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Complex Interaction Among Immune, Inflammatory, and Carcinogenic Mechanisms in the Head and Neck Squamous Cell Carcinoma

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Abstract

Inflammation is deeply involved in the development of most types of cancer. Many studies focus on the interaction between immune-inflammatory mechanisms and tumorigenesis in the head and neck squamous cell carcinoma (HNSCC). In this chapter, we emphasize the complexity of processes underlying this interaction and discuss the mechanisms of carcinogenesis in HNSCC with a special focus on metabolic changes, inflammation, and the immune landscape. Unveiling complex connections between immuno-inflammatory processes and tumor initiation, promotion, and progression will open new directions in the reliable identification of predictive factors and therapeutic targets in HNSCC.

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Keywords

Cancer · Head and neck squamous cell carcinoma · Immunity · Inflammation · Therapy · Tumorigenesis

1 Introduction

Inflammation is deeply involved in the development and progression of most cancers, even if, at first glance, the mechanisms of inflammation are not prominent actors (Taniguchi and Karin 2018). Inflammation has been recognized as a promoter at all stages of tumorigenesis (Greten and Grivennikov 2019). Hence, it is not surprising that researchers have focused on studying the relations between immune-inflammatory mechanisms and tumorigenesis in different types of cancer, including head and neck squamous altering the cell carcinoma (HNSCC) (Georgescu et al. 2020; Scheau et al. 2020; Neagu et al. 2019; Tampa et al. 2018a; Tampa et al. 2018b; Georgescu et al. 2017; Neagu et al. 2016).

HNSCC is the world's sixth most frequent cancer, with an increasing incidence during the last decades, as life expectancy and global population increase (Economopoulou and Psyrri 2017). Despite great progress in diagnosing and treating cancers, death rates associated with HNSCC did not decrease significantly, due most likely to a high rate of the first diagnosis in advanced stages of the disease (Jou and Hess 2017). When early diagnosed and treated, survival rates in patients with HNSCC exceed 80–90% (NIH 2017). When distant metastases occur, although rare compared to other cancers, a high death toll of 74% at 24 months is present (Wiegand et al. 2015). This condition is commonly diagnosed in adult and elderly population, but recent data show a decreasing trend of the onset age. Men are three times more likely to develop HNSCC, but lately, an increasing incidence has also been reported in women (Chi et al. 2015).

2 Etiopathogenic Features of HNSCC in Different Locations

HNSCC includes a series of malignancies with different anatomical locations, for example, lip, oral, sinus cavities, pharynx and larynx, which are grouped according to etiopathogenic similarities, as well as clinical, therapeutic, and evolution criteria (Faraji et al. 2017).

Various endogenous and environmental factors participate in the development and progression of regional HNSCC (Solomon et al. 2018; Wu et al. 2018; Lupu et al. 2017; Voiculescu et al. 2016). For example, ultraviolet (UV) radiation is the main risk factor for lip and skin SCC as damaged. Keratinocytes accumulate mutations (Lupu et al. 2020; Chan et al. 2019; Lupu et al. 2018a, b). The UV exposure is also associated with the release of pro-inflammatory cytokines, such as TNF-α, stimulating the differentiation of monocytes into macrophages and maintaining local inflammation, which may induce angiogenesis and tumor progression (Bottomley et al. 2019). Moreover, inhibition of antitumor response in CD4+ and CD8+ lymphocytes against keratinocytes with alterations induced by UV radiation has been reported (Suwanpradid et al. 2017). Exposure to UV radiation has also been investigated in the context of decreasing density of the antigen-presenting. Langerhans and dendritic epidermis-resident cells. The apoptosis of these cells may exert Th2 and Treg-related immunosuppressive effects altering the antitumor immune response (Otsuka et al. 2018; Pettersen et al. 2011).

In HNSCC, smoking and chronic alcohol consumption are involved in more than 75% of cases (Hashibe et al. 2007). When these factors are combined, their damaging effects are enhanced and the risk of developing HNSCC can increase by 35-fold (Economopoulou and Psyrri 2017). Tobacco use induces epigenetic alterations in oral mucosa, with modified expression of various

genes such as p53, GLUT-1, p16, and P13K in oral epithelial cells. It can impair various immune mechanisms involved in antitumor response and can activate oxidative stress reactions, leading to increased expression of pro-inflammatory genes and status of chronic inflammation (Jiang et al. 2019; Khowal and Wajid 2019; Seifi et al. 2014). Alcohol increases the permeability of oral mucosa for carcinogens. It also generates toxic compounds that can induce DNA damage and stimulate cell proliferation. Chronic alcohol intake is also associated with free radicals production that may induce immunosuppression (Feller et al. 2013).

Human papillomavirus (HPV) infection is mainly associated with oropharyngeal cancers, exhibiting a different behavior compared to tobacco- and alcohol-induced cancers (Tampa et al. 2020; Boda et al. 2018; Georgescu et al. 2018; Kobayashi et al. 2018; Boda et al. 2016). Almost half of these carcinomas are correlated with an active HPV status (Quabius et al. 2015). The most prevalent viral types are HPV16, HPV18, and HPV33 (Faraji et al. 2017; Ndiaye et al. 2014). Studies on a large number of patients have suggested that HPV+ tumors should be considered as distinct pathological entities within the wide group of HNSCC due to specific molecular features that correlate with improved response to therapy and prognosis (Dayyani et al. 2010). The 2017 classification of the tumor (T), nodes (N), and metastases (M) (TNM) has been updated according to these findings (Amin et al. 2017). Moreover, individualized therapies are proposed based on the HPV status (Cao et al. 2017; Husain and Neyaz 2017; Keck et al. 2015). There is a complex connection between HPV infection and chronic inflammation as the inflammatory cytokines can facilitate viral penetration and survival in the oral mucosa. They can also influence the proliferation of keratinocytes and viral activation (Tezal 2012; Tezal et al. 2012). Other studies have shown that HPV infection is associated with an increased T-cell infiltration and immune cell activation, considering the HPV status as a predictive factor for programmed cell death protein 1 (PD-1) inhibitors' therapeutic efficacy in HNSCC (Wang et al. 2019; Gameiro et al. 2018).

Occupational exposure to carcinogens like wood, textiles, or leather compounds is incriminated in the development of sino-nasal SCC. These tumors have a poor prognosis, especially when correlated with smoking, considering that most patients show advanced disease staging at the time of diagnosis (Elgart and Faden 2020).

A glance at the main risk factors of HNSCC and their mechanisms of action brings to attention the interconnections between inflammation, immune factors, and carcinogenic processes (see Fig. 1). To unravel the complexity of these processes, in the following sections we delineate the mechanisms of carcinogenesis in HNSCC with a special focus on metabolic changes, inflammation, and the immune landscape. We also highlight the importance of this topic for the discovery of new biomarkers and emerging therapies for HNSCC.

3 Mechanisms of Carcinogenesis in HNSCC

3.1 Genetic Traits in HNSCC

The mechanism of cancer initiation has been intensely studied over the years. The first step in the understanding of carcinogenesis was Rudolf Virchow's description of cancer cells (see McManus 1958). Shortly afterward, Theodor Boveri described the uncontrolled division of cells with a modified nuclear content in cancers, and these changes were linked to external factors (see Opitz 2016). Decades later, the first oncogene v-Src and the first tumor suppressor gene (TSG) were discovered, confirming the genetic basis of carcinogenesis (Alfred and Knudson 1971; Duesberg and Vogt 1970). Experimental murine models have been created through genetic engineering over the last years, with the intent of studying various types of cancer (Kersten et al. 2017). DNA sequencing techniques have revolutionized medical research allowing the characterization of the entire genome, including the mutations that trigger tumors (International Human Genome Sequencing Consortium 2004). Focal mutations, deletions, duplications, or

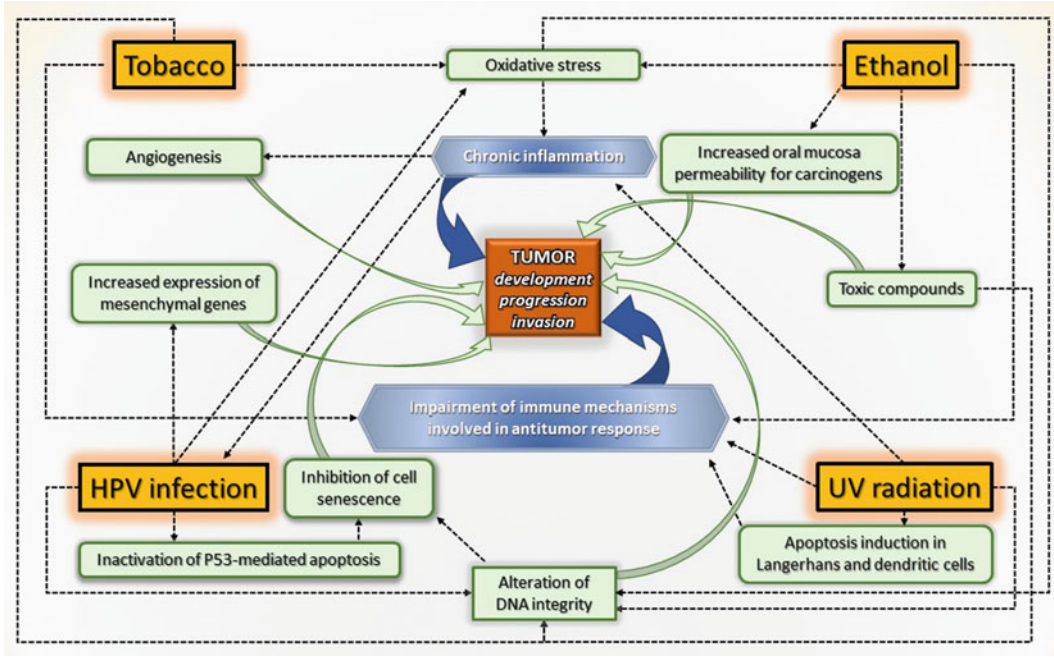

Fig. 1 Interconnections between inflammation, immune factors, and carcinogenic processes associated with the main risk factors of head and neck squamous cell carcinoma (HNSCC)

insertions of nucleotides contribute to the tumor mutational burden (TMB). A genetic database analysis has identified patterns of mutated genes, attributing genetic signatures to each type of neoplasia (Fancello et al. 2019; Chalmers et al. 2017).

