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Review

Herpesviruses in head and neck cancers.

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Abstract: Head and neck cancers arise from mucosa lining the oral cavity, oropharynx, hypopharynx, larynx, sinonasal tract, and nasopharynx and the etiology of head and neck cancers is complex and involves many factors, among which oncogenic viruses are also enumerated. Nevertheless, this type of cancers are among the most common cancers around the world. The thorough knowledge of the pathogenesis of viral infection is needed to fully understand its impact on cancer development.

Keywords: herpesviruses; oncogenic viruses; head and neck cancer

1. Introduction

Head and neck cancers (HNC) are diseases that can affect many places of cellular origin in the head and neck such as: paranasal sinuses, nasal cavity, mouth, throat, larynx, salivary glands and thyroid [1]. Cancer is a disease caused by the body's exposure to one or many physical or chemical, so-called oncogenic, factors, accidental errors in the replication process or errors in the process of DNA repair. All these factors contribute to the occurrence of cytogenetic changes caused by a series of mutations of individual genes, resulting in uncontrolled cell proliferation [2,3,4]. Global Cancer Observatory (GCO) data for 2018 estimate 354.864 cases of lip and oral cavity cancer, 296.851 brain and central nervous system cancers and 41.799 Kaposi sarcomas cases, in which fatal were 177.384, 241.037 and 19.902 respectively [5]. HNC was a disease mainly diagnosed in patients aged 45-50 [2,6]. An upward trend in the incidence of head and neck cancers after 1915 was shown also among young people [2,6,7,8]. This provides information about the high correlation of this type of cancer with environmental factors, smoking, alcohol consumption but also diet-related factors, oral hygiene and viral infections. In addition to factors such as alcohol and cigarettes, which are considered to be the main causes of about 75% of all cases of oral squamous cell carcinoma (SCC), viruses are an important factor. The most common viruses in the transformation of HNC were: Human papilloma virus (HPV) [9,10], herpesviruses, adenoviruses [11] and hepatitis C viruses [12,13]. Among extensive herpesviruses' family (Figure 1.), the role of only a couple has been confirmed in HNC, e.i. HHV-1-8.

In this paper, we will try to focus on the current state of knowledge and research about the impact of herpesviruses infection on the development of HNC.

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Figure 1. Systematic tree of *Herpesvirales* order based on ICTV [14].

2. HHV-1 (human herpesvirus 1), HSV (herpes simplex 1 virus) and HHV-2

It has been shown, that patients with head and neck squamous cell carcinoma (HNSCC) are often coinfected with HSV-, but the infection of the virus is usually asymptomatic [6,15]. It is considered

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that high prevalence of HSV-1 in patients treated for HNSCC is due to a high level of stress associated with hospital procedures and healing trauma [16]. Due to several molecular mechanisms that are observed during HSV-1 infection, as affecting apoptotic pathways by down-regulating p53 and interacting with DBA repair mechanisms, along with causing chromosomal instability, it was suspected, that HSV-1 may affect the radiation response of infected cells during HNSCC treatment [6]. Studies have shown [6], that HSV-1 infection modulates radioresistance of HPV16-positive hypopharyngeal carcinoma cells. As it is known that HSV-1 may coinfect HPV-infected premalignant or malignant cells, it is pivotal to know if HSV-1 infection can impact on HPV-infected cells survival [16]. Research of Turunen et al. [6] confirms that the main role of HSV-1 in HNSCC is inhibiting the intrinsic apoptotic pathway and lowering HPV-specific anti-apoptotic gene expression in the infected cells.

In different studies, concerning oral mucositis (OM), which is a side effect of antineoplastic treatment in patients with HNSCC it was shown [17], that presence of the HSV1 and HSV2 viruses has no correlation with the existence of OM.

There are also evidences, that HHV-1 is associated with oral squamous cell carcinoma (OSCC) [18,19]. Studies in Poland, performed on fresh-frozen tumor tissue fragments from 80 patients with OSCC, show that in 7,5% of samples HHV-1 was present, showing that HHV-1 is a potential coinfection in OSCC and may be an important co-factor in oropharyngeal cancer [20].

