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Infectious Agents Associated with Head and Neck Carcinomas

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Abstract

In addition to traditional risk factors such as smoking habits and alcohol consumption, certain microbes also play an important role in the generation of head and neck carcinomas. Infection with high-risk human papillomavirus types is strongly associated with the development of oropharyngeal carcinoma, and Epstein-Barr virus appears to be indispensable for the development of non-keratinizing squamous cell carcinoma of the nasopharynx. Other viruses including torque teno virus and hepatitis C virus may act as co-carcinogens, increasing the risk of malignant transformation. A shift in the composition of the oral microbiome was associated with the development of oral squamous cell carcinoma, although the causal or casual role of oral bacteria remains to be clarified. Conversion of ethanol to acetaldehyde, a mutagenic compound, by members of the oral microflora as well as by fungi including *Candida albicans* and others is a potential mechanism that may increase oral cancer risk. In addition, distinct *Candida* spp. also produce NBMA (N-nitrosobenzylmethylamine), a potent carcinogen. Inflammatory processes elicited by microbes may also facilitate tumorigenesis in the head and neck region.

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1 Introduction

Head and neck cancer is a broad term that encompasses cancers arising in the head and neck region. They may originate from the mucosal lining of the oral cavity, nasal cavity, paranasal sinuses, oropharynx, nasopharynx, hypopharynx, and larynx, or begin in the lip or in the salivary glands (Bose et al. 2013). Most of these malignancies are head and neck squamous cell carcinomas (HNSCCs). Head and neck cancer is the sixth most common cancer type worldwide with approximately 650 000 new cases annually (Ferlay et al. 2010). Despite the advancements of treatment methods, including chemotherapy, radiotherapy, and surgery, the 5-year survival rate of HNSCC patients improved only modestly in the past decades: it is around 50 %, mostly due to locoregional recurrences, distant metastases and additional primary tumors (Leemans et al. 2011).

The major risk factors for HNSCC are tobacco use and alcohol consumption and they seem to have a multiplicative combined effect. Genetic polymorphisms in enzymes that metabolize tobacco and alcohol have been linked to an increased risk for HNSCC (Cadoni et al. 2012; Maurya et al. 2014). Smokeless tobacco and chewing of betel quid are also known risk factors for oral cancer (Li et al. 2015; Sand et al. 2014). There is wide geographic variation in the incidence and anatomic distribution of HNSCC worldwide. This variation is predominately attributed to demographic differences in the habits of tobacco use and alcohol consumption. In the western part of the world the incidence of HNSCC has declined, mostly due to the decline of tobacco use. In contrast, oral cancer is the leading type of malignancies among men in high risk countries, such as India, Pakistan, Sri Lanka and Bangladesh, (Joshi et al. 2014). Similarly, the estimated incidence and mortality rate of lip, oral cavity and pharynx carcinomas is high in Central and Eastern European countries (Hungary, Slovakia, Romania), possibly due to traditional risk factors (Iriti and Varoni 2015).

According to the International Agency on Research for Cancer (IARC), in 2008 around two million of the estimated 12.7 million new cancer cases occurring worldwide could be attributed to infections (IARC Working Group 2012; de Martel et al. 2012). In addition to oncogenic viruses (HPV, MCPyV, EBV, HHV-8, HBV, HCV, HTLV-I) and bacteria (*Helicobacter pylori*) other infectious agents may also contribute to the development of malignant tumors. A series of microbe-induced pathological alterations including mutations, cell cycle modulation, inhibition of DNA repair, epigenetic dysregulation, inflammation and immune system impairment may facilitate tumorigenesis (Alibek et al. 2013).

One of the well-documented virus-cancer relationships is the association of high-risk human papillomavirus (HPV) infection with a subset of HNSCCs located predominantly to the oropharynx. In the US and Western Europe, there was a recent increase in oropharyngeal cancer incidence, compared to other head and neck cancers. This phenomenon was attributed to a higher prevalence of high-risk HPV strains in the oral mucosa (Mehanna et al. 2013; Näsman et al. 2009; Rietbergen et al. 2013).

The nearly ubiquitous Epstein-Barr virus (EBV) plays a major role in the development of a series of neoplasms including undifferentiated nasopharyngeal carcinoma (NPC). NPC is a rare cancer globally, but it is the leading cancer type in distinct high-risk populations, especially in Southern China, indicating that non-viral, genetic and environmental factors also contribute to NPC development (Jia and Qin 2012). Although compared to HPV and EBV the evidence is less direct, recent data also suggested a role for other viral, as well as bacterial and fungal infections in the etiology of head and neck cancer (Sand and Jalouli 2014).

Carcinogenesis is a multistep process driven by genetic and epigenetic alterations that result typically in the clonal or oligoclonal expansion of cells (Hanahan and Weinberg 2000). Over 90 % of HNSCCs arise from pre-existing potentially malignant lesions or conditions, e.g. oral leukoplakia and oral lichen planus. The treatment of high risk oral premalignancies, however, did not efficiently prevent either their recurrence or the development of oral carcinomas (Braakhuis et al. 2003; Leemans et al. 2011). This phenomenon was attributed to the existence of a "field effect", i.e. genetic alterations predisposing large areas of oral mucosa for tumorigenesis ('field cancerization'). Recurrences and novel new malignant transformations occur preferentially at such 'fields' (Braakhuis et al. 2003; Leemans et al. 2011). It is worthy to note that epigenetic abnormalities characteristic for laryngeal squamous cell carcinomas may also extend to the adjacent normal mucosa, indicating the occurrence of an "epigenetic field of cancerisation" (Paluszczak et al. 2011).

