Chapter 6

The Mechanisms of Proliferation and Energy Metabolism in Oral Cancer

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Additional information is available at the end of the chapter

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Abstract

Human oral squamous cell carcinoma (HOSCC) is the most common head and neck malignant neoplasm. Therapy is generally performed in multidisciplinary approach that used chemotherapy, radiotherapy, and surgery against patients with oral cancer; however, we cannot avoid dysfunction due to its side effects or surgical defects, and it significantly impacts the postoperative quality of life, unfortunately. Therefore, a better understanding of the molecular mechanisms driving oral carcinogenesis may lead to new diagnostic and therapeutic approaches to this disease and improve the prognosis of HOSCC patients. Cancer cells process a fundamental change in its bioenergetics metabolism from normal cells on an altered glucose and lipid metabolism. Recent insights into tumor metabolism have further revealed that oncogenic signaling pathways directly promote metabolic reprogramming to upregulate biosynthesis of lipids, carbohydrates, protein, DNA, and RNA, leading to enhanced growth of tumors. Therefore, targeting cell metabolism has become a novel direction for drug development in oncology. Moreover, molecular mechanisms causing these metabolic changes are just starting to be unraveled. This chapter presents recent findings on molecular markers that have been involved in the mechanisms of proliferation and energy metabolism of oral cancer and in addition provides new perspectives on oral cancer diagnosis and treatments.

Keywords: oral cancer, squamous cell carcinoma (SCC), cell adhesion molecules (CAMs), cytokines, anticancer agents, energy metabolism (glycolysis and lipid)

1. Introduction

Cancer development and fatality are gradually increasing worldwide. It is thought that the reasons are complex but associated with both aging and increase in the population [1, 2].

With the rapid global population increase and aging, the rising significance of cancer as a leading cause of death is partly correlated with a marked decline in mortality rates due to stroke and coronary heart disease in many countries. In addition, tobacco and alcohol consumption are known to be etiologically associated with carcinogenesis. Cancer is both a genetic and progressively systemic disease. In all types of cancer, somatic cells begin to divide uncontrollably and spread into surrounding tissues. Cancer cells can arise almost anywhere in the human body. Normal cells grow and divide according to the body's needs, and when they age or become damaged, they die and are replaced by new cells. However, when cancer arises, this orderly process breaks down: as cellular abnormalities increase, old or damaged cells survive rather than being removed, and new cells form when they are not needed. These extra cells can divide uncontrollably and may form malignant tumors. Although many cancers form solid tumors composed of masses of tissue, cancers of the blood, such as leukemias, generally do not form solid tumors [2–4]. Head and neck cancer is a common neoplasm that encompasses epithelial malignant tumors of the nasopharynx, larynx, and mouth, representing about 6% of all cases and accounting for an estimated over 650,000 new cancer cases and over 350,000 cancer-related deaths worldwide every year [5, 6]. Oral cancer is the most notably frequent cancer type in the head and neck region, squamous cell carcinoma being the most common single entity. Oral cancers comprise two categories: those affecting the oral cavity (lips, inner lips, cheeks, teeth, gums, the anterior two-thirds of the tongue, the floor, and palate) and those affecting the oropharynx (middle region of the throat, including the tonsils and base of the tongue). Such cancers may arise in any location, although there are certain areas that are affected more frequently, such as the tongue and gingiva. These areas represent about 90% of all malignancies of the oral cavity [7, 8]. However, despite significant advances in surgery and chemotherapy over the last few decades [9], oral cancer is still characterized by a poor prognosis and a low survival rate [10]. The 5-year survival rate of those diagnosed is ~ 60%.

In patients diagnosed with oral cancers at an advanced stage, there is a high incidence of metastasis to surrounding tissues, lymph nodes, and distant organs [5]. Metastasis is recognized as a process, whereby genetic instability in the primary tumor accelerates cell heterogeneity, allowing a few metastatic clones to eventually emerge and be positively selected to disseminate cancer at a distance [11]. This is the most annihilating stage of malignancy and the leading cause of cancer-related death. In metastasis, cancer cells break away from the primary cancer, travel through the blood or lymph system, and form new metastatic tumors elsewhere in the body. Each metastatic tumor is the same type of cancer as the primary tumor [12, 13], and the cells of each resemble each other upon microscopic observation. Moreover, they usually share common molecular features, such as the presence of specific genetic changes. It is clear that only a minority of malignant cells participate in the process of metastasis, due to interaction with host tissues and the intrinsic characteristics of the cancer cells themselves; thus, metastasis may imply an escape of these cells from the hostile environment they have created, characterized by features such as hypoxia, inflammation, and immunological surveillance [14–16].

This chapter details recent findings on molecular markers that are involved in the mechanisms of proliferation and energy metabolism of oral cancer and provides new perspectives on its diagnosis and treatments.

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2. Role of cell adhesion molecules (CAMs) in proliferation of oral cancer

CAMs are typically single-pass transmembrane receptors [17] compounded of three stored domains: an intracellular domain that interacts with a transmembrane domain, an extracellular domain, and the cytoskeleton. These domains can interact in several different ways [18]. The first way is through homophilic binding, where the same CAMs bind to each other. They are also capable of heterophilic binding, which means a CAM on one cell will bind to different CAMs on another cell. The third type of binding is that between cells and substrate, where a mutual extracellular ligand binds two different CAMs. There are four major superfamilies, or groups, of CAMs: the immunoglobulin super family of cell adhesion molecules (IgCAMs), the cadherins, the integrins, and the c-type lectin-like domain proteins (CTLDs). Proteoglycans are also believed to be a class of CAMs. One classification system involves distinction between calcium-dependent and calcium-independent CAMs [19]. The Ig-superfamily CAMs and integrins are not dependent on calcium ions, whereas selectins and cadherins are calcium-dependent. In addition, integrins participate in cell-matrix interactions, while other CAM families play some important roles in cell-to-cell interactions [20].