HHV-1 and HHV-2 is also understood by some researchers as a potential risk factor of head and neck carcinomas, together with tobacco, alcohol, oncogenic HPV [21]. This was also confirmed in Swedish studies performed patients with oral cancer [22] and American study, in which it was suggested that HSV1 may enhance the development of OSCC in individuals who are already at increased risk of the disease because of cigarette smoking or HPV infection [23].

On the other hand, there are also paper that do not confirm the correlation between herpes virus infection and the risk of head and neck cancer, but those studies are more related with HHV-2 infection. Maden et al. [24] found a non-significant level of risk of oral cancer associated with HHV-2 infection. The lack of significant association of HSV1 and HSV2 infection in patients with head and neck cancers was also confirmed by Parker et al. [25]. Similarly, insignificant were the results of patients with OSCC, toombak and non-toombak users [26]. Moreover, no correlation between OSCC development and the presence of HSV-1 was detected [27] and yet the question is still unanswered, whether HSV-1 and HSV-2 play an active role in head and neck cancer's development, or are just a bystanders in the decreased local immune-deficient tumor area.

Summing up, it may be stated, that the role and impact of HHV-1 and HHV-2 on head and neck cancers remain unclear. Efforts are put into the explanation of the crosstalk between those factors, with a special emphasis on possible treatment. One of the promising therapies may be the use of oncolytic herpes simplex virus NV1020, which is an effective model in mice, causing tumor regression [28].

3. HHV-3 (*Varicella-zoster virus*, VZV)

Reports on HHV-3 impact on head and neck cancers are very limited. There has been only one paper found on the case of a patient with OSCC with negative PCR result for VZV, but serological tests was VZV-positive. Unfortunately, the patient died regardless of VZV treatment [29]. On the basis of this report it was stated, that VZV infection should be excluded while diagnosing OSCC.

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4. HHV-4 / EBV *(Epstein-Barr virus)*

Over 90% of the adult population is infected with EBV [30,31]. It has the ability to infect both B lymphocytes and epithelial cells throughout the body, including the head and neck region [32]. It is the first virus directly related to carcinogenesis and has been classified as group 1 carcinogen [33].

EBV is constantly detected in nasopharyngeal cancers [34]. Studies have shown that EBV DNA is clonal, which may be evidence of a relationship between nasopharyngeal cancer development and virus infection [35]. Serological tests in patients with nasopharyngeal cancer have shown an increased value of IgA and IgG antibodies to viral capsid antigen, early antigens and nuclear antigens [36].

Samples from patients with oral squamous cell carcinoma (OSCC) of the oral cavity, analyzed for the presence of HPV, HSV, CMV and EBV viruses, allowed to identify EBV in 57.5% of the examined persons. In addition, 7.5% of patients were identified with HHV-1 virus and 10% with CMV. Co-infection with viruses was found in 30% of cases, including EBV and HPV co-infections most frequently [20].

Studies show the presence of EBV in patients with Hodgkin's Lymphoma (HL) [37,38,39]. In addition, a relationship between the virus and the heterogeneous Non-Hodgkin's Lymphoma (NHL) group (Burkitt's lymphoma, NK cell lymphoma, proliferative lymphoma) has been demonstrated [40,41]. It has been proved that the virus can cause proliferative diseases in people with immune disorders [52]. It is also believed that it plays an important role in the lymphomagenesis process [43]. It may also be associated with proliferative disorders in atopic lymphocytes and cancer cells after transplantation [44]. Its association with lymphomas in patients with immunosuppression and angiocentric lymphomas from the paranasal sinuses indicates a possible causal role of EBV in these forms of NHL [45].

A link was also found between plasmablastic lymphoma (PBL) and the presence of EBV in patients [46]. No effective and standard PBL treatment has been found so far; the basis of treatment is chemotherapy and occasional radiation therapy [32].

