucin-type transmembrane protein, which has a majority of physiological and pathological effects including regulation of organ development, cell motility, tumorigenesis and metastasis.[87] PDPN is expressed in a variety of normal cells, but overexpressed in cancer and cancer-associated cells of several cancer types, including squamous cell carcinoma of the lung, head and neck, malignant mesothelioma, and brain tumors. In addition, PDPN is a specific marker of lymphatic vessels, and increased PDPN correlates with cancer lymphangiogenesis and migration of cancer cells into the lymphatic system.[88,89] Thus, it is clear that PDPN overexpression plays a critical role in cancer progression and metastasis. In OSCC, studies have reported that PDPN was upregulated and associated with malignant phenotype.[90,91] Liu et al established a multifunctional gold nanoplatform conjugated with anti-PDPN antibody and anticancer drug Dox, to actively target OSCC for chemo/photothermal therapy.[92]

Sigma Receptors

Sigma receptors, including sigma-1 and sigma-2, are a unique class of membrane proteins ubiquitously expressed and highly conserved throughout the mammalian body, indicating their important roles in cellular function.[93] Encoded from different genes, sigma-1 receptor has been detected in plasma membrane and membranes of endoplasmic reticulum and mitochondria of various organs, and has evidently high expressions in embryonic stem cells during all stages of embryogenesis.[94] Sigma-2 receptor is expressed in the central nervous system, gastrointestinal tract, kidney, liver and heart, with lower expression levels than sigma-1.[95] Overexpression of sigma receptors is observed in various cancers, including NSCLC, breast cancer, melanoma, and so on, with a similar subcellular localization, suggesting their critical roles in both caspase-dependent and caspase-independent cell death pathways.[96] As reported by recent studies, sigma receptors were highly expressed in OSCC tissues. Modifying anisamide on the outer-leaflet of certain NPs has been developed for actively targeting sigma receptors and then transporting agents like siRNA to the OSCC cells[97,98]

Transferrin Receptor 1 (TfR1)

TfR1, a homodimer expressed in the cell membrane, binds to transferrin (Tf)-bound iron and transports it as the complex through the clathrin-mediated endocytosis. TfR1 expression depends on the cellular iron status. It increases in iron-deficient cellular context, while decreases in the presence of excess iron.[99] Rapidly proliferating cells and energy-requiring cells, such as cancer cells, activating lymphocytes and osteoclasts, exhibit high expressions of TfR1, due to the fast-growing need for iron. Emerging studies have reported that TfR1 showed specific overexpression in a wide number of cancers, and up to 100 times higher than that in normal tissues.[100] Hence, targeting TfR1 for cancer diagnosis and treatment has attracted extensive attention. Damiani et al have successfully developed a human ferritin heavy chain-based carriers which can actively target TfR1 on the surface of OSCC cells, and be freely internalized as a complex for further therapy.[101,102]

Integrin αvβ3

The integrin αvβ3, composed of an αv subunit and a β3 subunit, is an integrin essential for angiogenesis and tumor cell biology. The same as αvβ6, αvβ3 is one of the eight integrins that can recognize peptides containing the RGD sequence and facilitate extracellular matrix proteins-integrins interaction.[103] Rapidly dividing cells including cancer cells and certain nonmalignant cells especially osteoclasts and endothelial cells of blood vessels, express large amounts of αvβ3, whereas quiescent cells usually have little or no expressions.[104] Moreover, it has been reported that smooth muscle cells, skeleton muscle myoblasts, platelets and activated macrophages contain functional αvβ3 expressions, and the

normal colon, brain, salivary gland and thyroid gland express quite low, but detectable levels of αvβ3.[104,105] Thus, αvβ3 is important for not only malignant behaviors of cancer cells, but also some physiological functions maintaining. In OSCC, αvβ3 was reported to be expressed solely on the neovasculature of tumors using RGD-based tracers specific for αvβ3.[106,107] However, Lobeek et al identified that OSCC with highly keratinizing phenotype also showed αvβ3 expression on cancer cells using[68] Ga-RGD PET/CT imaging, while αvβ3 expressed at low levels in metastatic lesions as compared with primary OSCC tissues.[108] Researchers usually modified multi-functional nanoplatforms with RGD containing peptides to actively target αvβ3 for OSCC therapeutics,[109–111] indicating its potential role in targeted therapy.

