Review Article

Sex hormones in head and neck cancer: Current knowledge and perspectives

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ABSTRACT

Head and neck cancer (HNC) is an increasing problem worldwide. Oral carcinogenesis is a highly complex multifocal process. Molecular mechanisms contributing to initiation and progression of head and neck squamous cell carcinoma are still poorly known. Endocrine microenvironment is another imperative factor beside other well-documented risk factors like tobacco smoking, alcohol and infections in causing cancers of head and neck. These endocrine hormones play a role in tumor progression in case of cancers characteristically expressing sex hormone receptors, and it has been proven that these receptors also reside outside the sex organs in the larynx and lungs. However, the role of sex hormones in HNC is controversial, and few studies have been conducted to delineate their role in HNC. So, this review article is an attempt to draw an attention towards the potential role of sex hormones in pathogenesis of HNC and potential therapeutic modalities to prevent onset and progression of cancer.

Keywords: Cancer, hormones, oral, sex, tumor

INTRODUCTION

Head and neck cancer (HNC) is an increasing problem in certain geographic areas of the world, especially in central-east Europe.[1] The World Health Organization expects a worldwide rising oral squamous cell carcinomas (OSCC) incidence in the next decade. In the US, OSCC represents 2–4% of the annually diagnosed malignancies, being responsible for 8000 deaths every year.[2]

The mechanism of progression of HNC is obscure. Tumor-induced neo-angiogenesis and neo-lymphangiogenesis and altered stromal interactions[3] as well as immunological interactions[4] are involved in onset and progression of cancer. Although the complexity of the process remains largely unexplored, down-modulation of cell adhesion molecules and up-regulation of various proteases have been described to play a significant role.[4]

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Women have lower rates of HNC than men worldwide. The conspicuously lower incidence of this tumor among women than among men is suggestive of certain endocrine involvement in its development. It has been observed that compared with women, a substantially larger percentage of men with HNC were never smokers, which suggests men are preferentially exposed to additional risk factors. This gender-specific risk for oral cancer raises two different assumptions. First, there are noxious factors affecting selectively only male patients, and second, common risk factors affect both sexes, but females have some defense mechanisms owing to their special hormonal and metabolic features.[5]

Endocrine milieu is an imperative factor of tumor progression in case of cancers characteristically expressing sex hormone receptors such as breast, prostate and endometrial cancer. The sex hormone receptors are expressed outside the sexual organs such as the vascular endothelium the larynx or the lung epithelium. Accordingly, it is feasible to expect ectopic/illegitimate sex hormone receptors in various cancer types.[6]

Role of sex hormones in HNC is controversial and is a topic of debate from the last decade. Sex hormone

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receptors were demonstrated previously in laryngeal tissue using radioimmunoassay technique. The presence of the hormone-dependent proteins in normal human laryngeal tissue and laryngeal cancers supports the hypothesis that hormonal mechanisms may play an important role in carcinogenesis.[7,8]

Many research teams focused on the fact that hormone receptors are expressed in hormone independent tissues.[9]

Why the incidence of HNC is higher in men, and what kind of mechanisms are protecting the women from this type of cancer?

In an attempt to answer this controversial issue, analysis of a large series of HNC patients compared with control and alcoholic populations revealed significantly elevated FSH (Follicle stimulating hormone) and LH (Luteinizing hormone) levels, whereas estrogen elevation and testosterone decrease characterized the alcoholic patients.[10,11]

In the same set of patients, increased FSH and decreased testosterone levels predicted poor overall survival of HNC.[10] Destruction of liver function is followed by the destruction of metabolic processes, naturally including the metabolic processes of sex hormones (estrogen, testosterone). Majority of HNC patients are males, characterized theoretically by testosterone-rich sex hormone microenvironment.[10,11]