The presence of EBV has also been confirmed in the development of Burkitt's lymphoma [32]. Control tests in patients with Burkitt's lymphoma showed a higher level of EBV antibodies than in healthy people [32]. Current evidence indicates that EBV is an important pathogenic agent during the development of Burkitt's lymphoma [45].

PCR analyzed and DNA sequenced samples from Sudanese snuff (toombak) users and non-users showed that EBV was present in 65% of samples from toombak users. In addition, the virus was present in 84% of non-users [26]. The presence of EBV proteins and DNA has also been found in most patients with natural killer-cell lymphomas. This fact has a poor prognosis, even when timely diagnosed [32]. At present, many studies clearly show a correlation between the occurrence of head and neck cancers and the presence of EBV [32]. Studies also show no specific relationship between smoking or alcohol consuming and the incidence of cancer [26,32]. However, there is evidence demonstrating the co-infection of various viruses (mainly HPV and EBV) and their effect on cancer development [20,32,47]. Further research is needed to determine the potential role of EBV and the possible significance of HHV-1 as a co-infection factor in oropharyngeal cancer [20]. Despite the discovery of EBV in many patients with lymphoma, OSCC and other carcinomas, the etiological relationship between EBV and carcinogenicity has not yet been discovered.

5. HHV-5 *(Cytomegalovirus, CMV)*

Although CMV is considered as non-oncogenic virus, many clinical and experimental findings suggest a contribution of HCMV to malignancy and chemoresistance of infected tumor cells from different entities [48]. Paper dated many years ago [49], on patients with nosopharyngeal carcinoma from North Africa confirmed the presence of CMV. Analogous study was recently performed in Sudan, and CMV was identified in almost 1/3 of the samples, showing a relatively considerable association between CMV and nosopharyngeal carcinoma [50]. Also some observations were done in patients with head and neck cancer receiving radiotherapy or radiochemotherapy to determine the impact of CMV infection on the risk of death [51]. It was considered that the risk of death in plasma CMV-positive patients is significantly higher compared to patients with no CMV detected in plasma, so diagnosing and treating these viral infections is crucial for better cancer treatment [51].

There are evidences that CMV could be transmitted to tumor cells and may play an important role in modulating tumor microenvironment by either inhibiting or promoting the tumor cells themselves [52], so CMV may be a potential therapeutic target in these cancers.

6. HHV-6, HHV-7

It has been previously confirmed [53], that HHV-6 and HHV-7 exists in salivary glands, but whether those viruses have an impact on HNC is questionable. In paper on salivary gland neoplasm it was confirmed, that apart from the presence of those viruses in salivary glands, no correlation exists between HHV-6 and HHV-7 and salivary glands neoplasms [54]. No other proofs of those herpesviruses in HNC have been found in literature.

7. HHV-8 / KSHV *(Kaposi's sarcoma herpes virus)*

KS is the most common cancer associated with HIV / AIDS. Despite many successes in the diagnosis and treatment of KS [55,56], the pathogenesis process itself remains unexplained [55]. One of the possible causes of the occurrence and development of soft tissue tumors of the head and neck may be infection with the HHV-8 / KSHV virus. Research is underway to demonstrate the validity of this thesis. One of them was to examine larynx cell samples from both patients with larynx cancer and healthy individuals. The presence of HHV-8 DNA was detected using PCR techniques. Among the samples, the presence of the virus was confirmed in 2 samples, both from sick and healthy people. Based on the results of the study, no significant relation was found between the occurrence of larynx cancer and KSHV infection [57].

Despite the lack of specific studies indicating a link between HHV-8 and HNC, further research is needed to confirm or refuse this thesis.

8. Conclusions

Among members of *Herpesviridae* family, herpesviruses 1-8 are known to cause the most serious diseases of different etiology in humans. The potential role and involvement of these viruses in head and neck cancers has been briefly described, showing that HHV-1, HHV-2 and HHV-4 are those with the mostly evidenced. Clearly, further investigations are needed, especially involving molecular trials, to draw detailed conclusions on the impact and role of herpesviruses in head and neck cancers.

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