Secreted Protein Acidic and Rich in Cysteine (SPARC)

SPARC, also termed as osteonectin, is an extracellular matrix glycoprotein first isolated as the main non-collagenous component of bone, and induces calcium deposition after binding to collagen. Furthermore, SPARC has been investigated to be expressed by a variety of tissues undergoing repair or remodeling due to wound healing, disease, or natural process.[112] In cancer microenvironment, SPARC exhibits diverse functions depending on the specific cancer type. Some types of cancer have high levels of SPARC expression and this high expression correlates with disease progression and poor prognosis, while in some other types of cancer, SPARC acts as a tumor suppressor.[113] In OSCC, SPARC reveals higher expressions in tumor tissues especially in cancer cells and cancer-associated fibroblasts (CAFs) than that in normal tissues.[114,115] A study used human serum albumin (HSA) as a nanocarrier to actively target SPARC expressed on OSCC cells and CAFs, to exert PTT/photodynamic therapy (PDT)/chemotherapy after SPARC-mediated transcytosis of NPs and further release of functional agents.[114]

How Strategic is Targeting Oral Squamous Cell Carcinoma-Associated Microenvironment Biomarkers?

Except for targeting receptors mainly expressed on cancer cells, biomarkers of OSCC-associated regions can also be targeted for personalized therapeutics, in order to increase sensitivity to classical therapeutic strategies, prevent cancer recurrence and metastasis, and enhance overall treatment efficacy. For example, modifying the surface of multifunctional NPs with antibodies against low-density lipoprotein receptor (LDLR), which was reported to be a specific OSCC biomarker in hypoxia regions, has been proved to successfully target OSCC and exert tumoricidal effects using PDT/PTT and chemotherapeutic agents.[116] As the hypoxia region, which means the core area of tumors, has a close relationship with chemoresistance, actively targeting this region might be helpful for preventing chemoresistance-induced treatment failure.[117] Moreover, cancer stem cells (CSCs), a group of cancer cells capable of self-renewal and both initiating tumorigenesis and promoting metastasis, are also one of the leading causes of resistance to chemotherapy and radiotherapy. Su's research used the anti-CD44 antibody-modified superparamagnetic iron oxide NPs to target CD44-overexpressed CSCs in OSCC, and kill them under an alternating magnetic field-induced hyperthermia.[118] Similar study exists using hyaluronic acid, which is one of the ligands of CD44, for CSCs targeted therapy in OSCC.[119]

Tumor vasculature and metastatic lymph nodes of OSCC are also the essential targets for therapy, as OSCC is a stroma-rich tumor and metastasize mainly through the lymphatic system.[120] P-selectin, a cell adhesion molecule overexpressed in the vasculature of several cancers including OSCC, was targeted by fucoidan-based NPs for further delivery of anticancer agents.[121] Another study prepared a stromal cell-derived factor-1 (SDF-1)-modified nanosystem to co-deliver chemotherapeutic drug DOX and PTT photosensitizer ICG, and actively targeted CXC chemokine receptor 4 (CXCR4)-expressed metastatic lymph nodes using SDF-1′s binding to CXCR4, for synergistic PTT/chemotherapy in metastatic OSCC and cutting off the metastasis pathway.[122]

Furthermore, preventing bone invasion is a special aspect in OSCC targeted therapeutics, as jaw bones' close anatomical relationship with oral malignancies.[123] In such case, researchers have designed a delicate biomimetic nanoparticle using the HNSCC and red blood cell membrane hybrid exterior shell with PTT agents containing inside, and then modified with the octapeptide (Asp8) which has high binding affinities to hydroxyapatite, for exerting tumor and bone dual targeting effects.[124]

What are Other Active Targeting Strategies in Oral Squamous Cell Carcinoma?

