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HPV+ and HPV- head and neck squamous cell carcinoma by analysis of tumor microenvironment

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Abstract

Background: Head and neck squamous cell carcinomas (HNSCCs) are particularly aggressive epithelial tumors, that affect more than half a million patients worldwide each year. They represent a multi-factorial group of tumors caused by: alcohol, tobacco, and human papillomavirus (HPV) infections. Over the last ten years the overall 5-year survival rate of HNSCCs remained ~40–50%, inspite of significant improvement in clinical outcome of many tumor types. There are recent data that claim how some of these cells fulfill a suppressive role in the antitumor immune response. It is interesting that new clinical studies demonstrated that HPV (+) HNSCCs were among tumors with the highest immune infiltrates, while HPV (-) presented a reduced number of immune infiltrating cells.

Conclusions: Recent researches prove that tumor microenvironment of HNSCC has an important role in tumor progression, aggressivity, metastasis process, in addition to genetic aberrations and molecular alterations of cancer cells. New researches in stromal composition of the HNSCC may be useful in understanding of mechanisms of different responses to therapy, also can be used as a target for therapeutic purposes. Cancer-associated fibroblasts and immune cells, as well as their products found in neck squamous cell carcinoma significantly influence the biological properties of this tumor. Smoking is one of the risk factors of occurrence of most HPV-associated tumors. Promoting smoking cessation should become an essential contributor to the treatment of cancer in all oncologic pathologies. In cases when patients can't quit smoking completely within the shortest possible period of time, doctors should focus on harm reduction strategies – tobacco harm reduction.

Key words: head and neck cancer, squamous cell, tumor microenvironment, smoking, tobacco harm reduction.

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Introduction

Approximately 90% of head and neck cancers are squamous cell carcinomas [1, 2]. Squamous cell carcinomas (SCC) are the frequent malignant tumor of oral cavity, being responsible for a high number of cancer-related deaths worldwide [3]. In Western Europe, most head and neck squamous carcinomas (HNSCCs) have as etiological factors alcohol and tobacco (for oral cancers), but infection with high-risk human papilloma viruses (HPVs) is also now determined as an important etiological factor particularly for oropharynx [4-6]. According to the report published by GLOBOCAN 2018 (global cancer statistics), more than 800000 new HNSCC cases are diagnosed each year. Currently, the majority of head and neck cancers are present with regionally advanced lymph node metastases at the time of diagnosis. The patients are often given the standard treatment options of surgery, radiotherapy, chemotherapy, or a combination of these interventions, but 40–60% of treated patients experience recurrence and are irresponsive to subsequent therapeutic interventions [7]. Therefore, despite the significant improvement in overall survival for patients with other tumor types, the 5-year rate of HNSCCs has not changed much over the past decade.

Discussion

The aim of this review is to present the role and effect of noncancerous cells and their crosstalks with cancer cells. Furthermore it will describe the metabolic changes in tumor microenvir-onment, the new data about how some of these cells accomplish a suppressive role in the antitumor immune response. Finally, it will show the clinical significance of all these factors according to the actual literature.

Overview on the tumor microenvironment (TME)

Head and neck squamous cell carcinoma is genetically a group of heterogeneous tumors. The tumor microenvironment represents an interactive, organized, and dynamic environment where cancerous cells as well as many different cellular and biochemical structures exist together and are continuously in contact and interact with each other [8]. Squamous cell carcinomas microenvironment includes lymphocytes, macrophages, dendritic cells, vascular cells, and stromal cells.

The cellular elements of the TME often develop abnormal phenotypes in a spoil response to the cancer. Genetic changes in the carcinoma cells, like alterations of TP53, NOTCH1, and specific gene expression profiles, contribute to derangements in cancer and microenvironment cells increased reactive oxygen species (ROS), overproduction of cytokines, and epithelial to mesenchymal transition [8].

Stromal Cell Contributions

Besides tumoral cells, miscellaneous stromal components: cellular or acellular provide promoting and maintaining of HNSCC invasion. Deposition of specific extracellular matrix (ECM) proteins (collagen IV, collagen XVII, fibronectin, and laminin) is enhanced in HNSCC tumors and serves as a chemo-attractant for HNSCC cells in various *in vitro* invasion assays [9]. As HNSCC tumors progress towards metastatic disease, non-tumor cell types from the associated stroma have been shown to have direct and indirect roles in facilitating HNSCC invasion [10].