HNSCC arises frequently from premalignant lesions, with a gradual accumulation of mutations associated with long-time exposure to external carcinogens in addition to increased age-related DNA instability (Monisha et al. 2017). Mutations of the tumor suppressor TP53 gene have been identified in most cancers (Perri et al. 2016) and in more than 70% of HNSCC (Pérez Sayáns et al. 2019). Labeled "guardian of the genome", the TP53 acts through multiple intracellular signaling pathways controlling processes like DNA repair, cell cycle arrest, and apoptosis. A transition to altered phenotype induces resistance to apoptosis, genome instability, and decreased immunogenicity (Perdrix et al. 2017). In nicotine-induced HNSCC, TP53 mutations with loss of function are almost constantly present (Cancer Genome Atlas Network 2015), even from very early stages, affecting guanosine nucleotides (Denaro et al. 2011). Deletions in the tumor-suppressing CDKN2A gene are in the top five most frequent mutations in the smoking-induced HNSCC. When associated, mutations in CDKN2A and TP53 genes negatively impact survival (Pérez Sayáns et al. 2019).

In contrast, HPV-positive tumors exhibit a low mutational burden involving these two suppressor genes. The overexpression of specific viral HPV E6/7genes, amplification of PIK3CA and E2F1 genes, and a loss of TRAF3 are the most representative genetic changes (Cancer Genome Atlas Network 2015). HPV infection, acting through viral oncoproteins E6 and E7, inactivates tumor supressor genes pRb and p53 in the host cell, leading to a loss of cell-cycle control, chromosomal instability, impaired DNA repair, and alterations in cell senescence and apoptosis (Castellanos and Pan 2016; Kim 2016; Doorbar et al. 2015). The recent research has broadened the spectrum of effects induced by HPV infection, showing that the E6 oncoprotein increases the

levels of reactive oxygen species and oxidative stress. This effect increases DNA instability and may be associated with chronic inflammation (Cruz-Gregorio et al. 2019).

Other studies have reported alterations in several representatives of the "rat sarcoma" (RAS) oncogene family in HNSCC. The HRAS isoform is mutated in 6% of HNSCC and associated with enhanced immune activity, with a high density of immune effectors in tumor samples (Lyu et al. 2019). The KRAS isoform is isolated in 17% of patients with HNSCC and associated with altered immune mechanisms, promoting immune tolerance via transforming growth factor-beta 1 (TGF-β1) (Weidhaas et al. 2017; Calenic et al. 2015).

Other genetic changes are independent of the HPV status. The activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), consequent to a loss of TP53, exerts pro-carcinogenetic effects by stimulating cell proliferation, angiogenesis, and epithelial to mesenchymal transition (EMT) (Aggarwal et al. 2006; Bharti and Aggarwal 2002). Experimental studies on HNSCC have revealed that a high intracellular concentration of active NF-κB is associated with increased metastatic capacity. NF-κB inhibitors are successful in decreasing cell invasive features by decreasing enzymes related to metastasis, such as vascular endothelial growth factor (VEGF) and matrix metallopeptidase 9 (MMP-9) (Yan et al. 2010). The activation of NF-κB has been detected in precancerous lesions frequently associated with HNSCC and in radio- and chemoresistant diseases. Deactivation of NF-κB in tumor cells leads to tumor regression in experimental models, triggering great interest in cancer therapy development.

While mandatory, genetic mutations are insufficient to develop cancer. The malignant cell requires appropriate conditions to multiply in an environment that provides protection from systemic tumor clearance mechanisms (Wellenstein and de Visser 2018).

3.2 Metabolic Changes in HNSCC

Frequent mitoses, characteristic of malignant cells, require high energy resources, implying an increased intracellular metabolism to cover the energy demand. Intense metabolic activity increases oxygen requirements, and tumor cells shift towards glycolysis to supplement energy production, leading to a decreased intracellular pH and accumulation of acidic byproducts. Intracellular acidosis seems an important element in local tumor progression and metastasis (Hosseini et al. 2017). Acidic pH of 6.5–6.9 is detected in the peritumoral environment. The theory of "acid-mediated tumor invasion" claims that a peritumoral acidic environment triggers necrosis in normal cells through pH-induced metabolic changes and activates MMPs that degrade the extracellular matrix, facilitating metastasis. Local acidosis exerts inhibitory effects on antitumoral immunity, promoting tumor progression. Various cancer experimental models show significant expression of markers for acidosis LAMP (lysosomal-associated membrane protein) and hypoxia (glucose transporter 1 and carbonic anhydrase IX (CA-IX)) (Ibrahim-Hashim and Estrella 2019). The CO_2 produced in tumoral metabolic conditions is eliminated from the cell via CA-IX activity, a membrane transporter that hydrates CO_2 and exports it as HCO_3^- and H^+ (Tafreshi et al. 2014). CA-IX activity is accelerated at pKa values under 6.5, modulating the acidity of a peritumoral environment. The inhibition of antitumoral immune surveillance is another consequence of acidosis, with alterations in cytolytic functions, a reduction of cytokine secretion, and the inhibition of signal transducers and activators of transcription 5/extracellular signal-regulated kinases (STAT5/ERK) signaling pathway (Calcinotto et al. 2012). In vivo experiments demonstrate that the use of oral buffer products correlates with increased efficiency of monoclonal antibody-based therapies (Pilon-Thomas et al. 2016).

Oxidative stress is closely correlated with carcinogenesis. Malignant cells show increased production of reactive oxygen species (ROS)

induced by exogenous or endogenous stimuli. ROS promote carcinogenesis through DNA instability. The subsequent mechanisms are tyrosine phosphatase inactivation and activation of the hypoxia-inducible factor 1 alpha (HIF-1α) pathway, which sustains malignant cell proliferation and immune cell anergy by further shifting cell metabolism to glycolysis (Vomund et al. 2017). In head and neck cancers, exposures to antioxidative agents, glutathione, and thioredoxin exert a strong inhibitory effect on cell proliferation and tumor growth (Roh et al. 2017). Multiple genetic alterations and metabolic changes are associated with tumor growth and metastasis in HNSCC. The effervescence of intracellular and local carcinogenic events generates a systemic response to counterbalance the progression to malignancy.

3.3 Inflammation in HNSCC

Chronic inflammation is an important element in carcinogenesis. Numerous studies show that indices of inflammation, assessed in the tumor tissue or peripheral blood, correlate with patient survival and response to therapy, leading to the evaluation of different inflammatory factors as biomarkers in HNSCC (Tampa et al. 2018b). Cytokines are small proteins released mainly by T helper cells and macrophages that play an essential role in regulating the immune response. Even though the immune cells are the primary source of cytokines, any nucleated cell carries the enzymes required for the synthesis and release of cytokines (Zhang and An 2007; Dinarello 2000). Pro-inflammatory interleukins have been intensively studied in the pathogenesis of HNSCC. The tumor milieu is characterized by chronic inflammation induced by various cellular and humoral mediated processes involving tumor, stromal, and immune cells. Increased concentrations of pro-inflammatory chemokines are reported in association with an inflammatory infiltration rich in macrophages, fibroblasts, and monocytes. Wang et al. (2002) have analyzed 86 tissue samples of HNSCC and demonstrated the overexpression of interleukin 6 (IL-6) and IL-6 messenger RNA compared to normal mucosa. This study also reveals a correlation between receptor expression for IL-6 and the tumor size and grading. IL-6 mRNA overexpression is associated with advanced disease and lymph and distant metastases. A study that assessed the immune gene expression in advanced HNSCC defined two out of the four tumor types with distinct immune profiles, presumably correlating with the HPV status. Pro-inflammatory cytokines and immune cell effectors were at high concentrations in the tumor microenvironment, defined as an enriched immune microenvironment (EIME), and correlated with prognosis (Cao et al. 2017). Sato et al. (2013) have suggested that determining salivary levels of IL-6 after treatment could act as a biomarker for early local and regional recurrence in HNSCC, while Jinno et al. (2015) have argued that IL-6 overexpression is associated with chemoresistant disease.

Significant correlations are also reported between cytokine levels and the progression of premalignant lesions to invasive malignant disease. Schiegnitz et al. (2018) have identified increased serum concentrations of IL-6, IL-8, and soluble IL-2 receptors in patients with HNSCC compared to patients who are either healthy or suffer from premalignant conditions, with IL-6 demonstrating a high statistical significance with large tumors and lymph node metastasis. The same study reports that patients with premalignant lesions have higher levels of IL-8 than controls. Salivary levels of IL-8 have been analyzed in patients suffering from premalignant lesions and oral squamous cell carcinoma compared to healthy subjects. The results demonstrate that only subjects with invasive lesions show significantly higher concentrations of IL-8, thus recommending salivary IL-8 as a potential biomarker for the diagnosis and follow-up of oral squamous cell carcinoma, but not of premalignant lesions (Punyani and Sathawane 2013). The NF-κB pathway discussed above might be the underlying mechanism for IL-8-mediated HNSCC tumorigenesis, confirming the role of chronic inflammation in malignant transformation (Rao et al. 2010).

Interactions between inflammation and carcinogenesis described in oral squamous cell carcinoma have also been identified in cutaneous squamous cell carcinoma (Scheau et al. 2020). In UV-induced skin and lip cancers, activation of intracellular NF-κB signaling pathways triggers a cascade of inflammatory events, including the secretion of IL-8 by macrophages and monocytes, which eventually leads to tumor progression (Neagu et al. 2019; Balkwill and Coussens 2004). The involvement of chronic inflammation, fueled by the release of cytokines, underlies malignant transformation, local invasion, and metastases. Conversely, inhibition of the immune response by anti-inflammatory agents correlates with a decrease in UV-induced cancer incidence (Wright et al. 2006).

The anti-inflammatory cytokines IL-10 and IL-13 have been found significantly increased in saliva of HNSCC patients and tumor tissue of oral squamous cell carcinoma (Aziz et al. 2015; Chen et al. 2013). The increase correlates with poor prognosis, especially in early disease, suggesting that a strong immunosuppressive environment at the initial stages is conducive to aggressive tumor cell behavior, promoting tumor growth and progression.

3.4 Assessment of Inflammation in HNSCC in Clinical Setting

The detection of sophisticated elements for cancer diagnosis in early stages and disease follow-up requires expensive laboratory equipment, trained staff, expensive kits, which may be available in a research unit, but are difficult to access in the clinical setting for general use. The current clinical practice evaluates inflammation through cellular and biochemical markers of the systemic immune response, and several studies have reported results that support the prognostic value of markers in various cancers.