We wish to overview the contribution of infectious agents including viruses, bacteria and fungi to the development of HNSCC. A better understanding of microbe-induced molecular events, including genetic and epigenetic changes, in head and neck cancer development may pave the way for novel therapies and prevention strategies.

2 Human Papillomavirus

Human papillomaviruses (HPVs) of the *Papillomaviridae* family are small, non-enveloped viruses with a double-stranded, circular DNA genome of about 8000 bp. There are 174 completely characterized HPV types, classified on the basis of the capsid protein L1 gene sequences (Bzhalava et al. 2013). The discovery that distinct HPV types were associated with cervical carcinoma was a significant milestone in tumor virology (reviewed by zur Hausen 2009).

HPVs have strict host selectivity for humans. Cutaneous types infect the skin, whereas mucosal types infect nonkeratinized squamous epithelia lining the oral cavity, the esophagus and the vagina. HPVs can be grouped into high and low risk types based on their capacity to induce malignant transformation. High risk types include HPV 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58,59, 66, 68, 73 and 82; they were associated with high grade intraepithelial lesions of the cervix and with invasive cancer. In contrast, non-oncogenic or low-risk HPV types, including HPV 6, 11, 40, 42, 43, 44, 54, 61, 72, 81 and 89, were detected in low grade intraepithelial lesions (Woods et al. 2014).

HPV is associated with wide range of diseases from benign warts to invasive cancer. There is strong epidemiological evidence for the involvement of HPV infection in the generation of six non-skin cancer types, including the carcinomas of cervix, penis, vulva, vagina, anus and upper aerodigestive tract (de Martel et al. 2012). The majority of HPV related head and neck cancers are located to the oropharynx, an anatomic region comprised of the soft palate, uvula, tonsils, posterior pharyngeal wall, and the base of the tongue (Gillison et al. 2014). It was suggested that tonsillar crypts may trap the virus and inhibit mechanical clearance. In addition, the monolayer of epithelial cells that lines these crypts could be more susceptible to HPV infection than stratified epithelium (Elrefaey et al. 2014; Klussmann et al. 2001). It is worthy to note that the oropharyngeal SCCs associated with traditional risk factors, i.e. smoking and alcohol consumption, are usually moderately differentiated and show a keratinizing phenotype. In contrast, the majority of HPV-associated head and neck cancers lack significant keratinization and are of basaloid morphology (Westra 2009).

3 The HPV Genome

All open reading frames in the 8 kb HPV genome are located on one of the two DNA strands. Most HPV-infected cells carry circular, episomal HPV DNA molecules, whereas HPV-associated carcinomas harbor viral genomes integrated into the cellular DNA. The HPV genome can be divided into three major regions. Early gene transcription and replication is regulated by the long control region (LCR) that contains promoter and enhancer elements as well as the viral origin of replication. The downstream coding ORFs are

called early and late genes and their names refer to their location as well as the timing of their transcription. The products of the early genes (E1-E7) are necessary for the genome maintenance and replication. E5, E6 and E7 are the oncoproteins of HPV, although they have their important role in the normal lifecycle of the virus as well. The E2 protein, apart from having a role in genome replication, regulates the transcription of the other early genes. The late genes (L1 and L2) code for the structural proteins, with L1 being the major and L2 the minor capsid protein (Rautava and Syrjänen 2012; Stanley 2012).

4 HPV Epidemiology

As for the prevalence of HPV in oropharyngeal cancer cases, there are significant differences between various anatomical regions. A recent meta-analysis by Mehanna et al. found 47.7 % overall pooled HPV prevalence in oropharyngeal cancer, whereas 21.8 % of non-oropharyngeal squamous cell carcinomas were HPV positive. HPV prevalence was found to significantly increase over time from 40,5 % before 2000 to 72,2 % after 2005. The overall HPV prevalence of head and neck malignancies differed by geographical region as well: North-America and Europe had the highest prevalence. In the last decades Northern and Western European countries have reported a steep rise in the proportion of HPV associated oropharyngeal cancers (Mehanna et al. 2013; Marur et al. 2010; Näsman et al. 2009; Rietbergen et al. 2013; Louie et al. 2015). However, regions with low prevalence of HPV have reported lower prevalence of HPV DNA in HNSCC patients (López et al. 2014), and similarly low prevalence was found in relatively high-risk regions for HNSCC, in Central-Europe and Latin-America. In these communities traditional risk factors may play a more important role in the development of HNSCCs (Ribeiro et al. 2011; Marur et al. 2010).

HPV can be found in other types of head and neck cancers as well. Isayeva et al. analyzed the prevalence rates of HPV in oral cavity, laryngeal, sinonasal and nasopharyngeal carcinomas. Lower prevalence rates were detected (20.2 %, 23.6 %, 29.6 % and 31.1 %, respectively) compared to oropharyngeal cancers (Isayeva et al. 2012). They also found that the prevalence of HPV in potentially premalignant and premalignant oral lesions is significantly higher than the rate of oral HPV carriers. Interestingly, submucous fibrosis showed the highest HPV prevalence (11/12, 91.7 %). Submucous fibrosis is a potentially malignant condition of the oral cavity and it is linked to chewing of betel quid (Jalouli et al. 2010).