1. Mast cells are part of the immune myeloid line, that mediate immune responses by granule exocytosis, releasing histamine, serine proteases, carboxypeptidase A, proteoglycans, prostaglandin D2, leukotriene C4, tumor necrosis factor (TNF)-α, IL-3, IL-4, IL-5, IL-6, IL-8, and IL-16. In advanced stages of HNSCC, mast cells accumulate in the tumor stroma, and their presence is directly correlated with increased angiogenesis [11]. Additionally, heparanase, an enzyme involved in cleavage and remodeling heparin sulfate proteoglycans from the extracellular matrix, accumulates at the HNSCC invasive front, and is a marker of poor prognosis for lymph node metastasis and tumor recurrence [12]. Mast cells, along with tumor infiltrating neutrophils, endothelial cells, and macrophages exhibit heparanase activity [13]. Because, mast cells also secrete large amounts of heparin, they are the type of cells that probably are in charge for invasion-associated heparanase activity in the tumor microenvironment. Their presences also stimulate HNSCC tumor neo-vascularization and dissemination to loco-regional lymph nodes.

2. Neutrophils are enlisted to the tumor microenvironment by pro-inflammatory signals, including IL-8, transforming growth factor (TGF)-β, IL-4, IL-10, IL-13 and TNF-α [14]. In tumor microenvironment, neutrophils secrete VEGF-A, stimulating neovascularization through endothelial cell recruitment and proliferation, which can be suppressed by anti-VEGF-A antibodies or angiostatin treatment [13, 14]. Also, neutrophil-derived HGF and MMP-9 facilitate tumor cell migration and invasion towards the newly formed vascular bed [14].

3. Macrophages play a direct role in immune supervision via endocytosis of pathogens and cellular debris [15]. Infiltration into the tumor microenvironment with tumor associated macrophage (TAM) relates to lymph node involvement, tumor stage, and extracapsular spread [16]. Once they arrive in the tumor microenvironment, they secret several paracrine signaling loops that drive tumor cell invasion and metastasis. Macrophages are able to stimulate and maintain the HNSCC invasive phenotype, serve to basement membrane breakdown and recruitment of other cell types into the tumor microenvironment.

4. Fibroblasts are involved in demoplastic respons in cancer, as they can break and modify a variety of ECM proteins including type I and IV collagens, laminin, and fibronectin [17, 18]. Some studies suggest that HNSCC stroma is enriched in infiltrating cancer-associated fibroblasts (CAFs) and their highest concentration is near the invasive front of the tumor. CAFs have some characteristics of myofibroblasts, like enhanced proliferation, motility and secretion of matrix metalloproteinase-2 and hepatocyte growth factor (HGF). They express cytokeratins, vimentin, and α-smooth muscle actin (SMA) [19, 20]. Secretion of matrix metalloproteinase leads to extracellular matrix degradation and remodeling, while HGF enhances HNSCC cell motility [9, 17, 21]. The final result of fibroblasts in the tumor microenvironment is permutation of extracellular matrix proteins, allowing fibroblasts to lead tumor cells into surrounding tissues or creates pathways in the stroma for invasive tumor cells which result in HNSCC metastatic progression [22].

Involvement of HPV Virus in Head and neck cancers

A lot of studies relate that human papillomaviruses (HPVs) is implicated in the pathogenesis of HNSCCs. HPV16 represent a high-risk is the predominant HPV type in some forms of head and neck cancers, and it account about 90% of HPV DNA-positive tumors detected [22]. While, excessive smoking and alcohol usage represent major risk factors for the majority HPV (-) HNSCCs cases.