2.1. Neural cell adhesion molecule (NCAM)

Neural cell adhesion molecule (NCAM) is a family of cell surface glycoproteins playing an important role in the development of the nervous system, fasciculation, axonal outgrowth, regulation of cell migration, and branching [21]. NCAM has several isoforms derived from alternative splicing of a single gene [22–24]. In particular, the three major isoforms with molecular weights of 120, 140, and 180 kDa have similar extracellular parts but differ in the disposition of their domains, which are cytoplasmic for the two larger polypeptides [25, 26]. Furthermore, the expression of NCAM is upregulated by transforming growth factor (TGF)-β1 [27–29]. Although NCAM was initially considered to exist only in neural tissue, it has since been observed in the human kidney, lung, fetal muscle, and colon, as well as in elements of the hemopoietic system. Furthermore, it has been described that NCAM is expressed by a variety of human tumors and associated with perineural invasion by various neoplasms, such as gallbladder cancer, melanoma, bile duct cancer, and adenoid cystic carcinoma of the head and neck [30–35]. We have also demonstrated previously that NCAM is sporadically found in the adenoid cystic carcinoma, derived from human submandibular salivary gland, *in vivo* [36]. NCAM is believed to mediate adhesion between cells through a calcium ion-independent homophilic (NCAM-NCAM) binding mechanism and to mediate adhesion between neurons and the extracellular matrix through heterophilic binding (NCAM to another ligand or counter-receptor) [21]. It has been described that exogenously added NCAM can inhibit the proliferation of cultured neonatal astrocytes and of astrocytes responding to a penetrating lesion in the adult rat brain, *in vivo* [37, 38], suggesting that these effects are mediated by homophilic binding to NCAM on the astrocyte membrane.

Adenoid cystic carcinoma (ACC) is a well-known and typical malignant salivary gland tumor. ACCs are biologically aggressive and can bring metastases even when many years have passed

after excision of the primary tumor. Facial paralysis is especially frequent, causing perineural and/or neural invasion. We have attempted to examine the role of NCAM by investigating the effect of anti-NCAM antibody (MAb NCAM) and TGF-β1 in human salivary gland tumor cells. The expression and distribution of NCAM were also investigated in ACC tissues. We further found that apoptotic cell death was induced via a DNA damage signal through the mitochondria, inducing release of cytochrome *c* into the cytoplasm of salivary gland tumor cells [36]. However, MAb NCAM had no effect on human oral squamous cell carcinoma (HOSCC) cell lines, which do not express NCAM. As shown in **Figure 1**, these results indicate that the effect of MAb NCAM is specific to NCAM-expressing tumor cells, such as human salivary gland tumor cells; furthermore, blocking the ability of NCAM through MAb NCAM, as well as the homophilic (NCAM-NCAM) binding mechanism, rather than regulating a signaling pathway of cell proliferation, may in fact induce a negative signal such as apoptosis in human salivary gland tumor cells. In addition, homophilic (NCAM-NCAM) binding may activate multiple signaling pathways that differ among cell types. In view of the fact that NCAM expression on human salivary gland tumor cells is upregulated by TGF-β1, it can be hypothesized that a further homophilic (NCAM-NCAM) binding mechanism may be activated and that consequently the proliferative activity of HSG cells may also be upregulated by TGF-β1-mediated NCAM activity (**Figure 2**).

On the other hand, cimetidine, the most studied histamine type-2 receptor (H2R) antagonist used clinically, is commonly prescribed to treat gastroesophageal reflux disease as well as

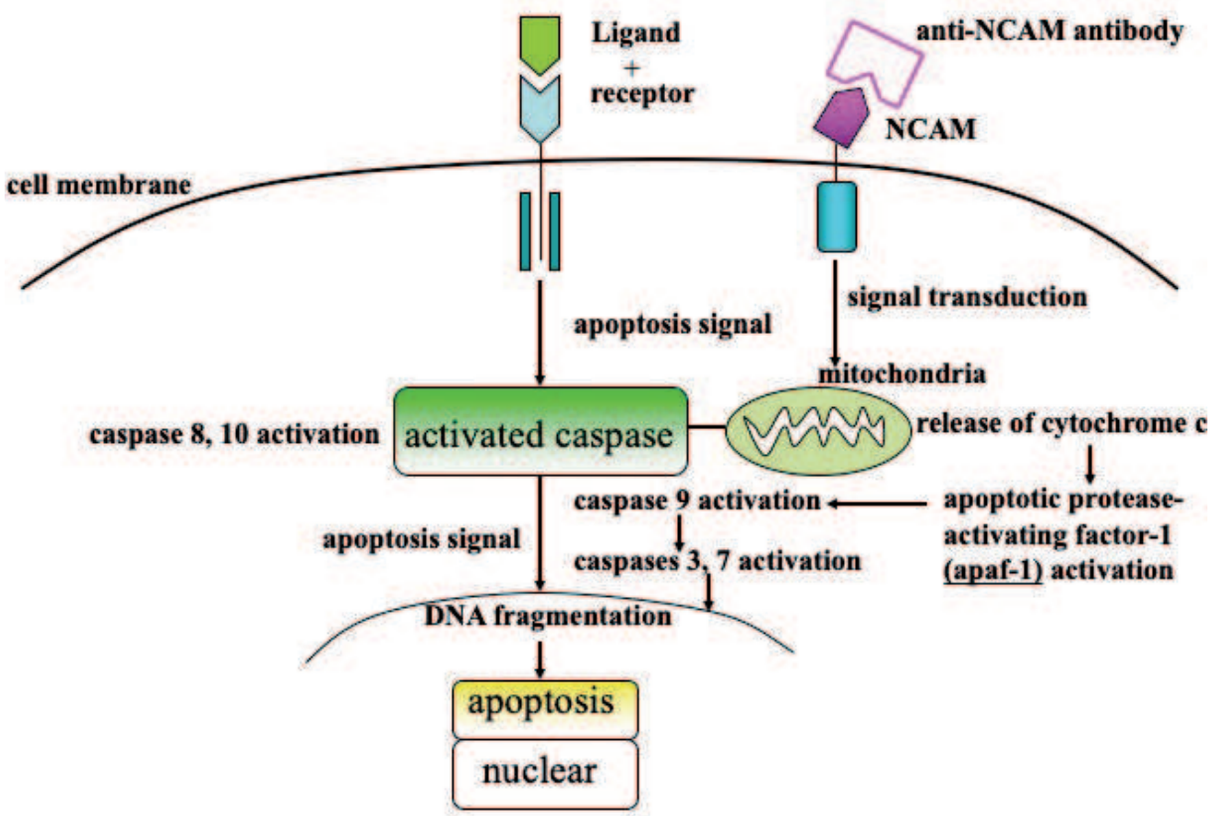

Figure 1. Schematic representation of MAb NCAM-induced apoptotic signal transduction pathways via the DNA damage signal through the mitochondria involved in apaf-1 and caspase activation in NCAM-expressing cells.