Circulating proteins involved in systemic inflammation have been studied as potential prognostic biomarkers in different malignancies. C reactive protein (CRP) increases in inflammation, infection, and trauma. Recent data show a strong correlation between the CRP level and cancer. A study that followed a large group of subjects from the general population for 16 years has reported an increased rate of malignancies in patients with a high serum CRP content. Additionally, increased baseline CRP in cancer patients was associated with poor prognosis (Allin et al. 2009). The onset of cancer correlates with sustained inflammatory status induced by the intense metabolic reactions in tumor tissue. This systemic inflammatory process, translated in increased serum content of CRP, among other changes, is described in cancer patients (Asegaonkar et al. 2015). In OSCC, higher values of CRP are detected in patients exposed to risk factors (smoking and alcohol) and correlate with an increased rate of regional progression through lymph node involvement and poor prognosis (Tai et al. 2017). Similar results in HNSCC are reported in several studies, correlating an aggressive tumor behavior with unfavorable prognosis and elevated levels of CRP (Peter et al. 2013; Khandavilli et al. 2009). Some authors studied CRP in relation to other parameters. Glasgow prognostic score and its refined variants include serum albumin, alongside CRP, and are used in stratifying the clinical risk of patients with various cancers (Pan et al. 2017; Saijo et al. 2017). These scores have been analyzed in patients with operable HNSCC and reported data to support their prognostic potential (Hanai et al. 2018; Selzer et al. 2016; Farhan-Alanie et al. 2015).

Serum fibrinogen correlates with disease progression in different cancers (Zhang et al. 2020; Xu et al. 2018). This glycoprotein, known for its role in coagulation, is also involved in the cancer-associated systemic inflammatory response, and elevated levels of fibrinogen correlate with poor prognosis in many malignancies (Grafetstätter et al. 2019). In solid tumors, progression to malignancy and local invasiveness correlate with changes in structural components present in the extracellular environment. Deposits of fibrinogen and fibrin have been identified in tumor stroma promoting fibroblast proliferation and angiogenesis mediated by overexpression of IL-1, VEGF (vascular endothelial growth factor), and FGF-2 (fibroblast growth factor 2) (Mosesson 2005;

Simpson-Haidaris and Rybarczyk 2001). The link between fibrinogen and cancer progression is still unclear. However, various studies reveal strong correlations with prognosis in patients with HNSCC. In locally advanced OSCC, high pretreatment fibrinogen values have been detected in patients with resistance to radio- and chemotherapy and correlated with disease recurrence and poor survival (Holzinger et al. 2016). Other studies have shown similar results in HNSCC, where a high serum fibrinogen content correlates with advanced disease, presence of metastases, and unfavorable prognosis (Yang et al. 2019; Lan et al. 2016).

4 Immune Landscape in Carcinogenesis

4.1 Defensive Mechanisms Against Cancer

The role of the immune system in carcinogenesis was suspected more than a century ago by W.B. Coley, a surgeon who reported a series of cases treated by bacterial inoculation in tumor mass. The therapy relied on triggering a local immune response that would destroy tumor cells (Coley 1910). The important role of the immune system in the protection against cancer was confirmed by the substantial increase in the incidence of cancers, especially viral related, in subjects with immunodeficiency syndromes of various causes (Vajdic and Van Leeuwen 2009).

In the complex antitumor defense machinery, intrinsic cellular mechanisms are doubled by extrinsic protection systems in which immune cells are key players. While intrinsic tumor suppression mechanisms are active and efficient, the immune response is not initiated. The accumulation of genetic alterations, such as mutations of the p53 suppressor gene, leads to an increased intracellular concentration of p53 peptide, shifting the metabolic pattern of the affected cell. Subsequently, opposing intracellular mechanisms are overcome and the mutant cell is beyond repair, entering a stabilization phase called cellular senescence, which implies changes in its secretory phenotype (Kuilman et al. 2010). It initiates the release of pro-inflammatory cytokines generating an immune reaction guided to destroy the senescent cell, thus preventing the progression to malignancy (Kuilman et al. 2008). An increased density of cells with the senescence-associated secretory phenotype (SASP) is reported in precancerous lesions of OSCC, which may act as the first step in cancer prevention by inducing a lymphocyte T CD4+ mediated immune response (Johnson et al. 2016; Campo-Trapero et al. 2008). Progressive mutations with p53 loss of function together with other gene alterations push mutant cells out of SASP status leading to the development of invasive features (Wellenstein and de Visser 2018). In this stage of carcinogenesis, if the balance favors the accumulation of mutations and overruns the clearance capacity of the immune system, malignant cells survive, setting the debut of cancer. In established malignancies, lymphocytes T CD8+ are the main antitumor effectors. Little mobilization of these cells in premalignant lesions could be a prevention mechanism of autoimmunity mediated by cytotoxic T lymphocytes (Ostroumov et al. 2018). Studies conducted on murine models show that CD4+ T lymphocytes that release interferon-gamma (IFN-γ) and TNF-α can reactivate the SASP mechanisms and induce growth arrest in tumor cells, promoting immune clearance of malignant cells, independently from intracellular protection mechanisms (Braumüller et al. 2013).

Three steps have been defined in the immune antitumor defense process: elimination, equilibrium, and escape (see Fig. 2). Throughout these steps, immune cells undergo tumor immunoediting, a process in which highly immunogenic cells with an intense expression of tumor-specific antigens (TSA) are removed. In the experimental setting, tumor cells generated in immunodeficient animal models do not progress to malignancy after transplantation into immunocompetent hosts, because the immunoediting and proliferation of poorly immunogenic cell lines do not take place (Smyth et al. 2006). In the initial elimination phase, newly created tumor cells are efficiently removed by the immune system (Mittal

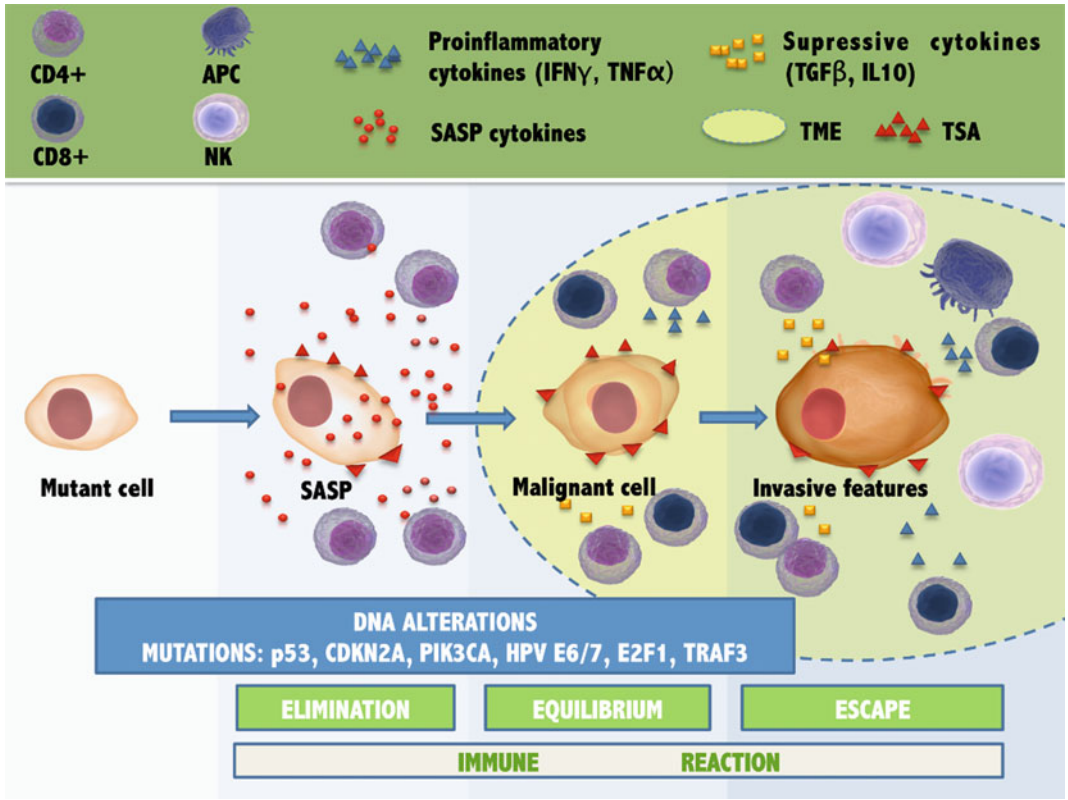

Fig. 2 Graphic representation of genetic and immune dysfunctions leading to carcinogenesis. Progressive accumulation of intracellular genetic alterations leads to a switch to senescence-associated secretory phenotype (SASP) with specific cytokine release that initiates activation of the immune response, mainly mediated by CD4+ lymphocytes. Intensely immunogenic cells, expressing tumor-specific antigens (TSA) are eliminated, leading to the selection of mutant clones with decreased immunogenicity in the equilibrium phase. Tumor microenvironment (TME) formation is initiated with modulatory effects on immune effectors promoting progression to cancer with invasive features. In the escape phase, progressive accumulation of immune cells: CD8+ lymphocytes, natural killer cells (NK), antigen-presenting cells (APC) together with CD4+ lymphocytes can be detected, with different, often antagonistic, effects on tumor growth

et al. 2014). This may explain the spontaneous tumor remission described in clinically manifest malignancies (Markowska and Markowska 1998). Overcoming the capacity of immune clearance of malignant cells pushes forward carcinogenesis into the equilibrium phase, where tumor progression is controlled by immune surveillance mechanisms. Malignant cells will not be fully eliminated, and by adding new mutations, they will generate cellular clones with decreased immunogenicity. The tumor microenvironment is initiated in this stage of carcinogenesis, which will promote survival of malignant cells and finally advancement to the escape phase of the immune response, favoring cancer progression (Bottomley et al. 2019). Equilibrium phase mechanisms might explain the pathogenesis of occult malignancies, frequently encountered in HNSCC, where the immune system counteracts local tumor development (Koebel et al. 2007). The clinical manifestation of cancer occurs when tumor cells have survived the intrinsic antitumor control mechanisms, the senescent cell elimination phase, and have passed immunoediting processes. However, tumor cells never achieve a complete immunotolerance state.