In addition to the already known receptors or biomarkers-mediated drug delivery, other active targeting strategies also exist. For example, researchers isolated a novel peptide HN-1 from an M13 single-stranded phage-based random peptide-display library when using human HNSCC cells to allow endocytosis to occur. HN-1, a 12-amino acid peptide, can specifically bind to and be efficiently internalized into HNSCC cells, but not normal cells or other types of cancer cells, indicating that HN-1 uptake does not occur ubiquitously.[125] Since then, various studies have used HN-1 to conjugate with anticancer drugs or tumor imaging agents for HNSCC-targeted therapeutics in vitro and in vivo.[126,127] In our previous study, HN-1 also showed a significantly enhanced ability to mediate cellular uptakes of nanoparticles.[128] However, although scientists considered that HN-1 may exert this targeting effect through specific interaction with a cellular receptor, the exact receptor is currently not known and requires further analysis. Additionally, studies also utilized cancer cell membrane-camouflaged biomimetic NPs to enhance the specific targeting capacities to cancer cells.[129] Moreover, as OSCC exhibits upregulated macropinocytosis, an endocytotic, nutrient-scavenging pathway that promotes albumin internalization into cells, therapeutic agents bound to albumin could also selectively target OSCC cells, except for via the SPARC receptor.[130]

The Future Perspectives

Exploring the molecular biology of cancer cells for more effective targeted therapeutics is an unavoidable trend in the winding way of tackling cancer, and selecting the tumor-specific biomarkers remains the prerequisite. In this review, receptors or biomarkers that were utilized for targeted treatments of OSCC were summarized. These receptors are either uniquely expressed or overexpressed in OSCC or OSCC-associated regions. However, several problems exist concerning the current literatures of OSCC targeted therapy. Firstly, most studies utilized generally the same cell lines to investigate the efficiency of receptor-mediated drug delivery to OSCC regions. Although the results were promising turned out, they still do not fit the reality very well as OSCC exhibits a heterogeneous nature and the specific chosen receptors shall be different and dependent on patients with distinct risk habits and anatomical sites where OSCC arises. Additionally, with the development of nanotechnology, receptors-mediated active targeting strategy modified in nanosystem has attracted great interests in the field of oncological research.[131,132] On one hand, the nanoparticle itself exhibits the passive targeting effect, namely the enhanced permeability and retention (EPR) effect due to its small size.[133] On the other hand, receptors or other factors-mediated active targeting strategies reviewed above could increase specificity and uptake efficiency, and overcome the multiple-drug resistance after initial accumulation, since EPR effect is not taken place in some hypovascular cancers, and permeability of new blood vessels could vary in a single cancer.[134–136] However, limitations are that no nanoparticles with active targeting strategies have gained the FDA approval to date, and only a few anticancer drugs conjugated with active targeting agents have been developed for clinical use in cancer therapeutics except for OSCC.[137]

On the positive side, summarizing the target receptors in OSCC personalized therapy and studying their biochemical characteristics and expression patterns could undoubtedly provide basic and valuable information for further clinical research and application. Currently, emerging studies have put their efforts to improve the targeting and tumor killing effects by optimizing therapeutic strategy. For example, Chen et al developed a drug delivery nanosystem with bone and OSCC cells dual targeting function, to maximize the treatment efficiency for OSCC with bone invasion.[124] In addition, cancer targeting has been improved by not only targeting molecules highly expressed on cancer cell membranes, but also self-reinforcing of the targeting molecule which has upregulated expression in response to cellular attack via cancer treatments.[138] Furthermore, cancer targeted therapy has been combined with other treatments like phototherapy, sono-dynamic therapy, immune therapy, etc. to completely destroy cancer and compensate for the poor efficiency of single receptor targeting.[139,140] Therefore, investigating the target receptors provides huge potential in further researches and oncological clinical applications including the field of early detection, prognosis prediction, clinical outcome evaluation, and personalized diagnosis and therapies,[141] while great challenges need to be solved with well-designed therapeutic strategy and further proper randomized clinical trials for personalized OSCC therapy.

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Disclosure

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