Independently of overall HPV prevalence in HNSCCs, HPV16 was the most abundant HPV type found in these malignancies. HPV16 accounted for 86.7 % of HPV positive oropharyngeal cancer; it was less prevalent, however, in other types of head and neck cancer. A smaller proportion was attributable to HPV18; other high risk types were rarely found in these cancers (Kreimer et al. 2005; Chaturvedi 2012). It was observed that HPV associated oropharyngeal cancers tend to have better prognosis than HPV-positive carcinomas located to other anatomic regions (Lindquist et al. 2007; Ang et al. 2010; El-Mofty 2012, Mellin et al. 2012, Sethi et al. 2012; Ramqvist et al. 2015).

5 Characteristics of Patients with HPV-Associated Head and Neck Cancer

People diagnosed with HPV related HNSCC tend to be younger (<60 years of age) than those with HNSCC caused by traditional risk factors (>60 years of age) (Marur et al. 2010; Genden et al. 2013). Although the absolute proportion of HNSCC affecting young adults (18–40 years of age) remains low (1–6 %), epidemiological studies have shown a steady rise in the incidence of oropharyngeal and oral cavity cancer in this population (Majchrzak et al. 2014).

Several aspects of sexual behavior are strongly associated with HPV positive HNSCC. These include younger age at first intercourse, total lifetime number of vaginal and oral sex partners and lack of barrier use during sexual intercourses (Gillison et al. 2008; Chaturvedi 2012; Burke et al. 2014).

The incidence of both HPV-positive and HPV-negative HNSCC are higher in men. The male to female ratio has declined in oral cancer, and now it is about 1.5:1; however in HPV-associated HNSCC the male:female ratio remains 3:1 (Gillison et al. 2012; Warnakulasuriya 2009). This phenomenon can't be explained exclusively by the differences in sexual behavior between the two genders, and suggests some male predisposition to oropharyngeal cancer. It might be attributed to a protective effect of seroconversion in women due to earlier cervical HPV infection (Safaeian et al. 2010), or to the higher oral HPV prevalence among men. The latter is possibly due to a more effective transmission of HPV through oral sex on women versus men (Gillison et al. 2012).

6 HPV Induced Carcinogenesis: Integration of the Viral Genome into the Host Cell DNA

After initial infection, the HPV genome persists in episomal form within the host cells. Typically, there is no integration of the viral genome into the cellular DNA during productive infection of differentiating epithelial cells. The virus relies on the cellular replication machinery for the replication of its own genome (Lazarczyk et al. 2009). Malignant transformation is associated with high-level expression of viral E6 and E7 oncoproteins. During HPV-initiated carcinogenesis, high-level E6 and E7 expression frequently occurs after the integration of the viral DNA into the host cell genome (Vinokurova et al. 2008). The integration breakpoint is usually within the E2 gene encoding a negative regulator of E6 and E7 transcription. Thus, the integration of the viral genome disrupts the regulatory function of E2 and leads to constitutively active high-level E6 and E7 expression and increased cell proliferation (Parfenov et al. 2014; Williams et al. 2011; Rautava and Syrjänen 2012). The integration event also causes genomic instability by inducing chromosomal rearrangements, DNA amplification and disruption of tumor suppressor genes (Parfenov et al. 2014). In certain neoplasms, however, the HPV DNA can also be found in episomal form, or there is a combination of episomal and integrated form. In HPV16-associated oropharyngeal cancer the episomal or combined forms of viral genomes dominate. In cases when HPV remained in episomal form, a higher episomal count and a high viral load was detected (Mellin et al. 2002; Deng et al. 2013; Parfenov et al. 2014; Olthof et al. 2015).

7 HPV Oncoproteins

Three of the HPV proteins encoded by the early region of the viral genome, E5, E6 and E7 were implicated in carcinogenesis. The E5 gene is frequently lost during integration and a large fraction of HPV-associated tumors do not express E5 protein (reviewed by Venuti et al. 2011). E5 might contribute to oncogenesis, however, in case of HPV genomes that persist as episomes in tumor cells (Venuti et al. 2011). E5 may play a role in immune evasion by reducing the MHC-I level on the cell surface (Stöppler et al. 1996; Campo et al. 2010). In addition, E5 may promote cell growth by enhancing epidermal growth factor receptor-mediated signaling (DiMaio and Mattoon 2001).

In high-risk HPV-associated oropharyngeal carcinoma cells, continuous expression of the E6 and E7 oncoproteins is essential for the maintenance of the transformed phenotype (Rampias et al. 2009). The mechanisms contributing to E6 and E7 mediated oncogenesis are complex. Here we wish to outline only some of the best documented carcinogenetic pathways.

E7 has neither direct DNA binding activity nor enzymatic activity, but it is able to interact with key cellular regulators. E7 binds and induces the degradation of the retinoblastoma protein (Rb), a tumor suppressor protein that regulates the G1-S transition of the cell cycle (reviewed by Rautava and Syrjänen 2012; Boyer et al. 1996). Rb interacts with the E2F family of transcription factors that activate genes indispensable for S-phase entry and progression (McLaughlin-Drubin and Münger 2010). Thus, binding of E7 to Rb results in constitutive expression of E2F responsive genes and

leads to DNA synthesis. Degradation of pRB induces the upregulation of $p16^{INK4A}$ (p16) tumor suppressor protein, and the elevated p16 level is used as a diagnostic marker in HPV positive HNSCC (Fakhry et al. 2014). E7, a pleiotropic regulator, also interacts with a series of other cellular proteins involved in the control of cell cycle and affects the gene expression pattern of host cells by binding to key epigenetic regulators (reviewed by Klingelhutz and Roman 2012; Moody and Laimins 2010).