When the immune cells, collected from the tumor microenvironment and processed in vitro, are transferred to lymphopenic mouse models with malignant melanoma, they induce tumor regression (Quezada et al. 2010; Dudley et al. 2008). The same results are reported after the autologous transfer of genetically engineered lymphocytes (Morgan et al. 2006). Ribatti (2017) labels this phenomenon with the term "tumor immunosurveillance". Tumor cell immunoediting and immune escaping are defined as fundamental elements of carcinogenesis (Hanahan and Weinberg 2011).

4.2 Tumor Microenvironment

The tumor microenvironment (TME) is an independently studied entity in cancer pathogenesis. The cellular component in TME is represented by tumor cells and non-tumor elements: stromal cells and immune cells, playing a major role in carcinogenesis through their complex interactions. Cancer pathogenesis should not be simplistically regarded as a sum of tumor cell features but rather as a distinct structure with independent pathophysiological characteristics. Inflammatory tumor infiltrations are present in all cancers, with variable intensity, ranging from patterns undetectable through standard evaluation techniques to intense inflammatory types of cancer. The complex interactions between stromal components of TME, inflammatory, and tumor cells are not yet completely unveiled (Thorsson et al. 2018; Cai and Jin 2017).

Tumor stromal acellular composition can vary from a high content of loose connective tissue to an increased number of collagen structures that grant a fibrotic aspect to the lesion. These stromal elements can organize tumor cell nests (TCN) of variable size, with presumed prognostic characteristics in several malignancies (Alsibai and Meseure 2018; van Pelt et al. 2018). A recent study has analyzed several specific tumor stroma parameters, such as stroma-tumor ratio (TSR), stroma type, and TCN size in patients with HNSCC, showing that the increased TSR, defined by a fibrotic stroma with frequent small-sized TCNs, is indicative for poor prognosis contrarily to the large TCN and low TSR, which correlate with a better response to chemotherapy (Karpathiou et al. 2019).

4.3 Immune Cells in HNSCC

The TME hosts various subtypes of differentiated immune cells, with contrasting effects on tumorigenesis and myeloid progenitors that exhibit carcinogenic activity (Hanahan and Weinberg 2011). T-cell tumor infiltrations and their interactions within TME have been rigorously studied, yet the complex mechanisms related to tumor progression, prognosis, and resistance to immune therapy are far from being uncovered (Anderson et al. 2017).

Studies have correlated local immune reaction with TMB of malignant cells. Malignancies exhibit diversity in cell mutational burden, the highest rate of mutations being identified in chronic exposure to risk factors that induce DNA alterations, such as UV exposure or smoking. In consequence, UV and nicotine-induced squamous cell carcinomas have been reported to possess one of the highest mutational burdens (Fancello et al. 2019). Tumors with a high TMB are characterized by an increased expression of tumor-specific antigens (Rooney et al. 2015). These antigens result from degrading self-proteins into 8–10 amino acid-long peptides that activate T-cells, triggering an antitumor immune reaction (Antunes et al. 2018). Both innate and adaptive immune systems are directed towards eliminating malignant cells, through mechanisms mediated by major histocompatibility complex (MHC), implying TSA-mediated activation of immune effectors. Except for viral-induced malignancies (HPV or EBV), tumor cells derived from self-structures expressing MHC Class I should not trigger an immune response. However, TSAs are presented mainly through MHC class I and can be recognized by the immune effectors (Schumacher et al. 2019). Decreased expression of MHC Class I molecules on tumor cells is another mechanism of immune escape. However, malignant cells with negative MHC Class I status

are eliminated by NK cells (Garrido 2019). NK cells show an increased affinity for cancers with low or lacking MHC Class I expression, called "missing self" cells, by recognizing the absence of normal elements on the cell surface known as "absence of the expected" (Kärre 2008). This phenomenon is used on developing molecules that promote NK-mediated tumor cell clearance, either independently or in association with T lymphocytes, especially in MHC Class I-negative cancers (Minetto et al. 2019). In HPV-positive HNSCC, MHC Class II plays an important role. Viral antigens bind to MHC Class II molecules that are overexpressed on tumor cells, acting as antigen-presenting cells. An intense immune response is generated that is associated with a significantly improved prognosis (Gameiro et al. 2019). However, overexpression of TSAs is present only on a subpopulation of tumor cells, triggering an ineffective immune response that may explain resistance to targeted therapies (McGranahan et al. 2016). Based on these findings, some cancers, including HNSCC, are divided into subtypes according to immune and genetic features that correlate with prognosis and response to therapy (Cao et al. 2017; Keck et al. 2015).

Tumor-infiltrating lymphocytes (TILs) show high variability in cancers. Cytotoxic T-cells (CD8+), helper T-cells (CD4+), regulatory T-cells (Treg), and B lymphocytes coexist in TME with the leucocytes of the innate immune family, such as NK cells, innate lymphoid cells (ILC), macrophages, neutrophils, monocytes, antigen-presenting cells (APC), and dendritic cells, exerting synergic or antagonistic effects.

Cytotoxic T-Cells (CD8+) The main effectors of adaptive immune responses, when present in large numbers in TME, predict a better prognosis in most cancers (Mazzaschi et al. 2018; Li et al. 2017). Similar results have been reported for patients with HNSCC, where the density and distribution of CD8+ lymphocytes in TME seem to have independent prognostic capabilities (see Table 1). A study conducted on 139 patients with oral squamous cell carcinoma has reported that high numbers of CD8+ T-cells in parenchyma around the invasion front and stromal CD8+ cells at the tumor periphery independently correlated with improved survival and low recurrence rates (Shimizu et al. 2019). HPV status in HNSCC plays an important role in the immune infiltration of TME. Thus, HPV-positive tumors show a higher CD8+ T-cell infiltration compared to HPV-negative ones in oropharyngeal squamous cell carcinoma, which also correlates with better prognosis when CD8+ T-cells concentrate in stromal areas (Oguejiofor et al. 2015). This finding most likely relies on the synergic immune recruitment mechanisms mediated by two distinct triggers, TSA and viral antigens, which intensify the local immune reactivity. Näsman et al. (2012) have reported similar results in tonsillar SCC in that patients with HPV-positive tumors display a higher number of CD8+ T-cells compared to HPV-negative ones, and an enriched CD8+ T-cell environment correlates with better survival. Another study conducted on 270 subjects with oropharyngeal squamous cell carcinoma has identified a small subgroup of patients with HPV-positive tumors that exhibited low concentrations of tumor-infiltrating lymphocytes (TILs), with a prognosis similar to HPV-negative tumors (Ward et al. 2014). CD8+ T-cells rely on interaction with CD4+ T lymphocytes to exert their cytotoxic functions.

Helper T Lymphocytes (CD4+) They initiate and maintain antitumor immune reaction by mobilizing CD8+ T-cells that recognize specific tumor antigens presented by MHC molecules and trigger tumor cell death (Ostroumov et al. 2018). T helper cells are involved in all aspects of antitumor immunity, including interaction and mobilization of innate immune system representatives. Different antigen-presenting cells migrate to draining lymph nodes and induce T-cell activation mediated by TSAs, generating T-lymphocyte clones with antitumor specificity that will perform their antitumor effects mainly at the tumor site. This process is called the tumor immune cycle (Chen and Mellman 2013). The role of CD4+ is controversial as these cells are defined as "double-edged swords" due to their opposing effects in cancer (Das et al. 2018). Naïve CD4+ T-cells undergo differentiation to

Table 1 Cytotoxic T cells in the pathogenesis of HNSCC

Density (TIL score)	Distribution compartment	Survival improvement	Decrease in recurrence rate	HPV infection status	Study type	References
High	Peripheral	Yes	Yes	N/A	139 cases OSCC	Shimizu et al. (2019)
High	N/A	Yes	N/A	Positive	83 cases TSCC	Näsman et al. (2012)
High	Tumor/stroma	Yes	Yes	Positive	270 cases OPSCC	Ward et al. (2014)
High	Stromal	Yes	Yes	Positive	218 patients OPSCC	Oguejiofor et al. (2017)
High	All	Yes[a]	N/A	Positive	203 cases HNSCC	Ngamphaiboon et al. (2019)

TIL Tumor-infiltrating lymphocyte score, *HPV* Human papillomavirus, *TSCC* Tonsillar squamous cell carcinoma, *OSCC* Oral squamous cell carcinoma, *OPSCC* Oropharyngeal squamous cell carcinoma, *HNSCC* Head and neck squamous cell carcinoma

[a]Concerns non-OPSCC only

activated T helper 1 populations (Th1) in an environment rich in IL-12 or T helper 2 cells (Th2) in the case of a high IL-4 concentration and the absence of IL-12 (Knutson and Disis 2005). Th1 are major antitumor effectors due to cytokine secretion and activation of tumor cell receptors that initiate cell death. Th1 cells act via IFN-γ and TNF-α to induce cancer cells into senescence and initiate their apoptosis (Braumüller et al. 2013). They regulate cytotoxic immune responses and contribute to tumor suppression. Increased expression of specific Th1 cell genetic markers in TME correlates with a good prognosis (Bindea et al. 2013). Some studies suggest that CD4+ T-cells can eliminate tumor cells, in the absence of CD8+ T-cell-mediated immunity, but the cooperation of both cell lines increases the efficiency of antitumor immunity (Fukunaga et al. 2004). In the case of HNSCC, data are not conclusive and often inconsistent regarding CD4+ T-cells. A study assessing the infiltration of CD8+ and CD4+ T-cells in HNSCC has failed to find any relationship of CD4+ T-cells with survival or the HPV status (Nordfors et al. 2013). Different results have been reported in another study where patients exhibiting a high density of activated CD4+ T-cells had better survival and improved local control (Badoual et al. 2006). A meta-analysis assessing prognostic correlations of different types of TILs in HNSCC has reported favorable outcomes in tumors with high TILs for both CD3+ and CD8+ T-cells but failed to find significant correlations for CD4+ T-cells (de Ruiter et al. 2017). The difficulty in assessing prognostic properties of CD4+ T-cells probably has to do with the subgroups of cells that have antagonistic effects in cancer. Regulatory T-cells (Treg Foxp3+) have been intensively studied and are suspected to promote tumorigenesis through immunosuppressive effects. In normal conditions, Tregs, marked with CD25+ and transcription factor Foxp3+, are responsible for maintaining immune tolerance and autoimmunity prevention (Sakaguchi 2005). Increased expression of Treg markers in TME and peripheral circulation is often associated with tumor progression. Tregs show inhibitory effects on CD4+, CD8+, and dendritic cells, inducing immune cell exhaustion through cytokine release, like TGF-β or IL-10 (Bauer et al. 2014; Jarnicki et al. 2006).