ROLE OF SEX HORMONES IN HEAD AND NECK CANCER

Estrogen and testosterone

Lukits *et al*., in 2007 first time demonstrated on a larger series of HNC samples that both oral cavity, laryngeal or hypopharyngeal, cancers express authentic estrogen receptors (both α and ß isoforms) as well as progesterone receptors in ~50% of cases identified both at mRNA as well as protein levels. Alcoholic patients who have chronic liver disease are considered as a risk group for development of cancer. Deteriorating liver function is frequently reflected in alteration of sex hormone metabolism involving testosterone and estrogen.[6]

Marsigliante *et al*., in 1993 observed positive correlation between expression of cathepsin D in malignant and in the corresponding non-malignant node negative laryngeal samples with receptors for androgen, glucocorticoid, estrogen and progesterone.[12] On the other hand Brysk *et al*., in 1998 ascertained cathepsin D in differentiation and metastasis of OSCC. So it can be assumed that estrogen can be implicated as one of the factors responsible for oral cancer.[13]

Mechanism of action of estrogen in head and neck cancer

Estrogen metabolites have been associated in the pathogenesis of breast and cervical cancer; 16alpha-hydroxyestrone(16alpha-OHE1) demonstrated proliferative effects whereas 2-hydroxyestrone(2-OHE1) had antiproliferative effects.[11] Yoo YH demonstrated that HNC patients metabolize estrogen differently than healthy controls, which may constitute a risk factor for HNC development.[11]

Estrogen is known to be carcinogenic and there are several mechanisms postulated for its carcinogenic and tumor-promoting effects. One of the most widely acknowledged mechanism of estrogen carcinogenicity is the multiple estrogen-receptor signal-transduction pathways associated with increased cell proliferation and inhibition of apoptosis.[14-16] This could involve the direct genomic action of estrogen binding to nuclear estrogen receptors (ERa and/or ERb), which then bind as dimers to estrogen-response elements (ERE) in the regulatory regions of estrogen-responsive genes in association with various basal transcription factors, co-activators, and co-repressors to alter expression of genes involved in cell cycle control[14] and other tumor-promoting factors such as vascular endothelial growth factor.[17]

Moreover, via non-genomic action, estrogen can also cause activation of protein kinases, including mitogen-activated protein kinases, and rapidly increase the levels of secondary messengers, such as cyclic AMP that can cross-talk with other growth factors (epidermal growth factor receptor and insulin-like growth factor 1 receptor) and signaling pathways, that are important in estrogen-dependent cell cycle regulation.[15,16]

Another potential mechanism is via estrogen metabolism whereby oxidative metabolites of estrogen are shown to have genotoxic (formation of DNA adducts and oxidative DNA damage), mutagenic, transforming, and carcinogenic effects.[18-20] These studies suggested that estrogen together with ER might play a distinct role in inducing OSCC. Shatolava *et al*.,[21] demonstrated for the first time in 2011 that a panel of estrogen metabolism genes is expressed in cultured human head and neck cells. Detection of transcripts for these genes in both premalignant lesions and head and neck squamous cell carcinoma (HNSCC) suggests that these enzymes contribute to cellular metabolism throughout tumorigenesis.

In addition, estrogen has been shown to cause over-expression of centrosome kinases (Aurora A and B) and centrosome amplification, which can lead to chromosomal instability, resulting in aneuploidy in early tumor foci that precipitates oncogenesis.[20] Egloff in 2009 in their

study between ER and epidermal growth factor receptor in HNSCC demonstrated that ER expression and function in HNSCC cell lines did not differ by sex of the patient from whom the cell lines were derived. In addition, ER expression was detected in the majority of HNSCC tumors, and expression levels did not differ by patient sex. So, they suggested that when all the parameters were taken together, these data indicate that ER likely contributes to HNSCC growth and invasion in both men and women.[22]

These evidences along with cancer epidemiological data of reproductive tissues had supported the classification of estrogen as a carcinogen. Further molecular and genetic studies on a larger sample size are required to clearly delineate the role of estrogen in HNC development.