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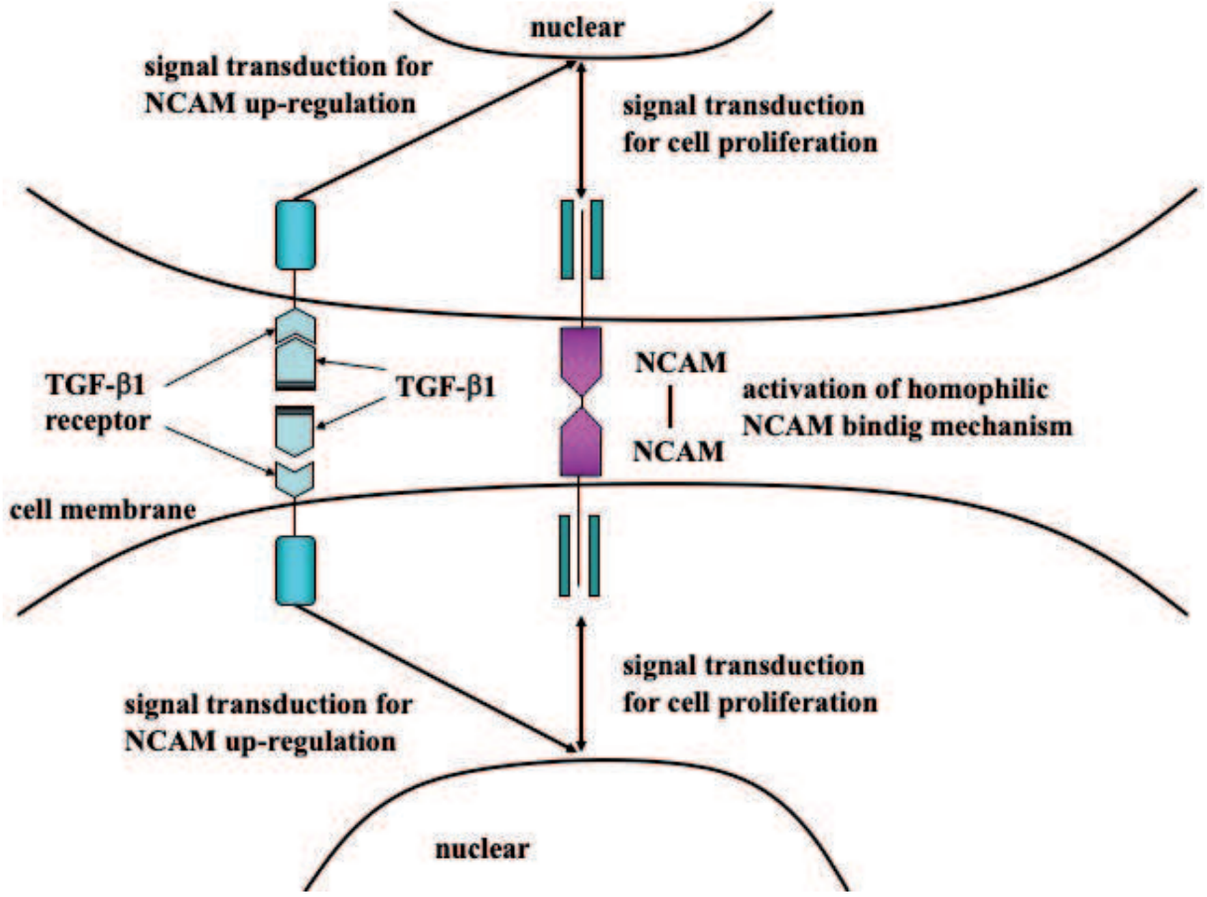

Figure 2. Schematic representation of TGF-β1-induced upregulation of NCAM expression and proliferative activity involved in homophilic (NCAM-NCAM) binding mechanism in NCAM-expressing cells.

gastric and duodenal ulcers [39]. Cimetidine has recently been shown to possess antitumor activity against gastric, kidney, and colon cancers, as well as melanomas [40–43]. A recent study has suggested that this behavior of cimetidine is mediated through three different effects: a direct inhibitory effect on tumor growth by blocking the cell growth activity of histamine via activation of H2 receptors and an indirect effect involving inhibition of tumor-associated angiogenesis, an immunomodulatory effect through augmentation of the host's immune response to tumor cells, and an inhibitory effect on cancer cell migration and adhesion to endothelial cells, thus inhibiting tumor angiogenesis and metastasis [44]. We have also examined the NCAM-associated impact of cimetidine on tumor growth and perineural/neural invasion in salivary gland tumors using an in vitro cell culture system and an *in vivo* nude mouse cancer model. These experiments clearly indicated that cimetidine effectively downregulated the expression of NCAM by inhibiting NF-κB transactivation, subsequently blocking salivary gland tumor cell adhesion to neural cells, and ultimately inducing apoptosis in salivary gland tumor cells, thus preventing the growth of salivary gland tumor masses in nude mice [45]. Although malignant glandular tumors are commonly known to be resistant to chemotherapy and/or radiation, the clinical application of cimetidine as an anticancer drug might provide an integral part of future therapeutic strategies against NCAM-expressing tumors such as adenoid cystic carcinoma.

Finally, it was suggested that NCAM might be associated with not only a cell-to-cell adhesion mechanism but also tumorigenesis, including the occurrence, development, and perineural/neural invasion of human salivary gland tumors.

Further studies will be required to identify the signal transduction pathways by which treatment with cimetidine suppresses the growth of salivary gland tumors and to establish a strategy for cimetidine-based therapy for those tumors.