The E6 protein of high-risk HPVs forms complex with, and targets the tumor suppressor protein p53 for proteasomal degradation by recruiting the cellular ubiquitin ligase E6AP. In addition, the E6-p53 interaction interferes with the binding of p53 to DNA and blocks p53 acetylation (McLaughlin-Drubin and Münger 2010). Because HPV-associated oropharyngeal cancers harbor wild type, non-mutated p53 that has a pro-apoptotic activity, it was suggested that disrupting the E6-p53 complex may induce apoptosis in HPV related malignancies (Li and Johnson 2013; Caicedo-Granados et al. 2014).

Genomic instability is an early event in HPV-associated carcinogenesis (Moody and Laimins 2010). In addition to the integration of the HPV genome into the host cell DNA, HPV E6 and E7 may also contribute to the development of chromosomal aberrations, partly by blocking p53, an important factor maintaining the stability of the genome, and partly by inducing centrosome abnormalities (McLaughlin-Drubin and Münger 2010).

It is worthy to note that HPV directly inhibits interferon synthesis and signaling *via* the interaction of E6 and E7 proteins with components of the interferon signaling pathways (reviewed by Stanley 2012). Such a mechanism may facilitate the immune escape of HPV-positive carcinomas.

8 Epstein-Barr Virus: The First Human Tumor Virus

Epstein-Barr virus (EBV), a human gammaherpesvirus, is associated with both lymphomas and carcinomas, including Burkitt's lymphoma (BL), Hodgkin's lymphoma, midline granuloma, post-transplant lymphoproliferative disorders (PTLDs), X-linked lymphoproliferative syndrome, nasopharyngeal carcinoma (NPC), gastric carcinoma, and others (reviewed by Shah and Young 2009; Sugden 2014). In immunosuppressed and immunodeficient patients, EBV-related leiomyosarcomas, i.e. smooth muscle neoplasms may also develop (Dalal et al. 2008). EBV, the first human tumor virus, was discovered in BL cell cultures. Although it was initially considered a purely lymphotropic virus, an *in situ* hybridization study of anaplastic NPCs revealed the presence EBV DNA in the carcinoma cells, but not in infiltrating lymphocytes, suggesting a role for EBV in the malignant transformation of epithelial cells, too (Epstein et al. 1964; Sugden 2014; Wolf et al. 1973).

9 Estein-Barr Virus: Basic Facts

Epstein-Barr virus (EBV, also known as human herpesvirus 4, HHV-4) belongs to the genus *Lymphocryptovirus* within the subfamily *Gammaherpesvirinae* of the family *Herpesviridae*. The prototype EBV genome is 172 kbp in length and it is packaged into the virions as a linear DNA molecule. Upon infection of B-lymphoid and epithelial cells, the linear EBV genome undergoes circularization, and latent EBV genomes typically persist as circular episomes attached to the nuclear matrix. Latent EBV episomes co-replicate with the cellular DNA and display a restricted gene expression pattern. In contrast, all viral genes are expressed and a large number of linear EBV genomes are generated upon induction of lytic, productive EBV replication. Depending on the host cell phenotype, latent EBV genomes adopt distinct gene expression patterns (latency types) and the activity of latent viral promoters is regulated by the cellular epigenetic machinery (reviewed by Takacs et al. 2010). In turn, latent, growth-transformation associated EBV proteins affect the host cell transcriptome and epigenome through the interaction with cellular epigenetic regulators (reviewed by Niller et al. 2009).

10 EBV and Nasopharymgeal Carcinoma: Epidemiology

EBV is a ubiquitous herpesvirus spreading among humans most commonly through saliva and other bodily fluids. The majority of the population undergoes inapparent primary infection in early childhood. The virus replicates in oropharyngeal epithelial cells, but also infects B lymphocytes, and latent EBV genomes are carried by resting, memory B cells for life. Primary EBV infection in teenagers or adults causes infectious mononucleosis (IM, also called glandular fever), a self-limiting disease (reviewed by Niller et al. 2007; Sugden 2014).

Nasopharyngeal carcinoma was the first cancer of the head and neck region that was found to be associated with a human virus (Wolf et al. 1973).

There are two major types or classes of nasopharyngeal carcinoma, keratinizing squamous cell carcinoma accounting for 20 % of NPC cases, and non-keratinizing squamous cell carcinoma. Keratinizing squamous cell carcinomas of the nasopharynx occur sporadically throughout the world at a relatively low incidence. They are either EBV-positive or EBV negative, depending on the geographical area (Nicholls et al. 1997). The non-keratinizing type represents 80 % of NPC cases and it is invariably associated with EBV (reviewed by Shah and Young 2009). Although EBV infects human populations all over the world, the incidence of the non-keratinizing type of NPC, including both differentiated and undifferentiated forms carrying latent EBV episomes in almost 100 % of cases, occurs with a high incidence at restricted geographical locations, i.e. it is an endemic tumor in Southeast Asia, Tunisia, and among Alaskan and Greenland Inuit (reviewed by Shah and Young 2009; Niller et al. 2007).