In some cancers, TME displays an immunosuppressive effect on CD4+ T-cells by stimulating their differentiation into the Treg subtype (Zheng et al. 2009). In cutaneous SCC, disease aggressiveness correlates with a high density of Treg cells and increased concentrations of IL-10 and TGF-β (Azzimonti et al. 2015). However, contrasting results have been reported for HNSCC where tumor infiltration with FoxP3+

T-cells is identified in patients with improved prognosis (de Ruiter et al. 2017). A similar favorable prognostic correlation for intense Treg infiltration has been reported in colorectal cancers (Salama et al. 2009). The innate immune system has been widely studied in cancers, along with adaptive immunity.

Natural Killer (NK) Cells These cells are the main representatives of innate immunity and are considered equivalents of cytotoxic T-cells in the adaptive immune system. NK cells trigger death in infected or cancer cells via the release of enzymes, perforins, and cytokines, like TNF family members (Spits et al. 2016). Tumor cells have protection mechanisms against innate immunity that rely on TGF-β release with alterations in cytotoxic abilities of NK cells (Cortez et al. 2017). Immature NK cells (CD3-CD56brightCD16-) are activated by cytokines and IFN-γ. Mature NK cells (CD3-CD56dimCD16+) release cytoplasmic inclusions with enzymes and perforins that act directly on malignant cells inducing their lysis. CD16+ receptor expressed on NK cells binds with tumor cells through IgG molecules initiating their activation. Co-activatory stimuli, such as IL-2, IL-12, IL-15, IL-18, and IFN-γ are necessary to induce NK cell cytotoxic function leading to malignant cell clearance (Hu et al. 2019; Minetto et al. 2019). These molecules can be detected in TME. High concentrations of activated NK cells as a complementary defense system, alongside immunity mediated by T and B lymphocytes, has been associated with better outcomes (Nair and Dhodapkar 2017). Tumor cells use protective mechanisms against being recognized by NK cells. Denaturation of peptide constituents from specific ligands affects NK receptor interaction, altering the NK-mediated immune defense (de Andrade et al. 2018).

Lymphocytes B There is a debate regarding the role of lymphocyte B infiltrates in cancers. Studies in experimental models have shown that in genetically modified mice with depletion of lymphocytes B, there is no progression to epithelial malignancies (de Visser et al. 2005). In HNSCC, a correlation has been reported between the HPV status and B cell population, with prognostic potential. Patients with an intense lymphocyte B infiltrate alongside CD8+ cells have a significantly improved prognosis. It is suggested that activated B cells release the chemokine (C-X-C motif) ligand 9 (CXCL9) cytokine that supports the recruitment of CD8+ lymphocytes, promoting tumor cell clearance (Hladíková et al. 2019). The role of B cells in HNSCC pathogenesis has been emphasized in another study that reports high intra-tumoral percentages of antigen-presenting, activated, and memory B cells (Lechner et al. 2019). These findings encourage further research and support the potential role of B cells as new therapeutic targets in HNSCC.

Tumor-Associated Macrophages (TAM) High densities of tumor-associated macrophages (TAMs) were identified in many cancers, including epithelial malignancies, acting as tumor-promoting agents (Li et al. 2020). TAMs release VEGF and MMP, facilitating angiogenesis, local invasion, and metastasis (Evrard et al. 2019). In advanced HNSCC, in patients with enhanced immune profile with associating high densities of TAM, signaling for immune checkpoint ligands is upregulated, which also correlates with poor prognosis (Cao et al. 2017). A recent meta-analysis has reported that a high density of TAMs in HNSCC is associated with advanced tumors, nodal staging, and vascular and lymphatic invasion (Kumar et al. 2019). Refinement of TAM detection, which seems of prognostic significance, is suggested in another meta-analysis. Immunosuppressive subtype M2 of TAMs (CD163+) strongly correlates with a worse prognosis in patients with HNSCC (Troiano et al. 2019).

Antigen-Presenting Cells (APC) These cells play an important role in carcinogenesis. TSAs are presented through the MHC, initiating an adaptive immune response with the generation of antigen-specific T-cell clones (Bottomley et al. 2019). In HNSCC, dendritic cells (DCs) act as APCs together with lymphocytes B, TAMs, and other immune cells (Wondergem et al. 2020). There are contradictory data concerning DCs and their influence on the

prognosis in HNSCC, with some studies reporting a favorable outcome in association with a high density of DCs (Jardim et al. 2018) while others report opposing results (Hilly et al. 2016).

4.4 Immune Checkpoints in HNSCC

The complexity and diversity of TME and the multitude of interactions between all its elements make it hard for the scientific community to unveil many of its mysteries. A recent discovery of immune checkpoint molecules has revolutionized the world of immunology and pathophysiology in cancer and enriched the pallet of cancer therapies with an innovative approach through immune checkpoint inhibitors.

In advanced HNSCC, an enhanced immune cell infiltrate often exhibited overexpression of checkpoint molecules. These molecules, which normally act as a protection mechanism against excessive immune reactions and autoimmunity, have a negative influence on cancers. Signaling pathways initiated through the checkpoint molecules weaken the reactivity of T-cells and induce an anergic status known as "immune exhaustion". It can affect both CD4+ and CD8+ T-cells and is reversible under the action of checkpoint blockade therapies, rendering back function to exhausted immune cells (Ostroumov et al. 2018).

Cytotoxic T lymphocyte antigen 4 (CTLA-4), expressed mainly by T-cells, is a transmembrane protein with affinity for B7 molecules, expressed on APCs. B7 molecules, represented by two subtypes CD80 and CD86, bind with CD28 expressed on T-cells, with costimulatory action in addition to TCR activation (Carreno and Collins 2002). The binding of CD80/CD86 to the costimulatory receptor CD28 activates T lymphocytes with simultaneous overexpression of CTLA4 (Mei et al. 2020). Competitive binding of CTLA4 to B7 molecules, due to a higher affinity of CTLA4 for CD80/CD86 rather than for CD28, induces T-cell exhaustion and an overall effect of immunosuppression (Postow et al. 2015).

Programmed cell death protein-1 (PD-1), expressed on activated immune cells, has a negative regulatory effect on T-cells, after binding to its specific ligands, PD-L1 and PD-L2, present on tumor and immune cells (Mei et al. 2020). This leads to an intracellular signaling blockade that interferes with normal activation and proliferation of T-cells (Alsaab et al. 2017). However, studies have shown that in different malignancies, through repeated mutations, clones of immune cells resistant to PD-1 blockade are selected (Hugo et al. 2016; Koyama et al. 2016). Expression of PD-1 and PD-L1 in HNSCC is influenced by the inflammatory cytokines IFN-γ and TNF-α and shows high dynamics, which can explain resistance to immunotherapy (Oguejiofor et al. 2017). PD-1 and PD-L1 are also considered the key players in the initiation and progression of HPV-induced HNSCC (Lyford-Pike et al. 2013). The prognostic value of PD-L1 has been suggested in a study on 203 patients with HNSCC showing a high infiltration with CD8+ in correlation with improved overall survival. However, patients with moderate and high expression of PD-L1 have a worse prognosis compared to those with low PD-L1 expression, defined as less than 1% (Ngamphaiboon et al. 2019).

Immune exhaustion affecting CD4+ T-cells features an overexpression of inhibiting coreceptors, like T-cell immunoglobulin mucin-3 (TIM-3). The binding of TIM-3 with the specific ligand galactin-9 induces CD4+ T-cell apoptosis and a functional deficit in CD8+ T-cells (Mei et al. 2020). Studies in experimental models have reported an increased tumor recurrence rate associated with immune exhaustion of CD4+ T-cells, suggesting that combined immune therapies would be more effective in controlling recurrent malignancies (Koyama et al. 2016). Exhausted immune cells are characterized by alteration of proliferation, cytokine secretion, and deficient recognition of specific antigens. The clinical expression of immune exhaustion is tumor progression and recurrence (Xia et al.

2019). The heterogenic character of HNSCC raises challenges in immunotherapy research due mainly to etiological and immunological differences that require an individualized approach for each patient (Perri et al. 2020).

5 Biomarkers in the Management of HNSCC

The determination of immune biomarkers may significantly influence the management of cancer patients. The prognostic feature of biomarkers in cancers could allow the stratification of patients into risk groups, facilitating early identification of patients with resistance to therapy or aggressive disease. Also, the potential of repeated measurements when analyzing circulating biomarkers assists the patient monitoring and provides early notification of tumor progression. Unraveling the mechanisms of antitumor immunity is one of the steps in the identification of new therapeutic targets that may guide and modulate the antitumor immune response.

In HNSCC, as in many cancers, biomarkers are an emerging subject of interest. Studies have revealed a large number of molecules that promise to predict prognosis, resistance to therapy, or recurrence (Tampa et al. 2018b). Our research group has extensively studied neuroendocrine factors as potential HNSCC biomarkers that can further clarify the pathogenesis and disease progression (Solomon et al. 2018; Lupu et al. 2017). Currently, prognosis in HNSCC is mainly dictated by clinical staging and primary location. Therefore, 5-year survival rates can be higher than 90% in the early stages of lower lip tumors and drop below 40% in advanced oral tumors with distant metastasis (Hladíková et al. 2019). The tumor HPV status is another marker with confirmed prognostic potential in many studies (Kobayashi et al. 2018, Chakravarthy et al. 2016), although one study identified a subset of HPV-positive tumors that did not differ in terms of prognosis from HPV-negative disease (Ward et al. 2014). Local and systemic antitumor immunity has been intensively assessed as biomarkers in HNSCC. Tumor-infiltrating lymphocytes (TILs) have been identified as prognostic markers independent of HPV status, and an increased density of TILs and CD8+ T-cells correlates with higher survival rates (Heikkinen et al. 2019; de Ruiter et al. 2017; Distel et al. 2009). A quick semiquantitative method for evaluating TILs, called TILws (weight sum score), facilitates their use as prognostic biomarkers in the clinical setting (Spector et al. 2019).