2.2. Coxsackievirus and adenovirus receptor (CAR/CXADR)

Coxsackievirus and adenovirus receptor (CAR/CXADR), a transmembrane glycoprotein, was initially characterized as a viral attachment site on the surface of epithelial cells (**Figure 3**) [46]. Later it was identified as a component of the tight junction (TJ) complex, an interacting partner for a number of other TJ proteins and a regulator of TJ formation [47–52]. Furthermore, CAR is known to be a cell-cell adhesion molecule [53, 54]. In terms of function, loss of CAR has been considered to diminish intercellular adhesion, increase proliferation, and promote the migration as well as invasion of cancer cells [55, 56]. On the basis of these observations, a tumor-suppressive role of CAR in human cancers has speculated. Although it has recently been described [55–58] that CAR is observed in various organs, it is still unclear whether it is expressed in oral cancer. Therefore, we examined the role of CAR in SCC in the oral cavity (data not shown). This revealed that CAR was constitutively expressed in five oral SCC cell lines. To analyze the function of CAR, we then examined the proliferative activity of SAS cells

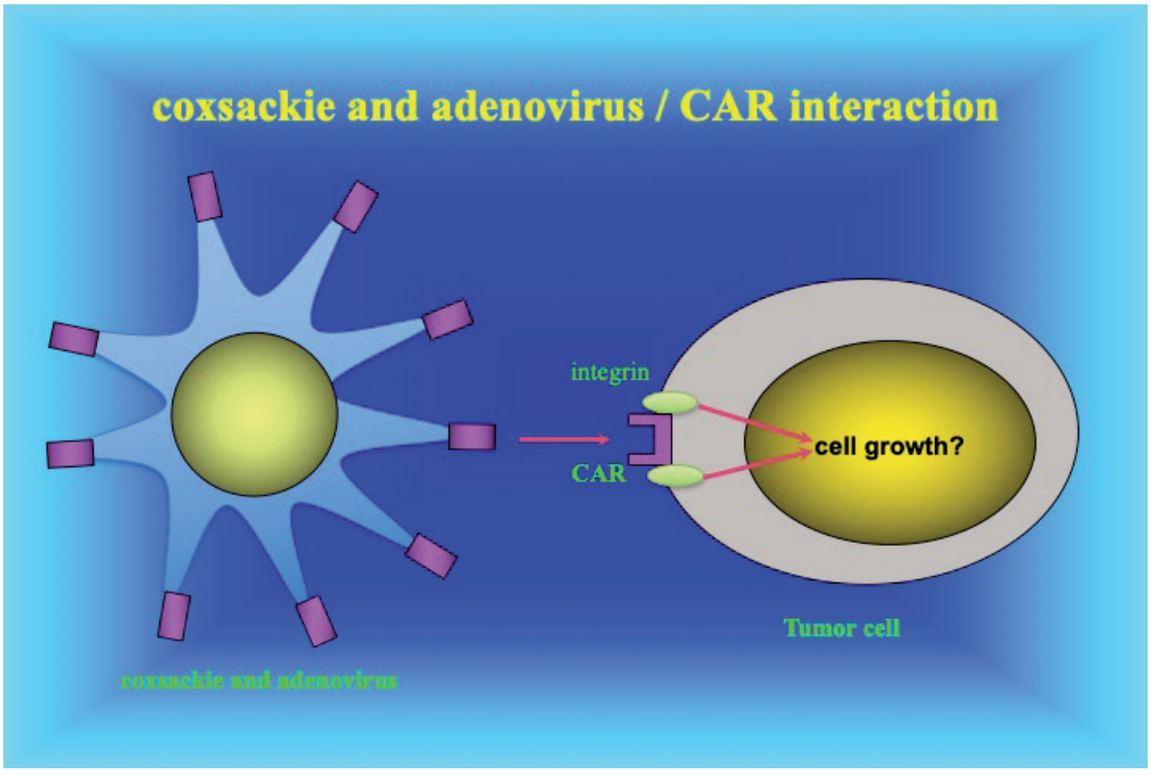

Figure 3. Schematic representation of coxsackievirus and adenovirus receptor on the tumor cells.