11 Risk Factors Affecting the Incidence of Nasopharyngeal Carcinoma

Several genetic risk factors were identified in China, especially in the Guangzhou area, that may contribute to the high NPC incidence. These include an allele encoding a member of cytochrome-P450 super-family of proteins involved in the activation of carcinogenic compounds, a gene coding for a glutathione S-transferase that contributes to the detoxification of carcinogens, as well as genes located to or near to HLA loci and genes encoding enzymes and regulators of the DNA repair machinery (reviewed by Lung et al. 2014; Niller et al. 2007). It is worthy to note that epigenetic inactivation of cellular genes, mainly by promoter hypermethylation, also plays an important role in the generation of NPC (reviewed by Niller et al. 2014; Li et al. 2011).

Additional risk factors are volatile nitrosamines that may act as initiators of chemical carcinogenesis and phorbol ester-like compounds that may act as promoters, stimulating the proliferation of cells carrying mutated, initiated genomes. Such compounds are present in medical herbal teas or in the diet, including salted fish. Phorbol-ester-like compounds such as diterpene-esters may also induce lytic EBV replication, i.e. reactivation of latent EBV genomes in B cells infiltrating the nasopharyngeal epithelium (Ito et al. 1983; Ho et al. 1978). Increased local EBV load may facilitate the infection of epithelial cells, an early event in NPC development.

12 NPC: Carcinogenesis

As briefly outlined above, in addition to EBV infection, genetic factors and environmental carcinogens also play a role and act in concert during the initiation and progression of NPC. Based on these observations, Lo et al. elaborated a collaborative model for NPC tumorigenesis (Lo et al. 2012). They suggested that DNA damage elicited by carcinogens (e.g. nitrosamines from salted fish and preserved food) and local chronic inflammation might cause chromosomal aberrations that could be detected in the dysplastic lesions of the nasopharynx. A typical finding was the deletion of the short arm of chromosome 3 (3p) affecting several tumor suppressor genes. In addition, epigenetic mechanisms such as promoter hypermethylation also contribute to the silencing of tumor suppressor genes already in

EBV-negative dysplastic lesions. Centrosome abnormalities and the generation of multipolar spindles may also induce genetic instability at this stage. Loss of the *p16* tumor suppressor gene may result in the overexpression of cyclin D1 that favours stable latent EBV infection of nasopharyngeal epithelial cells. EBV infection and the clonal proliferation induced by latent EBV proteins and RNAs may accelerate neoplastic development (Lo et al. 2012).

Viral gene expression patterns of NPC typically corresponds to the so called latency type II.: in addition to the nuclear protein EBNA1 (EBV nuclear antigen 1), a variable expression of LMP1 (latent membrane protein 1) and LMP2A (latent membrane protein2A) is observed in NPC (reviewed by Niller et al. 2007). LMP1 is an oncoprotein, its expression in rodent cells results in malignant transformation. The EBV genome encodes non-translated microRNAs as well that act as posttranscriptional regulators of mRNA and protein levels. Hsu et al. observed that miR-BART9 targets the E-cadherin mRNA and promotes migration and metastasis formation by NPC cells (Hsu et al. 2014).

13 Other Viruses Possibly Associated with Head and Neck Carcinomas and Oral Precancerous Lesions: Torque Teno Virus (TTV) and Hepatitis C Virus (HCV)

Torque Teno viruses (TTVs) belong to the family of *Anelloviridae* and have a small, circular, single stranded DNA genome (reviewed by Spandole et al. 2015). Although the first TTV-like sequence was found in the serum of a patient with post-transfusion hepatitis, at present, TTV is not linked to either hepatitis or any other disease as a causative agent (Nishizawa et al. 1997; Okamoto 2009). TTVs are ubiquitous viruses with a nearly 100 % prevalence that establish persistent infection (Saback et al. 1999; Hsieh et al. 1999; Zhong et al. 2001; Ninomiya et al. 2008; Hussain et al. 2012; Vasilyev et al. 2009). Children may be infected by the end of their first year and simultaneous infections may also occur (Ninomiya et al. 2008). TTVs can be found in wide range of tissues and body fluids including liver, bone marrow, lymph nodes, spleen, pancreas, thyroid, lungs, kidneys, PMBCs, saliva, urine, tears, nasal secretion, feces, throat swabs, bile and semen (Spandole et al. 2015). In addition, TTV related sequences were detected in many different human diseases including AIDS, neoplasia, asthma and rheumatoid arthritis (Moen et al. 2002; Thom and Petrik 2007; Pifferi et al. 2005; Saláková et al. 2009; Figueiredo et al. 2007; Suzuki et al. 2014; de Villiers et al. 2007; Gergely et al. 2006). Regarding head and neck cancer, TTV related sequences were found in laryngeal cancer (de Villiers et al. 2002). Furthermore, co-infection with genogroup 1 TTV and HPV was associated with poor clinical outcome of laryngeal carcinoma and the co-prevalence of these viruses was significantly higher in lesions of oral squamous cell cancer and oral lichen planus compared to healthy mucosa (Szládek et al. 2005; Fehér et al. 2009). TTV DNA activates Toll-like receptor 9 (TLR9) and induces the production of different pro-inflammatory cytokines. Thus, TTV may affect the severity of diseases where inflammation plays an important role (Rocchi et al. 2009; Maggi and Bendinelli 2009). In addition, TTVs encode a microRNA (TTV-tth8 miRNA) that interferes with interferon signaling (Kincaid et al. 2013). TTV-tth8 miRNA may play a role in immune evasion by TTV and by TTV infected cells by interacting with the mRNA of a regulatory protein, N-myc (and STAT) interactor (NMI) that modulates interferon and cytokine signaling (Kincaid et al. 2013).