6 Emerging Therapies for HNSCC Patients

The increased interest for antitumor immunity has sparked, following the observation that the stimulation of immune elements caused tumor regression even in advanced disease stages. Therefore, immune system modulation has been intensively investigated and became a part of the anticancer arsenal, with outstanding results in some types of neoplasia (Dobosz and Dzieciątkowski 2019; Trapani and Darcy 2017).

Standard treatment in HNSCC consists of surgery, radiotherapy, or a combination of the two and is guided by disease staging and anatomical location, disregarding biological characteristics of the tumor. Early stages (I and II) may be treated by surgical resection or radiotherapy, with similar results in disease control. Combined therapy is recommended in advanced stage II and stage III cases. Standard therapy includes resection of cervical lymph nodes or extended neck radiotherapy (National Cancer Institute 2015). Neoadjuvant chemotherapy is investigated in locally advanced diseases and the TPF regimen (docetaxel, cisplatin, and fluorouracil) improves local disease control and prognosis after surgery (Haddad et al. 2018). A 4% increase in the survival rate has been reported when chemo- and radiotherapy are combined in unresectable advanced disease (Pignon et al. 2001).

Immunotherapy and target therapy for advanced and metastatic HNSCC have been recently approved. These therapies mediate the activation or reactivation of the immune system by modulating its antitumor effects. The first targeted therapy approved by the Food and Drug

Administration (FDA) and the European Medicines Agency for the treatment of recurrent and metastatic disease was cetuximab, an inhibitor of epidermal growth factor receptors (EGFR). Cetuximab added to chemotherapy increases the response rate to treatment by 13% in HNSCC (Vermorken et al. 2008). In 2019, the same regulatory institutions approved the use of anti-PD1 monoclonal antibodies, nivolumab and pembrolizumab, for treatment of recurrent and metastatic disease in chemoresistant patients. These agents block PD-1 receptors overexpressed on T-cells and prevent specific ligand binding, such as PD-L1 and PD-L2 expressed by tumor cells, which exert inhibitory effects on immune cells (Xia et al. 2019). Pembrolizumab is approved as the first-line therapy in association with chemotherapy in patients with metastatic or unresectable disease but can also be administered alone in tumors with PD-L1 overexpression, with a combined positive score of ≥ 1 (Cohen et al. 2019a). Other therapeutic regimens of monoclonal antibodies are under review for advanced HNSCC. For instance, a human monoclonal antibody against CTLA-4, tremelimumab, prevents binding of the inhibiting receptor CTLA4 expressed on immune cells with the specific ligands CD86 and CD80. CTLA4 blockers act on Treg cells inducing their depletion and increasing the ratio of effector-to-Treg cells (Selby et al. 2013). Phase III study EAGLE has evaluated the association between a new anti-PD1 agent, durvalumab, and tremelimumab in patients with metastatic and recurrent disease, reporting no significant differences in survival rates compared to the group receiving cetuximab and chemotherapy (Ferris et al. 2020). Molecules that stimulate NK-mediated immunity are also studied in patients with HNSCC as they are the main effectors in antitumor defense, alongside CD8+ T-cells. Monalizumab is the first member of this class that acts on the natural killer cell receptor (NKG2A) expressed by CD8+ and NK cells present in TME. Preliminary results from an ongoing study investigating the association of monalizumab and cetuximab in 40 patients with recurrent or metastatic disease are encouraging (Cohen et al. 2019b). NK-activating interleukins are also studied as potential therapeutic agents in HNSCC. Infusion of IL-2 in experimental models led to severe adverse reactions and an exponential increase of Tregs inducing antitumor tolerance, invalidating any potential benefits in repelling cancer (Nelson 2004). Infusion of NK cells has been experimentally attempted, and when associated with IL-15 it determined complete tumor regression (Miller et al. 2005). Treg expansion induced by IL-2 might be overcome through the administration of IL-15. Preclinical studies have shown that IL-15 can activate NK and CD8+ T-cells without inducing Treg expansion (Waldmann 2015). Studies evaluating the effects of IL-15 administration have reported a significant increase in NK cells and, secondary, in CD8 + T-cells that additionally contribute to increasing NK cell density through a CD16-mediated pathway (Miller and Lanier 2019; Nair and Dhodapkar 2017).

HNSCC prevention is also of major interest, especially considering the increased incidence of HPV-related disease. As global anti-smoking campaigns induced a decrease in smoking-related HNSCC (Rettig and D'Souza 2015), anti-HPV vaccination is anticipated to yield similar results. A series of vaccines targeting HPV-positive HNSCCs is under testing, and preliminary results support their role in preventing the progression of dysplasia to cancer (Wang et al. 2018). Intratumor injection of viral agents is also investigated in advanced HNSCC (Old et al. 2016), after good results in the treatment of malignant melanoma have been reported, which led to FDA approval of oncolytic virus, talimogene, in this malignancy (Bommareddy et al. 2017). HNSCC is accessible for this type of therapy, and the reported effects on circulating T-cells in patients with solid tumors that do not respond to treatment support the role of viral therapy in fighting cancer by stimulating the antitumor immune response (Taipale et al. 2015). Thus, there are outstanding prospects for preventing and curing oncological ailments. HNSCC is regarded with a great interest

for emerging therapies that will advance the management of this disease.

7 Conclusions

Major improvements in disease control and survival in HNSCC have been correlated with staging. Thus, early diagnosis is of paramount importance to detect patients at high risk of an unfavorable outcome, allowing the appropriate therapeutic approach. Numerous studies have shown that inflammation is a key player in HNSCC progression, regardless of cancer location and the main risk factors involved. Moreover, immunity has been highlighted as a major factor in disease control. Further studies in this area of research will allow unveiling new mechanisms in the complex connections between immuno-inflammatory processes and carcinogenesis and will open new possibilities to identify more reliable and widely applicable predictive factors and therapeutic targets in HNSCC.

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References

Aggarwal B, Sethi G, Nair A, Ichikawa H (2006) Nuclear factor-κB: a holy grail in cancer prevention and therapy. Curr Signal Transduction Ther 1(1):25–52

Alfred G, Knudson J (1971) Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A 68:820–823

Allin KH, Bojesen SE, Nordestgaard BG (2009) Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. J Clin Oncol 27 (13):2217–2224

Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, Kashaw SK, Iyer AK (2017) PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. Front Pharmacol 8:561

Alsibai KD, Meseure D (2018) Significance of tumor microenvironment scoring and immune biomarkers in patient stratification and cancer outcomes. In: Histopathology. IntechOpen, Rijeka. https://doi.org/10.5772/intechopen.72648. Accessed on 14 Jan 2021

Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP (2017) The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 67(2):93–99

Anderson KG, Stromnes IM, Greenberg PD (2017) Obstacles posed by the tumor microenvironment to T cell activity: a case for synergistic therapies. Cancer Cell 31(3):311–325

Antunes DA, Devaurs D, Moll M, Lizée G, Kavraki LE (2018) General prediction of peptide-MHC binding modes using incremental docking: a proof of concept. Sci Rep 8(1):4327

Asegaonkar SB, Asegaonkar BN, Takalkar UV, Advani S, Thorat AP (2015) C-reactive protein and breast cancer: new insights from old molecule. Int J Breast Cancer 2015:145647

Aziz S, Ahmed SS, Ali A, Khan FA, Zulfiqar G, Iqbal J, Khan AA, Shoaib M (2015) Salivary immunosuppressive cytokines IL-10 and IL-13 are significantly elevated in oral squamous cell carcinoma patients. Cancer Investig 33(7):318–328

Azzimonti B, Zavattaro E, Provasi M, Vidali M, Conca A, Catalano E, Rimondini L, Colombo E, Valente G (2015) Intense Foxp3+ CD25+ regulatory T cell infiltration is associated with high-grade cutaneous squamous cell carcinoma and counterbalanced by CD8+/Foxp3+ CD25+ ratio. Br J Dermatol 172:64–73

Badoual C, Hans S, Rodriguez J, Peyrard S, Klein C, Agueznay Nel H, Mosseri V, Laccourreye O, Bruneval P, Fridman WH, Brasnu DF, Tartour E (2006) Prognostic value of tumor-infiltrating CD4+ T-cell subpopulations in head and neck cancers. Clin Cancer Res 12(2):465–472

Balkwill F, Coussens LM (2004) Cancer: an inflammatory link. Nature 431(7007):405–406

Bauer CA, Kim EY, Marangoni F, Carrizosa E, Claudio NM, Mempel TR (2014) Dynamic Treg interactions with intratumoral APCs promote local CTL dysfunction. J Clin Invest 124(6):2425–2440

Bharti AC, Aggarwal BB (2002) Nuclear factor-kappa B and cancer: its role in prevention and therapy. Biochem Pharmacol 64(5–6):883–888

Bindea G, Mlecnik B, Tosolini M, Kirilovsky A, Waldner M, Obenauf AC, Angell H, Fredriksen T, Lafontaine L, Berger A, Bruneval P, Fridman WH, Becker C, Pagès F, Speicher MR, Trajanoski Z, Galon J (2013) Spatiotemporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer. Immunity 39(4):782–795

Boda D, Neagu M, Constantin C, Voinescu RN, Caruntu C, Zurac S, Spandidos DA, Drakoulis N, Tsoukalas D, Tsatsakis AM (2016) HPV strain distribution in patients with genital warts in a female population sample. Oncol Lett 12(3):1779–1782

Boda D, Docea AO, Calina D, Ilie MA, Caruntu C, Zurac S, Neagu M, Constantin C, Branisteanu DE, Voiculescu V, Mamoulakis C, Tzanakakis G, Spandidos DA, Drakoulis N, Tsatsakis AM (2018) Human papilloma virus: apprehending the link with carcinogenesis and unveiling new research avenues (review). Int J Oncol 52(3):637–655

Bommareddy PK, Patel A, Hossain S, Kaufman HL (2017) Talimogene laherparepvec (T-VEC) and other oncolytic viruses for the treatment of melanoma. Am J Clin Dermatol 18(1):1–15

Bottomley MJ, Thomson J, Harwood C, Leigh I (2019) The role of the immune system in cutaneous squamous cell carcinoma. Int J Mol Sci 20(8):2009

Braumüller H, Wieder T, Brenner E, Aßmann S, Hahn M, Alkhaled M, Schilbach K, Essmann F, Kneilling M, Griessinger C, Ranta F, Ullrich S, Mocikat R, Braungart K, Mehra T, Fehrenbacher B, Berdel J, Niessner H, Meier F, van den Broek M, Häring HU, Handgretinger R, Quintanilla-Martinez L, Fend F, Pesic M, Bauer J, Zender L, Schaller M, Schulze-Osthoff K, Röcken M (2013) T-helper-1-cell cytokines drive cancer into senescence. Nature 494 (7437):361–365