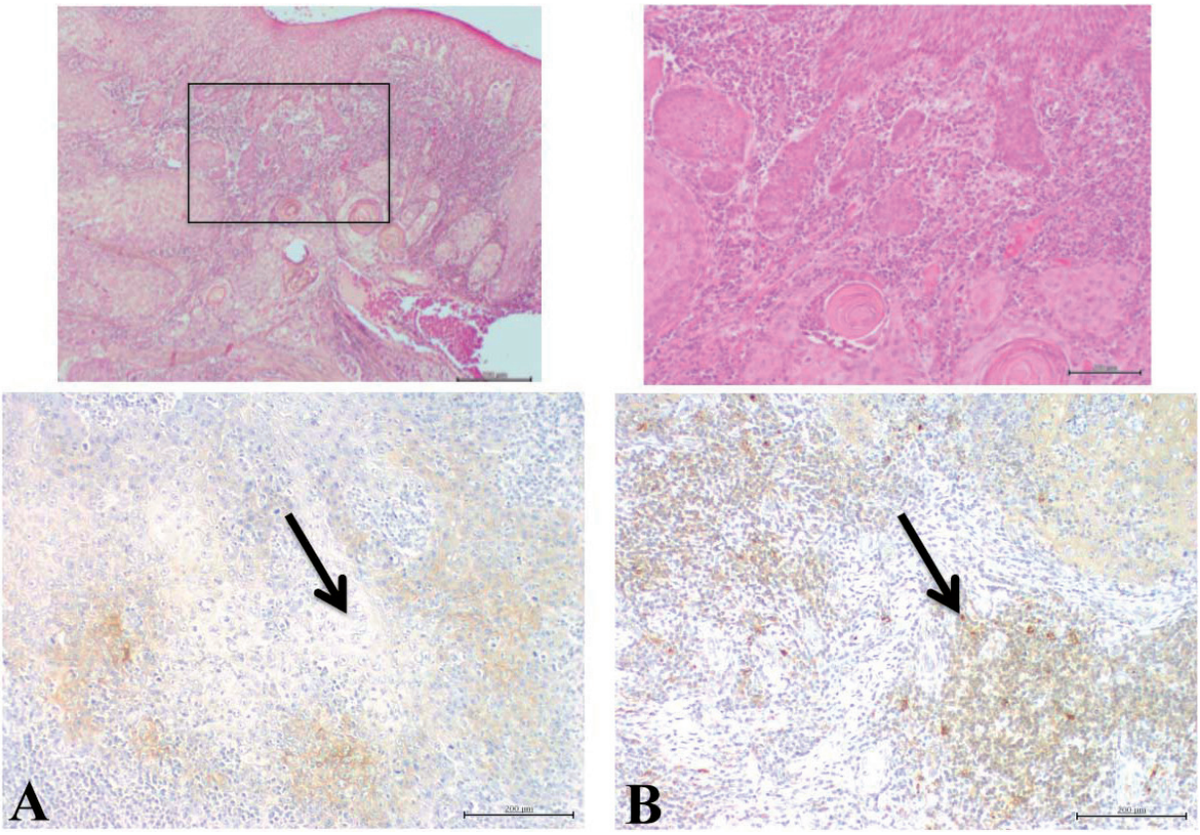

Figure 4. (A) The positive reaction for PAb CAR was observed on the membrane of tumor cells in 19 of 40 cases (47.5%) of SCCs. (B) NF-κB immunoreactivity were clearly detected in 30 of 40 cases (100%) in the HOSCC tissues. The immunoreactivity for CAR especially tended to fade away in the invasive front of oral SCC tissues. NF-kappaB (+)/CAR (−), 15/21 cases (71.4%).

after *CAR* gene knockdown. However, *CAR* knockdown did not promote the proliferative activity of SAS cells. Although the expression level of CAR was decreased by *CAR* knockdown, that of NF-κB p65 (RelA) showed little change. Furthermore, SAS cell numbers were notably reduced by CAR overexpression. Finally, it was suggested that the overexpression of CAR in SAS cells led to apoptosis via activation of caspase-9. In addition, the localizations of CAR and RelA in 40 samples of HOSCC at various stages were investigated using immunohistochemistry. A positive reaction for polyclonal antibody (PAb) CAR was weakly observed on the membrane of carcinoma cells in 19 of 40 cases (47.5%) of HOSCC. The immunoreactivity for CAR further tended to fade at the invasive front of oral SCC (**Figure 4**). In the meantime, RelA immunoreactivity was strongly positive, particularly on the nucleus of carcinoma cells at the invasive front, in 30 of 40 cases (75%) of HOSCC. These observations suggest that CAR plays a significant role in the inhibition of oral cancer cell growth.

3. Role of cytokines in oral cancer cell proliferation

Cytokines are composed of a large family of secreted proteins that bind to and signal through defined cell surface receptors on a wide variety of target cells, playing an important role in

the maintenance of homeostasis. Furthermore, many cytokines share structural features and effects during inflammation, development, or immune responses.

The concept of a control mechanism for cellular growth via regulation of apoptosis has recently been erected in a wide variety of tissue systems. Changes in the balance between cell survival and death are definite signs of emergence of various tumors. Therefore, modulation of apoptosis is required so as to maintain the homeostasis of a living organism. The expression of cytokines and their receptors in human oral cancers has attracted a great deal of interest because of their potential importance in tumor immunity. In particular, it has been described that members of the tumor necrosis factor (TNF) family, including Fas/FasL and TNF-related apoptosis-inducing ligand (TRAIL), regulate the deletion of unnecessary immune cells through induction of apoptosis [59–61]. However, despite their expression of these obvious antigens, tumor evasion by the immune system is often inefficient. It is considered that tumor cells may also evade immune attack by expressing TRAIL, Fas ligand, or other molecules that induce apoptosis in activated T cells [62].

3.1. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)

TRAIL, also called APO2 ligand (APO2L), is a novel member of the TNF cytokine family that was originally characterized by its ability to induce apoptosis [59, 60]. It is recognized that at least four closely related receptors bind to TRAIL: death receptor-4 (DR4) and DR5/KILLER, which contain cytoplasmic death domains and signal apoptosis [60, 61]; decoy receptor-1 (DcR1) [61–63], which lacks a cytoplasmic tail and inhibits TRAIL function; and DcR2 [64, 65], which contains a cytoplasmic region with a truncated death domain that does not transduce the death signal [67]. TRAIL interacts with its agonistic receptors DR4 and DR5, inducing apoptosis in a wide variety of cancer cell lines derived from breast carcinoma, lung carcinoma, colon carcinoma, lymphoma, malignant melanoma, and malignant glioma [59, 60, 68, 69]. Although DR4 is expressed in many normal human tissues and cells, including spleen and peripheral blood leukocytes, TRAIL induces apoptosis in various cancer cells, but not in normal cells [70]. This may be explained by the fact that TRAIL also interacts with the antagonistic decoy receptors DcR1 and DcR2, which are expressed in normal tissues but not in cancer cells (**Figure 5**) [66, 67]. Neither DcR1 nor DcR2 receptors induce apoptosis, but they protect cells from TRAIL-induced apoptosis [64–66]. Until now, the biological involvement of the complex TRAIL receptor system has remained unclear, and the existing data are conflicting. Nevertheless, because of its selective cytotoxicity against tumor cells, TRAIL is regarded as a promising anticancer weapon that might be highly effective *in vivo* with few side effects, as it has little or no function on normal tissues.