Hepatitis C virus (HCV), an enveloped, positive-sense single stranded RNA virus is a member of the *Flaviviridae* family; HCV causes chronic liver disease (Mohd Hanafiah et al. 2013). HCV infection is also associated with several extrahepatic manifestations (EHMs) (Zignego et al. 2007). One of the EHMs is oral lichen planus (OLP). It is worthy to note, however, that the association of HCV infection and OLP was stronger in Mediterranean countries and in Japan, whereas in northern Europe OLP was not associated with chronic liver disease caused by HCV (Carrozzo 2008). OLP is a chronic inflammatory disease that affects the skin and also the oral mucosa. The malignant transformation rate of

Table 1 Viruses associated with head and neck carcinoma

Virus	Major viral oncoproteins	Neoplasm or precancerous lesion
Human papillomavirus	E6, E7	Oropharyngeal carcinoma, non-keratinizing; basaloid phenotype
Epstein-Barr virus	LMP1, LMP2A, EBNA1 (?)	Nasopharyngeal carcinoma, non-keratinizing type
Torque teno virus	?	Laryngeal carcinoma (?)
Hepatitis C virus	?	Oral lichen planus (?)

OLP was found to be quite low (1.09 %); still, it may play a role in the development of oral cancer (Fitzpatrick et al. 2014).

Further studies may clarify the role of TTV and HCV in HNSCC development.

Table 1 summarizes the viruses associated with head and neck carcinomas.

14 Bacteria Associated with Head and Neck Carcinoma

Although tobacco smoking, alcohol intake and HPV16 infection appear to be major, independent risk factors of a HNSCC, especially oral carcinoma, a series of observations indicate that oral bacteria and fungal infections of the oral cavity may also be associated, either casually or causally, with oral neoplasia. In a pioneering study, Nagy et al. analysed the biofilm flora present on the surfaces of oral squamous cell carcinomas and on the contiguous healthy mucosa (Nagy et al. 1998). They found a higher number of both aerobic and anaerobic colony forming units at the tumour sites than at the apparently healthy mucosa. They also compared the distribution of aerobic and anaerobic bacterial species at these anatomical sites. The frequency of most aerobic species was similar at both sites, except *Serratia liquefaciens*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *beta-hemolyzing Streptococci*, and *Enterococcus faecalis* that were isolated more frequently from the biofilm samples obtained from the surfaces of oral carcinomas. Regarding anaerobic species, the frequency of peptostreptococci and lactobacilli was comparable at both sites, whereas *Actinomyces* spp., *Propionibacterium* spp., *Clostridium* spp., *Veilonella* spp., *Fusobacterium* spp., *Prevotella* spp., *Porphyromonas* spp., and *Bacteriodes ureolyticus/gracilis* was isolated more frequently from the tumor surface than from the control mucosal surface (Nagy et al. 1998). It is worthy to note that the fungus *Candida albicans* was detected in a significant fraction of oral carcinomas, but not at control sites (Nagy et al. 1998). Nagy et al. concluded that the cancer lesion itself may predispose patients with oral carcinoma to both local and systemic infections (Nagy et al. 1998). In a follow-up study, they demonstrated that topical antimicrobial treatment of oral squamous cell carcinoma lesions effectively reduced the number of biofilm-associated bacteria (Nagy et al. 2000). It is worthy to note that radiotherapy or cytostatic treatment of HNSCC patients also affected the composition of oral microbiota, resulting in an increased risk of local and systemic infections by pathogenic or opportunistic microbes (reviewed by Meurman 2010).

Hooper et al. aimed at the localization of bacteria within a surface-decontaminated oral squamous cell carcinoma (OSCC) sample; they performed *in situ* hybridization with a FITC-labeled oligonucleotide recognizing a sequence within the 16S rRNA gene of *Bacteria* (Hooper et al. 2007). They found bacteria throughout the tumor tissue. Analysis of bacterial species by PCR cloning and sequencing of the 16S rRNA gene revealed that there was a trend for an enrichment of *Clavibacter michiganensis*, *Fusobacterium naviforme*, *Ralstonia insidiosa* and *Prevotella* spp. in the tumor-derived samples whereas control tissue samples were enriched in *Granulicatella adiacens*, *Porphyromonas*

gingivalis, *Sphingomonas* spp. and *Streptococcus mitis/oralis* (Hooper et al. 2007). Hooper et al. speculated the acidic and hypoxic microenvironment may select for the growth of certain bacterial species within tumors. They also raised the point that tumor-associated bacteria may play a role in carcinogenesis (Hooper et al. 2007). Others also emphasized that in addition to *Helicobacter pylori,* which is the causative agent of gastric carcinoma and gastric lymphoma in humans, other bacterial species could also be involved in tumorigenesis (Lax and Thomas 2002).