Cai DL, Jin LP (2017) Immune cell population in ovarian tumor microenvironment. J Cancer 8(15):2915–2923

Calcinotto A, Filipazzi P, Grioni M, Iero M, De Milito A, Ricupito A, Cova A, Canese R, Jachetti E, Rossetti M, Huber V, Parmiani G, Generoso L, Santinami M, Borghi M, Fais S, Bellone M, Rivoltini L (2012) Modulation of microenvironment acidity reverses anergy in human and murine tumor-infiltrating T lymphocytes. Cancer Res 72(11):2746–2756

Calenic B, Greabu M, Caruntu C, Tanase C, Battino M (2015) Oral keratinocyte stem/progenitor cells: specific markers, molecular signaling pathways and potential uses. Periodontol 69(1):68–82

Campo-Trapero J, Cano-Sánchez J, Palacios-Sánchez B, Llamas-Martínez S, Lo Muzio L, Bascones-Martínez A (2008) Cellular senescence in oral cancer and precancer and treatment implications: a review. Acta Oncol 47(8):1464–1474

Cancer Genome Atlas Network (2015) Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature 517(7536):576–582

Cao B, Wang Q, Zhang H, Zhu G, Lang J (2017) Two immune-enhanced molecular subtypes differ in inflammation, checkpoint signaling and outcome of advanced head and neck squamous cell carcinoma. Onco Targets Ther 7(2):e1392427

Carreno BM, Collins M (2002) The B7 family of ligands and its receptors: new pathways for costimulation and inhibition of immune responses. Annu Rev Immunol 20:29–53

Castellanos MR, Pan Q (2016) Novel p53 therapies for head and neck cancer. World J Otorhinolaryngol Head Neck Surg 2:68–75

Chakravarthy A, Henderson S, Thirdborough SM, Ottensmeier CH, Su X, Lechner M, Feber A, Thomas GJ, Fenton TR (2016) Human papillomavirus drives tumor development throughout the head and neck: improved prognosis is associated with an immune response largely restricted to the oropharynx. J Clin Oncol 34:4132–4141

Chalmers ZR, Connelly CF, Fabrizio D et al (2017) Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 9:1–14

Chan JW, Yeh I, El-Sayed IH, Algazi AP, Glastonbury CM, Ha PK, Yom SS, van Zante A (2019) Ultraviolet light-related DNA damage mutation signature distinguishes cutaneous from mucosal or other origin for head and neck squamous cell carcinoma of unknown primary site. Head Neck 41:E82–E85

Chen DS, Mellman I (2013) Oncology meets immunology: the cancer-immunity cycle. Immunity 39(1):1–10

Chen CJ, Sung WW, Su TC, Chen MK, Wu PR, Yeh KT, Ko JL, Lee H (2013) High expression of interleukin 10 might predict poor prognosis in early stage oral squamous cell carcinoma patients. Clin Chim Acta 415:25–30

Chi AC, Day TA, Neville BW (2015) Oral cavity and oropharyngeal squamous cell carcinoma-an update. CA Cancer J Clin 65:401–421

Cohen EEW, Bell RB, Bifulco CB, Burtness B, Gillison ML, Harrington KJ, Le QT, Lee NY, Leidner R, Lewis RL, Licitra L, Mehanna H, Mell LK, Raben A, Sikora AG, Uppaluri R, Whitworth F, Zandberg DP, Ferris RL (2019a) The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC). J Immunother Cancer 7:1–31

Cohen RB, Lefebvre G, Posner MR, Bauman JR, Salas S, Even C, Saada-Bouzid E, Seiwert T, Colevas D, Calmels F, Zerbib R, André P, Boyer-Chammard A, Fayette J (2019b) Monalizumab in combination with cetuximab in patients (pts) with recurrent or metastatic (R/M) head and neck cancer (SCCHN) previously treated or not with PD-(L)1 inhibitors (IO): 1-year survival data. Ann Oncol 30(Suppl_5):v449–v474. https://doi.org/10.1093/annonc/mdz252

Coley WB (1910) The treatment of inoperable sarcoma by bacterial toxins (the mixed toxins of the Streptococcus erysipelas and the Bacillus prodigiosus). Proc R Soc Med 3(Surg Sect):1–48

Cortez VS, Ulland TK, Cervantes-Barragan L, Bando JK, Robinette ML, Wang Q, White AJ, Gilfillan S, Cella M, Colonna M (2017) SMAD4 impedes the conversion of NK cells into ILC1-like cells by curtailing non-canonical TGF-β signaling. Nat Immunol 18(9):995–1003

Cruz-Gregorio A, Aranda-Rivera AK, Aparicio-Trejo OE, Coronado-Martínez I, Pedraza-Chaverri J, Lizano M (2019) E6 oncoproteins from high-risk human papillomavirus induce mitochondrial metabolism in a head and neck squamous cell carcinoma model. Biomol Ther 9(8):351

Das D, Sarkar B, Mukhopadhyay S, Banerjee C, Mondal SB (2018) An altered ratio of CD4+ and CD8+ T lymphocytes in cervical cancer tissues and peripheral blood – a prognostic clue? Asian Pac J Cancer Prev 19:471–478

Dayyani F, Etzel CJ, Liu M, Ho CH, Lippman SM, Tsao AS (2010) Meta-analysis of the impact of human papillomavirus (HPV) on cancer risk and overall survival in head and neck squamous cell carcinomas (HNSCC). Head Neck Oncol 2:1–11

de Andrade LF, En Tay R, Pan D, Luoma AM, Ito Y, Badrinath S, Tsoucas D, Franz B, May KF Jr, Harvey CJ, Kobold S, Pyrdol JW, Yoon C, Yuan GC, Hodi FS, Dranoff G, Wucherpfennig KW (2018) Antibody-mediated inhibition of MICA and MICB shedding promotes NK cell-driven tumor immunity. Science 59 (6383):1537–1542

de Ruiter EJ, Ooft ML, Devriese LA, Willems SM (2017) The prognostic role of tumor infiltrating T-lymphocytes in squamous cell carcinoma of the head and neck: a systematic review and meta-analysis. Onco Targets Ther 6:1–10

de Visser KE, Korets LV, Coussens LM (2005) De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. Cancer Cell 7(5):411–423

Denaro N, Lo Nigro C, Natoli G, Russi EG, Adamo V, Merlano MC (2011) The role of p53 and MDM2 in head and neck cancer. ISRN Otolaryngol 2011:931813

Dinarello CA (2000) Proinflammatory cytokines. Chest 118(2):503–508

Distel LV, Fickenscher R, Dietel K, Hung A, Iro H, Zenk J, Nkenke E, Büttner M, Niedobitek G, Grabenbauer GG (2009) Tumour infiltrating lymphocytes in squamous cell carcinoma of the oro- and hypopharynx: prognostic impact may depend on type of treatment and stage of disease. Oral Oncol 45 (10):e167–e174

Dobosz P, Dzieciątkowski T (2019) The intriguing history of cancer immunotherapy. Front Immunol 10:2965

Doorbar J, Egawa N, Griffin H, Kranjec C, Murakami I (2015) Human papillomavirus molecular biology and disease association. Rev Med Virol 25(Suppl Suppl 1):2–23

Dudley ME, Yang JC, Sherry R, Hughes MS, Royal R, Kammula U, Robbins PF, Huang J, Citrin DE, Leitman SF, Wunderlich J, Restifo NP, Thomasian A, Downey SG, Smith FO, Klapper J, Morton K, Laurencot C, White DE, Rosenberg SA (2008) Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. J Clin Oncol 26(32):5233–5239

Duesberg PH, Vogt PK (1970) Differences between the ribonucleic acids of transforming and nontransforming avian tumor viruses. Proc Natl Acad Sci U S A 67:1673–1680

Economopoulou P, Psyrri A (2017) Epidemiology, risk factors and pathogenesis of squamous cell tumours. In Head and Neck Cancers: Essentials for clinicians. https://oncologypro.esmo.org/content/download/113133/1971849/file/2017-ESMO-Essentials-for-Clinicians-Head-Neck-Cancers-Chapter-1.pdf

Elgart K, Faden DL (2020) Sinonasal squamous cell carcinoma: etiology, pathogenesis, and the role of human papilloma virus. Curr Otorhinolaryngol Rep 8:111–119

Evrard D, Szturz P, Tijeras-Raballand A, Astorgues-Xerri-L, Abitbol C, Paradis V, Raymond E, Albert S, Barry B, Faivre S (2019) Macrophages in the microenvironment of head and neck cancer: potential targets for cancer therapy. Oral Oncol 88:29–38

Fancello L, Gandini S, Pelicci PG, Mazzarella L (2019) Tumor mutational burden quantification from targeted gene panels: major advancements and challenges. J Immunother Cancer 7(1):183

Faraji F, Zaidi M, Fakhry C, Gaykalova DA (2017) Molecular mechanisms of human papillomavirus-related carcinogenesis in head and neck cancer. Microbes Infect 19:464–475

Farhan-Alanie OM, McMahon J, McMillan DC (2015) Systemic inflammatory response and survival in patients undergoing curative resection of oral squamous cell carcinoma. Br J Oral Maxillofac Surg 53 (2):126–131

Feller L, Chandran R, Khammissa RAG, Meyerov R, Lemmer J (2013) Alcohol and oral squamous cell carcinoma. SADJ 68:176–180

Ferris RL, Haddad R, Even C, Tahara M, Dvorkin M, Ciuleanu TE, Clement PM, Mesia R, Kutukova S, Zholudeva L, Daste A, Caballero-Daroqui J, Keam B, Vynnychenko I, Lafond C, Shetty J, Mann H, Fan J, Wildsmith S, Morsli N, Fayette J, Licitra L (2020) Durvalumab with or without tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: EAGLE, a randomized, open-label phase III study. Ann Oncol 31(7):942–950

Fukunaga A, Miyamoto M, Cho Y, Murakami S, Kawarada Y, Oshikiri T, Kato K, Kurokawa T, Suzuoki M, Nakakubo Y, Hiraoka K, Itoh T, Morikawa T, Okushiba S, Kondo S, Katoh H (2004) CD8+ tumor-infiltrating lymphocytes together with CD4+ tumor-infiltrating lymphocytes and dendritic cells improve the prognosis of patients with pancreatic adenocarcinoma. Pancreas 28(1):e26–e31