TRAIL is expressed in most normal human cells and tissues, including the peripheral blood leukocytes, spleen, lung, and prostate, but not the brain [60]. However, the expression of TRAIL in human neoplasms is largely unknown. Accordingly, we have examined whether TRAIL and its receptors are expressed in HOSCC tissues or cell lines and whether these cell lines are sensitive to TRAIL-induced apoptosis [71]. This revealed that the mRNA and protein levels of TRAIL and its receptors are co-expressed in HOSCC cell lines in the absence of paracrine fratricide or autocrine suicide. Moreover, TRAIL protein was also detected in 24 of 50

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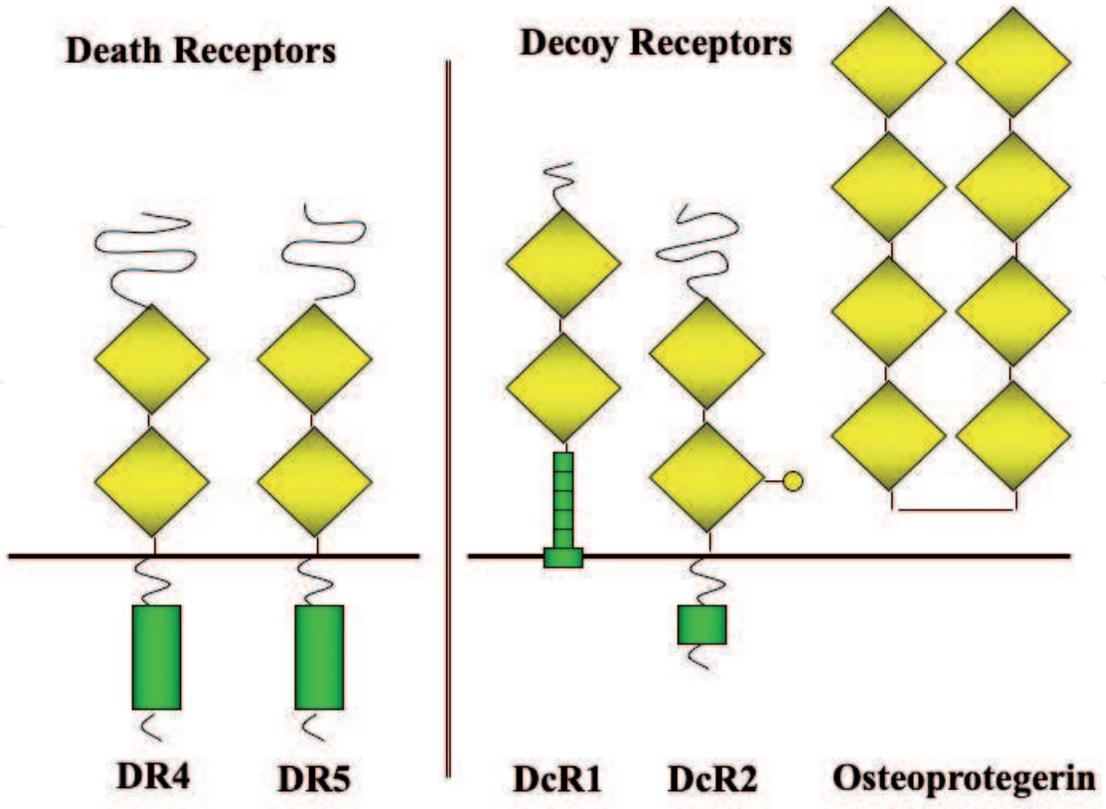

Figure 5. Schematic representation of the death receptors and decoy receptors on the tumor cell.

samples (48%) of HOSCC tissue, and there was no correlation among the WHO grades. These findings suggest that HOSCC has the potential to escape immune surveillance by killing host T lymphocytes via DR4/TRAIL and DR5/TRAIL interactions, as suggested for FasL [72–74].

The expression of decoy receptors in cancer cells is, however, a phenomenon that objects against previous reports [62, 63]. Indeed, several authors have currently described that a decoy receptor is expressed in various cancer types and our results are consistent with their findings [75–77]. Therefore, cancer cells may also avoid TRAIL-induced apoptosis by expressing a decoy receptor.

On the other hand, cells differ significantly in their response to TRAIL. As contrasted to HUVEC or other oral cancer cells, only KB cells undergo significant apoptosis following exposure to recombinant human (rh)TRAIL. The reason why KB cells, despite their expression of a decoy receptor, react to rhTRAIL remains unresolved.

Commonly, the most proximal step in suppression of a death receptor pathway is inhibition of ligand binding. This may be acquired by lack, or the presence of decoy receptors [65–68], or mutations of death receptors [78, 79]. However, it has recently been described that there is no correlation between the expression of TRAIL receptor and susceptibility to TRAIL-induced apoptosis in various cancer types [75–77]. Furthermore, the existence of antiapoptotic proteins, such as bcl-2, bcl-xL, and/or fas-like IL-1-converting enzyme (FLICE)-like inhibitory protein [80, 81], also seems to be significant, as they are resistant to death receptor-mediated

apoptosis. Holistically, our results also suggest that there may be no correlation between the expression of TRAIL receptor and sensitivity to TRAIL-induced apoptosis in HOSCC cell lines and that TRAIL-resistant cells (HSC-2, HSC-3, HSC-4, and Ca9-22) may express cytoprotective proteins that block TRAIL-induced apoptosis or that the apoptotic effect of TRAIL is regulated by other mechanisms. It has also been described that TRAIL, in combination with an anticancer drug, acts cooperatively to induce apoptosis in various cancer cells that are resistant to TRAIL or chemotherapy [75, 82, 83]. This combination of TRAIL with chemotherapeutic reagents might be a useful therapeutic strategy against TRAIL-resistant cell lines such as HSC-2, HSC-3, HSC-4, and Ca9-22 used in our investigation.

In fact, we are currently investigating the synergistic effects of α-mangostin and TRAIL on induction of apoptosis via the mitochondrial pathway in squamous cell carcinoma of the oral cavity [84]. To summarize, mangosteen (*Garcinia mangostana*) is a tree discovered in Southeast Asia, and the pericarp of its fruit has been used in folk medicine for the treatment of many human diseases. The rinds of mangosteen fruit contain a high concentration of xanthone, a type of polyphenol. One form of xanthone, α-mangostin, has been described to exhibit chemopreventive effects against chemically induced colon cancer through a decrease of c-Myc expression, suppressing tumor growth in a mouse model of mammary cancer. A recent study has proved the inhibitory effect of α-mangostin on the growth of prostate cancer. However, it is still unclear whether α-mangostin induces cell death in oral cancer. Then, the present study examined the impact of α-mangostin on HOSCC. First, we analyzed the expression of c-Myc in five HOSCC cell lines (HSC-2, HSC-3, HSC-4, Ca9-22, and SAS). The highest level of c-Myc mRNA expression was found in SAS cells and the lowest in HSC-4 cells. Therefore, SAS cells were treated with α-mangostin, which was observed to exert a weak cytocidal effect. Since α-mangostin has been described to exert synergistic effects on cancers when combined with anticancer drugs, we tried to evaluate these synergistic effects of α-mangostin in combination with TRAIL. We found that this combination induced apoptosis in SAS cells through the mitochondrial pathway via activation of caspase-3/caspase-7 and caspase-9, following the release of cytochrome c. In addition, this apoptosis was induced by S/G2/M-phase arrest. Immunoreactivity for c-Myc was revealed in the cytoplasm of cancer cells in 16 (40%) of the 40 cases of HOSCC. These data showed that the combination of α-mangostin and TRAIL may have considerable potential for the treatment of oral cancer.