Pushalkar et al. used denaturing gradient gel electrophoresis and 16S rRNA gene sequencing to compare the oral microbiota of OSCC patients (Pushalkar et al. 2012). There were no significant differences in phylogenies at tumor and non-tumor sites, although four *Streptococcus* species as well as *Peptostreptococcus stomatis*, *Gemella haemolysans*, *Gemella morbillorum*, and *Johnsonella ignova* were highly associated with the tumor site. At the non-tumor site *Granulicatella adiacens* was prevalent. Pushalkar et al. noticed site- specific and subject-specific differences in the distribution of bacterial species. They suggested that certain oral bacteria may associate with different stages of OSCC and may contribute to the acidic and hypoxic milieu characteristic for neoplasms (Pushalkar et al. 2012).

Schmidt et al. performed pyrosequencing and also next generation sequencing (using the Illumina MiSeq instrument) to reveal the diversity of microbiomes in samples obtained by swabbing of oral cancer lesions and clinically normal mucosal surfaces (Schmidt et al. 2014). Based on the analysis of the V4 region of the bacterial 16S rRNA genes, they classified 65,037 sequences at the genus level and 17,115 sequences at the species level. They observed a reduced abundance of the phyla *Firmicutes* (especially *Streptococcus*) and *Actinobacteria* (especially *Rothia*) in cancer and pre-cancer samples compared to the anatomically matched clinically normal patient samples. In contrast, the proportion of *Fusobacteria* increased at the tumor site. Although there were inter-individual differences, these changes appeared to be consistent. Schmidt et al. argued that in spite of the diversity of the oral microbial community, only distinct, biofilm-forming oral bacteria adhere to oral tissues, followed by secondary colonizers. They suggested that altered surface properties at OSCC lesions may affect the adherence of bacteria, and a shift in bacterial populations may induce inflammatory responses favouring tumor progression (Schmidt et al. 2014). It is worthy to note that *Fusobacterium nucleatum*, a Gram-negative oral bacterium capable to invade the oral mucosa, was recently implicated in colon carcinogenesis (Castellarin et al. 2012; Kostic et al. 2012, 2013).

Bebek et al. amplified, cloned and sequenced variable regions 1–4 of the prokaryotic 16S rRNA gene to characterize bacterial populations in paired HNSCC and normal mucosa samples (Bebek et al. 2012). They also analysed the DNA methylation pattern of four cellular promoters (*MDR1*, *IL8*, *RARB*, *TGFBR2*) directing the expression of genes implicated in inflammation and tumorigenesis. Interestingly, hypermethylation of the *MDR1* promoter, a phenomenon regularly associated with promoter silencing, correlated with the presence of bacteria belonging to the *Enterobacteriaceae* family and the *Tenericutes* phylum (Bebek et al. 2012). *MDR1* codes for multidrug resistance protein 1, a drug efflux pump for xenobiotic compounds and MDR1 hypermethylation may contribute to the progression of gastric carcinoma (Tahara et al. 2009). Bebek et al. speculated that inflammatory processes elicited by bacteria may facilitate tumorigenesis by inducing hypermethylation of distinct cellular promoters (Bebek et al. 2012). It is worthy to note that the phylum *Tenericutes* includes the genera *Mycoplasma* and *Ureaplasma* which are prevalent in oral samples from STD patients (Nakashima et al. 2014). Others identified *Mycoplasma salivarium* as a dominant colonizer of oral carcinoma in two Fanconi anaemia patients, and it was also observed that *Mycoplasma fermentans* and *Mycoplasma penetrans* induced malignant cell transformation *in vitro* (Henrich et al. 2014; Tsai et al. 1995; Feng et al. 1999; Zhang et al. 1997).

The distribution of bacterial species detected in the saliva may reflect the microbial diversity of the soft tissues located in the oral cavity. Thus, in principle, the salivary microbiota could be used as a diagnostic marker of OSCC. Mager et al. observed that the salivary counts of *Capnocytophaga gingivalis*, *Prevotella melaninogenica*, and *Streptococcus mitis* were elevated in the saliva of OSCC patients compared to the unstimulated saliva samples of OSCC-free subjects (Mager et al. 2005). Mager et al. speculated that alterations of tumor cell receptors may facilitate the adherence of certain bacteria and the resulting shift of soft tissue microbiota in the oral cavity may affect the levels of bacteria in the saliva (Mager et al. 2005). A recent study also found a shift in the saliva microbiome of OSCC patients: the most prevalent genera were *Streptococcus*, *Gemella*, *Rothia*, *Peptostreptococcus*, *Lactobacillus*, and *Porphyromonas*. In contrast, in control saliva samples *Prevotella*, *Neisseria*, *Leptotrichia*, *Capnocytophaga*, *Actinobacillus*, and *Oribacterium* dominated (Pushalkar et al. 2011).

Although the exact role of oral bacteria in carcinogenesis remains to be clarified, one potential mechanism is the generation of carcinogenic metabolites by certain oral bacteria (Meurman and Uittamo 2008). It was demonstrated that both non-pathogenic *Neisseria* strains and strains of *Streptococcus salivarius* and *Streptococcus intermedius* as well as *Corynebacterium* spp. and *Stomatococcus* spp. are capable to convert ethanol to acetaldehyde, a mutagenic and carcinogenic substance (Muto et al. 2000; Homann et al. 2000; Kurkivuori et al. 2007). Such a mechanism may explain how poor dental status associated with bacterial overgrowth may increase oral cancer risk in patients with tooth loss, poor dentition and inadequate oral hygiene (Homann et al. 2000, 2001). Homann et al. demonstrated an increase in salivary acetaldehyde production from ethanol in saliva samples of patients with poor dental status (Homann et al. 2001).