HNC and Tobacco Use, Harm Reduction Strategies

Head and neck cancers are a heterogeneous group of tumors, responsible for more than 650000 cases and 330000 deaths per year worldwide, and one of the most important etiological factors is tobacco smoking [23]. The first contact organ for tobacco smoke is mucosal tissue of the upper respiratory tract and the upper part of the digestive tract. Smoke contains chemical compounds, cytotoxic to the upper airway tissue, and can cause significant DNA damage. Therefore,the mutagenicity of tobacco smoke cannot be completely excluded as a risk factor for HNC [24]. Tobacco smoke is composed of over 7000 chemicals, of which at least 69 are cancer-causing [25]. The biggest misconception is policymakers and community in general believes that nicotine is the cancer-causing culprit in cigarettes. Cigarette smoking and the many chemicals it exposes a person to, not nicotine itself, present the highest risk.

According to Cancer Research UK [26], nicotine is addictive but does not cause cancer. Most damage to health caused by smoking is due to other chemicals in smoke, such as benzo[a]pyrene, tobacco-specific nitrosamines, and benzene, which are the primary causes of smoking-related diseases [27]. The risk of developing cancer is always higher for tobacco smokers than for non-smokers. Electronic nicotine delivery system such as tobacco heating system (THS) for our country has become increasingly popular in the last 3 years and is considered less harmful than traditional tobacco products, due to the lower content of toxic and carcinogenic compounds [28].

THS – uses an electronically controlled mechanism to precisely heat specially designed tobacco sticks at operating temperatures well below combustion (less than 350°C). As a result, the generated aerosol is composed of mainly water, glycerin and nicotine while the levels of harmful and potentially harmful constituents are significantly decreased compared to cigarettes smoke [28, 29].

The Netherlands Institute of RIVM identified carcinogenicity impact of switching from smoking cigarettes to consuming heated tobacco, the risk of cancer was reduced by 10 to 20 times, depending on different types of cancer [30].

Harm Reduction as a solution for adult smokers

Harm reduction refers to a range of practical strategies aimed at lessening the negative social and physical consequences associated with particularly risky human behaviors. Harm reduction policies are supported by 84 countries worldwide, with 74 countries having explicit supportive reference to harm reduction in national policy documents.

Quitting smoking is one of the most effective public health measures and tobacco harm reduction can supplement tobacco control. Tobacco harm reduction remains a controversial topic in tobacco control. Tobacco harm reduction involves providing tobacco users who are unwilling or unable to quit using nicotine products with less harmful nicotine containing products for continued use. Some Public Health experts believe that these products have great potential to reduce mortality and morbidity among smokers who completely switch to them. Others believe that we will be addicting another generation to tobacco products [31].

Researchers investigate the tumor-stroma interplay in high-risk human papilloma virus positive HPV+ and HPV- head and neck cancers from patients diagnosed with HNSCC. Immunosuppression in HPV positive HNSCC, is significant increased by viral infection, which may explain why, these tumors for the most part develop within the immune tissue of tonsillar lymphoid follicles, an anatomic site that should favor immunologic antitumor response [32]. The immunosuppression produced by inflammatory cytokines maintains latent infection and favors tumor genesis, which is initiated when the viral DNA integrates into the host genome and drives genomic instability. Once infected and transformed by HPV, tumor cells activate additional mechanisms to escape the immune system by preventing exposure of tumor antigens and promoting apoptosis of effector T lymphocytes and down-regulation of NK cells [4]. New knowledge in immunological characteristics of HPV^+ and HPV^- HNSCCs may improve therapeutic targeting and immunotherapy strategies for different subtypes of HNSCCs.

Conclusions

Recent research proves that tumor microenvironment of HNSCC has an important role in tumor progression, aggressivity, metastasis process, in addition to genetic aberrations and molecular alterations of cancer cells. New researches in stromal composition of the HNSCC may be useful in understanding of mechanisms for different responses to therapy, also can be used as a targeted for therapeutic purposes. Cancer-associated fibroblasts and immune cells, as well as their products found in neck squamous cell carcinoma significantly influence the biological properties of this tumor. Smoking is one of the risk factors of occurrence of most HPV-associated tumors. Promoting smoking cessation should become an essential contributor to the treatment of cancer in all oncologic pathologies. In cases when patients can't quit smoking completely within the shortest possible period of time, doctors should focus on harm reduction strategies – tobacco harm reduction.

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DB conceptualized the idea, conducted literature review, wrote the manuscript, revised and approved the final text.

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No approval was required for this review study.

Conflict of Interests
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