Further investigation of TRAIL-mediated cell death, including the interaction of TRAIL and its receptors in oral cancer cells under various conditions, will be required to establish a strategy for TRAIL-based oral cancer therapy, which does not cause liver toxicity.

3.2. Hepatocyte growth factor (HGF) and its receptor, c-Met

The tyrosine kinase receptor c-Met ordinarily binds with hepatocyte growth factor (HGF), which triggers its involvement in processes such as cell differentiation, cell growth, angiogenesis, and embryogenesis [85, 86]. However, c-Met activation is also associated with processes related to malignant transformation, such as invasion, tumor growth, angiogenesis, and metastasis [87–91]. In addition to autocrine or paracrine signaling via HGF, c-Met may also be activated via the mutation, protein overexpression or amplification, or transcriptional alteration (via

microRNA-mediated dysregulation) of MET [92–94]. c-Met overexpression and MET amplification are thought to be associated with a poorer prognosis in some types of tumors, including non-small cell lung cancer and gastric cancer [94]. In HOSCC, it has also been reported that c-Met expression is associated with cisplatin resistance and a strong propensity for metastasis *in vivo* [95], as well as a poor prognosis [96]. However, details of the involvement of c-Met in oral carcinogenesis are still unclear. Accordingly, we investigated how the relationship between the expression of c-Met and several tumor activation-related markers such as NF-κB is associated with oral carcinogenesis (data not shown). In addition, the expression and distribution of c-Met and NF-κB were also examined in HOSCC tissues (data not shown). The results of real-time qRT-PCR and immunoblot analysis indicated overexpression of c-Met mRNA and protein in SAS cells. Therefore, SAS cells were used in this study. To investigate how c-Met functions in SAS cells, c-Met knockdown analysis was performed. c-Met knockdown appeared to reduce the number of SAS cells. To confirm whether this had been due to apoptosis, caspase activity was then analyzed, and this revealed that apoptosis had indeed occurred via activation of caspases-9 and caspases-3/caspases-7 in SAS by c-Met knockdown. Furthermore, SAS showed cell cycle arrest at S/G2/M phase during this apoptotic cell death. Subsequently, to determine NF-κB expression after c-Met knockdown, we also used a siRNA approach to reduce the expression of c-Met and determine the effects on NF-κB activity. As expected, the level of c-Met mRNA was markedly reduced by c-Met siRNA. Moreover, c-Met knockdown by c-Met siRNA clearly decreased the activation of NF-κB mRNA in SAS cells, in comparison with controls. These data indicated that c-Met upregulated NF-κB activation and consequently that c-Met knockdown led to apoptosis of SAS cells. These combined data suggested that c-Met produced by autologous cancer cells promoted tumor growth. Furthermore, our *in vivo* studies demonstrated c-Met-specific immunoreactivity, consistent with the observation of NF-κB-positive cells in HOSCC biopsy samples (c-Met expression, 9/20 (45%); NF-κB expression, 18/20 cases (90%)). This result suggests that c-Met expression correlates with increased activation of NF-κB. Based on these in vitro and *in vivo* observations, it can be hypothesized that c-Met function leads to NF-κB activation and subsequently anti-apoptosis and that as a consequence, it may be associated with tumorigenesis, including growth, development, and angiogenesis in HOSCC.

Further investigations of the role of c-Met will be required to fully understand c-Met-mediated tumor proliferation and to establish a therapeutic strategy for c-Met-based oral cancer.

4. Energy metabolism in oral cancer

4.1. Glucose metabolism in oral cancer

In normal tissues, adenosine triphosphate (ATP) is mainly produced in mitochondria via complete oxidative phosphorylation (OXPHOS) of glucose. Conversely, only 10% of ATP is produced from glycolysis in which glucose is replaced to lactate [97]. Interestingly, cancer tissues possess high levels of glycolysis in the cytosol even under aerobic conditions, which is upregulated by PI3K/Akt signaling in the mitochondria, a phenomenon known as the "Warburg effect" or "aerobic glycolysis" [98–103]. More than 80 years ago, Otto Warburg