Table 2 summarizes the bacteria associated with head and neck carcinomas and their putative role in carcinogenesis.

15 Fungi Associated with Head and Neck Carcinoma

In parallel to the alterations of the bacterial flora in oral cancer (see above), Nagy et al. described the presence of *Candida albicans* in a significant fraction of oral carcinomas, but not at control sites (Nagy et al. 1998). Furthermore, similarly to certain oral bacteria, it was documented that both *Candida albicans* strains and non-Candida albicans yeasts were capable of salivary acetaldehyde production from ethanol, and *Candida albicans* could frequently be detected in oral epithelial dysplasia, a premalignant lesion with an increased risk of oral cancer (Tillonen et al. 1999; McCullough et al. 2002; Nieminen et al. 2009, reviewed by Sitheeque and Samaranayake 2003; Bakri et al. 2010).

Chronic hyperplastic candidiasis (CHC, also referred to as candidal leukoplakia) is a clinical term for *Candida*-infected oral leukoplakias of the oral mucosa that are characterized by hyphal invasion and parakeratinosis. Although most frequently *Candida albicans* could be detected in CHC lesions, other species including *Candida dubliniensis*, *Candida tropicalis*, *Candida pintolopesii*, *Candida glabrata* and *Sacharomyces cerevisiae* were also detected in adherent chronic white patches of the oral mucosa (Cernea et al. 1965; Jepsen and Winther 1965; Krogh et al. 1986, reviewed by Bakri et al. 2010). *C. albicans* may either colonize existing premalignant or malignant oral lesions, or may promote the generation of precancerous conditions and their progression to cancer (Cernea et al. 1965; Jepsen and Winther 1965; Nagy et al. 1998; Sitheeque and Samaranayake 2003; Bakri et al. 2010; Sanjaya et al. 2011). A strong argument for a carcinogenic role of *Candida* infection is the production of carcinogens by certain *Candida spp.*: in addition to the mutagenic acetaldehyde (see above), formation of the potent carcinogen N-nitrosobenzylmethylamine (NBMA) was also observed (Krogh et al. 1987; Krogh 1990). Production of proteinases and pro-inflammatory mediators by *Candida* spp. may also contribute, indirectly, to carcinogenesis

Table 2 Bacteria associated with oral carcinomas and their putative role in carcinogenesis or tumor progression

Bacterium	Putative role	Reference
Serratia liquefaciens	?	Nagy et al. (1998)
Klebsiella pneumoniae	?	
Citrobacter freundii	?	
beta-hemolyzing Streptococci	?	
Enterococcus faecalis	?	
Actinomyces spp.	?	
Propionibacterium spp.	?	
Clostridium spp.	?	
Veilonella spp.	?	
Fusobacterium spp.	?	
Prevotella spp.	?	
Porphyromonas spp.	?	
Bacteriodes ureolyticus/ gracilis	?	
Clavibacter michiganensis	?	Hooper et al. (2007)
Fusobacterium naviforme	?	
Ralstonia insidiosa	?	
Prevotella spp.	?	
Streptococcus spp.	Contribution to the acidic and hypoxic milieu	Pushalkar et al. (2012)
Peptostreptococcus stomatis		
Gemella haemolysans, *Gemella morbillorum*		
Johnsonella ignova		
Fusobacterium spp.	?	Schmidt et al. (2014)
Enterobacteriaceae (family)	Induction of cellular promoter hypermethylation; induction of pro-inflammatory changes	Bebek et al. (2012)
Tenericutes (phylum)		
Streptococcus salivarius	Conversion of ethanol to mutagenic acetaldehyde	Muto et al. (2000), Homann et al. (2000), Kurkivuori et al. (2007)
Streptococcus intermedius		
Corynebacterium spp.		
Stomatococcus spp.		

Table 3 Fungi associated with oral carcinomas and their putative role in carcinogenesis

Fungus	Putative role	References
Candida spp.	Salivary acetaldehyde production from ethanol	Tillonen et al. (1999)
	Formation of carcinogen (nitrosobenzylmethylamine, NBMA)	Krogh et al. (1987), Krogh (1990)

by degrading cell surface proteins, basement membrane and extracellular matrix components and by eliciting chronic inflammation (reviewed by Bakri et al. 2010). Table 3 summarizes the fungi associated with head and neck carcinomas and their putative role in carcinogenesis

16 Conclusions

In the head and neck region, besides traditional risk factors such as smoking habits and alcohol consumption, certain microbes also play a role in

the generation of malignant epithelial tumors. Infection with high-risk human papillomavirus types is strongly associated with the development of oropharyngeal carcinoma and Epstein-Barr virus appears to be indispensable for the development of non-keratinizing squamous cell carcinoma of the nasopharynx. Infection with other viruses including torque teno virus and hepatitis C virus may increase the risk of initiation or progression head and neck carcinomas. A shift in the composition of the oral microbiome was also associated with oral squamous cell carcinoma, although the exact role of oral bacteria remains to be clarified. Conversion of ethanol to acetaldehyde, a mutagenic compound, by members of the oral microflora as well as by fungi including *Candida albicans* and others may increase oral cancer risk. In addition, distinct *Candida spp*. also produce NBMA (N-nitrosobenzylmethylamine), a potent carcinogen. Inflammatory processes elicited by microbes may also facilitate tumorigenesis in the head and neck region.

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