ROLE OF OTHER HORMONES

Bhatavdekar *et al*., (1994) observed a decreased ratio of testosterone:estradiol and increased levels of FSH, LH and prolactin in tongue cancer patients. These hormonal abnormalities clearly suggest a disturbance in the pituitary–adrenal–testicular axis. So, they suggested that these hormones might be playing an important role in the development and progression of tongue cancer.[23] Recently, Bauernhofer suggested that elevated prolactin levels can be a marker of poor prognosis for HNC.[24] Elevated FSH and LH levels compared with healthy male controls were detected only in the HNSCC group; therefore, the changes of these pituitary hormones are characteristic for cancer patients. These results suggest that functional abnormality of the hypothalamus–hypophysis–liver axis might have a role in the development of HNSCC.[10]

Sex hormones in salivary gland cancer

Expression of these sex hormone receptors has been demonstrated for various HNC subtypes. Both ER isoforms as well as the progesterone receptor were detectable in cancer cells of the oral cavity, the salivary gland and in laryngeal/hypopharyngeal cancers, whereas the tumor stroma was mostly negative. Expression of ERa inversely correlated with that of ERb in esophageal carcinomas, and a correlation of ERb levels with tumor de-differentiation and staging was suggested.[25]

Salivary gland tumors have been reported to share similarities with mammary gland tumors, and expression of progesterone receptor in salivary gland cancer appears to be indeed associated with tumor progression. *In vitro*, progesterone treatment inhibited proliferation of salivary gland cancer cells. Moreover also, the androgen receptor was reported to be expressed in salivary gland cancer, such as carcinomas and pleomorphic adenomas, salivary duct carcinomas and basal cell adenocarcinomas, indicating molecular similarities among prostate tumors and androgen receptor-positive salivary gland cancer.[26]

THERAPY OF HEAD AND NECK CANCER

The rationale for molecular-targeted prevention of oral cancer is promising. Nevertheless, considering the impressive benefit of endocrine therapy in breast cancer, targeting sex steroid hormone receptor as a potential therapeutic strategy is also discussed for HNC, and the results of just completed clinical trials are eagerly awaited.[27]

Ishida *et al*., in 2007 clearly showed that ER antagonist, but not agonist, induced cell death of cultured OSCC established from human tongue carcinomas. These results suggested that ER antagonist causes the interference of cell adhesion, which consequently results in cell death. This prevents tumors from undergoing further growth and surviving without the contact of extracellular matrix. Treatment with ER antagonist (tamoxifen), but not agonist (estradiol), caused apoptotic cell death of SCC cells in a concentration- and time-dependent manner. Tamoxifen reduces the phosphorylation of focal adhesion kinase (FAK), resulting in decreased phosphorylation of extracellular signal-related kinase (Erk) and mitogen-activated protein kinase, which is accompanied by disorganization of the cytoskeletal component actin. Therefore, tamoxifen causes cell death by directly interfering in cell adhesion. Expression of epidermal growth factor receptor was also inhibited by treatment with a high concentration of tamoxifen. In addition, tamoxifen strongly inhibited invasion of SCC. These results imply that estrogen inhibition can be modulate and prevent invasion and metastasis of OSCC. Such molecular understanding will be required to decide which receptor should be targeted by which modulator for future clinical applications. Since hormonal therapies may also affect a variety of physiological processes, therapeutic benefit of such treatments has to be in balance against potential adverse effects.[25,26]

CONCLUSION

The expression of sex hormones in clinical samples of HNCs needs to be evaluated with prudence, because probability of variation can be there between the studies in establishing correlation between clinicopathological parameters and expression patterns. Furthermore, even the endocrine milieu of the host was proved to be a determining factor in modulating the onset and progression of Head and neck squamous cell carcinoma (HNSC). Gene expression profiling techniques combined with proteomics could allow the comparison and interpretation of comprehensive studies in the future and help to define and select useful genetic and biomarkers of progression of HNSC. Potential target

molecule therapies could be of great help in preventing progression of HNC.

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