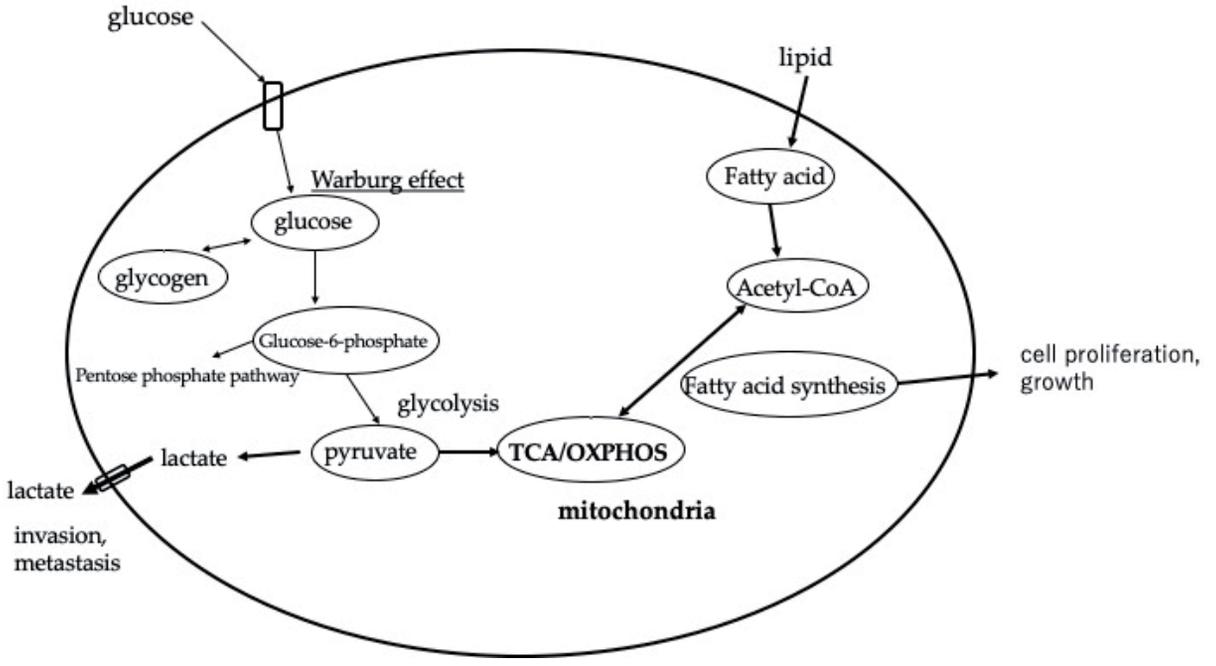

Figure 6. Schematic representation of the connecting glucose and lipid metabolism in cancer cells.

found that cancer cells expended much more glucose to generate lactic acid than normal cells even under conditions of O_2 sufficiency. This finding was the first indication that cancer cells have an alteration of glucose metabolism. Warburg [99] considered that these defects of respiration caused a form of metabolic disturbance that was significant for carcinogenesis. After Warburg, many biologists attempted to clarify the molecular basis of aerobic glycolysis occurring in tumor cells. Accumulated evidence suggested that many cancer-related genes, such as p53, c-Myc, and Ras, are all associated with modulation of the Warburg effect [104]. As a master regulator of the cancer hypoxic response, hypoxia-inducible factor (HIF)-1 plays very important roles in modulating aerobic glycolysis to meet the biosynthetic demands of cancer cells and to protect them from damage due to hypoxic stress [105]. Warburg theorized that cancer cells shift from oxygen-dependent efficient ATP production via OXPHOS in mitochondria to the less efficient cytoplasmic glycolysis. As a result, cancer cells need to burn up more glucose to maintain their energy requirements for survival and growth. It has been reported that HIF-1α activates the expression of glucose transporter 1, 3 (Glut1, Glut3) under hypoxic conditions [106, 107], which acquires sufficient glucose uptake by tumor cells. We also examined HIF, and details can be found in Chapter 10 of the InTech book *Tumor Microenvironment and Myelomonocytic Cells* [108]. Although clarification of glucose metabolism is considered vital for understanding energy metabolism in oral cancer, lipid metabolism has also been receiving attention recently (**Figure 6**).

4.2. Lipid metabolism in oral cancer

Lipids are composed of phospholipids, triglycerides, cholesterol esters, cholesterol, fatty acids, sphingolipids, and other molecules, which are critical components of cellular membranes

[109–113]. In addition to their role as structural components, lipids also act as energy resources and as signaling molecules to sustain cell growth [114–116]. Lipid metabolism is known to be largely altered in cancers [117–120], and worsening lipogenesis has been indicated to be a predominant characteristic of most tumors [114, 115, 121]. In oral cancer, cancer tissues include higher levels of unsaturated fatty acids than those in normal tissue (data not shown). Recent studies have revealed intrinsic molecular alterations in lipid metabolism. Especially, fatty acid synthase (FAS) is a key enzyme for synthesis of fatty acid from acetyl CoA, which is expressed at high levels in the adipose tissue and liver but at low levels in other tissues in humans [122]. FAS is overexpressed in several human cancers, including those of the ovary, bladder, stomach, breast, lung, prostate, oral cavity, and melanoma, and this overexpression is associated with poor prognosis [123, 124]. Furthermore, glutathione peroxidase 4 (GPX4) expression in tumors is positively correlated with tumor survival and linked to pathways that regulate cell proliferation, motility, and tissue remodeling [125]. Knockdown of GPX4 suppresses the formation and progression of cancer and leads to non-apoptotic cell death, ferroptosis. We have also examined the role of GPX4 in HOSCC (data not shown). Ferroptosis is a non-apoptotic form of cell death that can be triggered by conditions or small molecules that inhibit the glutathione-dependent antioxidant enzyme GPX4 or glutathione biosynthesis. This lethal process is defined by depletion of plasma membrane polyunsaturated fatty acids and the iron-dependent accumulation of lipid reactive oxygen species. It has also been reported that GPX4 is negatively regulated by the p53 gene [126]. These data suggest that GPX4 plays a significant role in proliferation and progression and may serve as a potential therapeutic target in HOSCC. Thus, GPX4 would be useful as a predictor of poor outcome in patients with oral cancer, and its antibody might be applicable as an inhibitor of oral cancer progression. Identification of the signaling pathways underlying these events might help to elucidate the mechanism of development of oral cancer. Further investigations into the role of GPX4 will be required to fully understand GPX4-mediated cancer proliferation and to establish a GPX4-based therapeutic strategy for oral cancer.

5. Conclusions

Unlike surgery, chemotherapy, and radiotherapy, which can have serious side effects on the human body, the use of agents that have no such side effects, such as TRAIL, cimetidine, mangostin, and antibodies, for cancer therapy mobilizes and regulates systemic functions, enhancing the body's ability to fight cancer. Therefore, these medicines may be more appropriate for patients with inoperable advanced cancer, those in periods of chemotherapy intermission, or those during postoperative recovery. There has been an increased emphasis on such agents for prevention of cancer and inhibition of cancer metastasis. There has been an impressive renaissance in the search for semi-synthetic drugs or derivatives from natural compounds. Progress in this regard not only adds to the chemical bank but also leads to a better comprehension of the chemical basis of treatments lacking side effects for the treatment of cancers using drugs obtained from natural sources.

Further studies will be required to establish a strategy for basic molecular and clinical approaches for effective oral cancer therapy, which should be tailored to individual patients.

Conflict of interest

We have no financial relationships to disclose.

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