Gameiro SF, Ghasemi F, Barrett JW, Koropatnick J, Nichols AC, Mymryk JS, Maleki Vareki S (2018)

Treatment-naïve HPV+ head and neck cancers display a T-cell-inflamed phenotype distinct from their HPV-counterparts that has implications for immunotherapy. Onco Targets Ther 7(10):e1498439

Gameiro SF, Ghasemi F, Barrett JW, Nichols AC, Mymryk JS (2019) High level expression of MHC-II in HPV+ head and neck cancers suggests that tumor epithelial cells serve an important role as accessory antigen presenting cells. Cancers (Basel) 11(8):1129

Garrido F (2019) MHC/HLA class I loss in cancer cells. Adv Exp Med Biol 1151:15–78

Georgescu SR, Sârbu MI, Matei C, Ilie MA, Caruntu C, Constantin C, Neagu M, Tampa M (2017) Capsaicin: friend or foe in skin cancer and other related malignancies? Nutrients 9(12):1365

Georgescu SR, Mitran CI, Mitran MI, Caruntu C, Sarbu MI, Matei C, Nicolae I, Tocut SM, Popa MI, Tampa M (2018) New insights in the pathogenesis of HPV infection and the associated carcinogenic processes: the role of chronic inflammation and oxidative stress. J Immunol Res 2018:5315816

Georgescu SR, Tampa M, Mitran CI, Mitran MI, Caruntu C, Caruntu A, Lupu M, Matei C, Constantin C, Neagu M (2020) Tumor microenvironment in skin carcinogenesis. Adv Exp Med Biol 1226:123–142

Grafetstätter M, Hüsing A, González Maldonado S, Sookthai D, Johnson T, Pletsch-Borba L, Katzke VA, Hoffmeister M, Bugert P, Kaaks R, Kühn T (2019) Plasma fibrinogen and sP-selectin are associated with the risk of lung cancer in a prospective study. Cancer Epidemiol Biomark Prev 28(7):1221–1227

Greten FR, Grivennikov SI (2019) Inflammation and cancer: triggers, mechanisms, and consequences. Immunity 51:27–41

Haddad RI, Posner M, Hitt R, Cohen EEW, Schulten J, Lefebvre JL, Vermorken JB (2018) Induction chemotherapy in locally advanced squamous cell carcinoma of the head and neck: role, controversy, and future directions. Ann Oncol 29:1130–1140

Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674

Hanai N, Sawabe M, Kimura T, Suzuki H, Ozawa T, Hirakawa H, Fukuda Y, Hasegawa Y (2018) The high-sensitivity modified Glasgow prognostic score is superior to the modified Glasgow prognostic score as a prognostic predictor for head and neck cancer. Oncotarget 9:37008–37016

Hashibe M, Brennan P, Benhamou S et al (2007) Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the international head and neck cancer epidemiology consortium. J Natl Cancer Inst 99(10):777–789

Heikkinen I, Bello IO, Wahab A et al (2019) Assessment of tumor-infiltrating lymphocytes predicts the behavior of early-stage oral tongue cancer. Am J Surg Pathol 43:1392–1396

Hilly O, Strenov Y, Rath-Wolfson L, Hod R, Shkedy Y, Mizrachi A, Koren R, Shpitzer T (2016) The predictive value of dendritic cells in early squamous cell carcinoma of the tongue. Pathol Res Pract 212 (12):1138–1143

Hladíková K, Koucký V, Bouček J, Laco J, Grega M, Hodek M, Zábrodský M, Vošmik M, Rozkošová K, Vošmiková H, Čelakovský P, Chrobok V, Ryška A, Špíšek R, Fialová A (2019) Tumor-infiltrating B cells affect the progression of oropharyngeal squamous cell carcinoma via cell-to-cell interactions with CD8+ T-cells. J Immunother Cancer 7(1):1–16

Holzinger D, Danilovic I, Seemann R, Kornek G, Engelmann J, Pillerstorff R, Holawe S, Psyrri A, Erovic BM, Farwell G, Perisanidis C (2016) Prognostic impact of pretreatment plasma fibrinogen in patients with locally advanced oral and oropharyngeal cancer. PLoS One 11(6):e0158697

Hosseini M, Kasraian Z, Rezvani HR (2017) Energy metabolism in skin cancers: a therapeutic perspective. Biochim Biophys Acta Bioenerg 1858:712–722

Hu W, Wang G, Huang D, Sui M, Xu Y (2019) Cancer immunotherapy based on natural killer cells: current progress and new opportunities. Front Immunol 10:1–16

Hugo W, Zaretsky JM, Sun L, Song C, Moreno BH, Hu-Lieskovan S, Berent-Maoz B, Pang J, Chmielowski B, Cherry G, Seja E, Lomeli S, Kong X, Kelley MC, Sosman JA, Johnson DB, Ribas A, Lo RS (2016) Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. Cell 165(1):35–44

Husain N, Neyaz A (2017) Human papillomavirus associated head and neck squamous cell carcinoma: controversies and new concepts. J Oral Biol Craniofac Res 7(3):198–205

Ibrahim-Hashim A, Estrella V (2019) Acidosis and cancer: from mechanism to neutralization. Cancer Metastasis Rev 38:149–155

International Human Genome Sequencing Consortium (2004) Finishing the euchromatic sequence of the human genome. Nature 431(7011):931–945

Jardim JF, Gondak R, Galvis MM, Pinto CAL, Kowalski LP (2018) A decreased peritumoral CD1a+ cell number predicts a worse prognosis in oral squamous cell carcinoma. Histopathology 72(6):905–913

Jarnicki AG, Lysaght J, Todryk S, Mills KHG (2006) Suppression of antitumor immunity by IL-10 and TGF-β-producing T cells infiltrating the growing tumor: influence of tumor environment on the induction of CD4+ and CD8+ regulatory T cells. J Immunol 177(2):896–904

Jiang X, Wu J, Wang J, Huang R (2019) Tobacco and oral squamous cell carcinoma: a review of carcinogenic pathways. Tob Induc Dis 17:29

Jinno T, Kawano S, Maruse Y, Matsubara R, Goto Y, Sakamoto T, Hashiguchi Y, Kaneko N, Tanaka H, Kitamura R, Toyoshima T, Jinno A, Moriyama M, Oobu K, Kiyoshima T, Nakamura S (2015) Increased

expression of interleukin-6 predicts poor response to chemoradiotherapy and unfavorable prognosis in oral squamous cell carcinoma. Oncol Rep 33 (5):2161–2168

Johnson SD, Levingston C, Young MRI (2016) Premalignant oral lesion cells elicit increased cytokine production and activation of T-cells. Anticancer Res 36 (7):3261–3270

Jou A, Hess J (2017) Epidemiology and molecular biology of head and neck Cancer. Oncol Res Treat 40:328–332

Karpathiou G, Vieville M, Gavid M, Camy F, Dumollard JM, Magné N, Froudarakis M, Prades JM, Peoc'h M (2019) Prognostic significance of tumor budding, tumor-stroma ratio, cell nests size, and stroma type in laryngeal and pharyngeal squamous cell carcinomas. Head Neck 41:1918–1927

Kärre K (2008) Natural killer cell recognition of missing self. Nat Immunol 9(5):477–480

Keck MK, Zuo Z, Khattri A, Stricker TP, Brown CD, Imanguli M, Rieke D, Endhardt K, Fang P, Brägelmann J, DeBoer R, El-Dinali M, Aktolga S, Lei Z, Tan P, Rozen SG, Salgia R, Weichselbaum RR, Lingen MW, Story MD, Ang KK, Cohen EE, White KP, Vokes EE, Seiwert TY (2015) Integrative analysis of head and neck cancer identifies two biologically distinct HPV and three non-HPV subtypes. Clin Cancer Res 21(4):870–881

Kersten K, de Visser KE, van Miltenburg MH, Jonkers J (2017) Genetically engineered mouse models in oncology research and cancer medicine. EMBO Mol Med 9 (2):137–153

Khandavilli SD, Ceallaigh PÓ, Lloyd CJ, Whitaker R (2009) Serum C-reactive protein as a prognostic indicator in patients with oral squamous cell carcinoma. Oral Oncol 45(10):912–914

Khowal S, Wajid S (2019) Role of smoking-mediated molecular events in the genesis of oral cancers. Toxicol Mech Methods 29(9):665–685

Kim SM (2016) Human papilloma virus in oral cancer. J Korean Assoc Oral Maxillofac Surg 42:327

Knutson KL, Disis ML (2005) Augmenting T helper cell immunity in cancer. Curr Drug Targets Immune Endocr Metabol Disord 5:365–371

Kobayashi K, Hisamatsu K, Suzui N, Hara A, Tomita H, Miyazaki T (2018) A review of HPV-related head and neck cancer. J Clin Med 7(9):241

Koebel CM, Vermi W, Swann JB, Zerafa N, Rodig SJ, Old LJ, Smyth MJ, Schreiber RD (2007) Adaptive immunity maintains occult cancer in an equilibrium state. Nature 450(7171):903–907

Koyama S, Akbay EA, Li YY, Taube JM, Westra WH, Akpeng B, Bruno TC, Richmon JD, Wang H, Bishop JA, Chen L, Drake CG, Topalian SL, Pardoll DM, Pai SI (2016) Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. Nat Commun 7:1–9

Kuilman T, Michaloglou C, Vredeveld LCW, Douma S, van Doorn R, Desmet CJ, Aarden LA, Mooi WJ, Peeper DS (2008) Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. Cell 133:1019–1031

Kuilman T, Michaloglou C, Mooi WJ, Peeper DS (2010) The essence of senescence. Genes Dev 24:2463–2479

Kumar AT, Knops A, Swendseid B, Martinez-Outschoom U, Harshyne L, Philp N, Rodeck U, Luginbuhl A, Cognetti D, Johnson J, Curry J (2019) Prognostic significance of tumor-associated macrophage content in head and neck squamous cell carcinoma: a meta-analysis. Front Oncol 9:656

Lan M, Chen C, Huang Y, Mao M, Han F, Liao J, Deng M, Duan Z, Zheng L, Wu S, Lu T, Jian Y (2016) Elevated plasma fibrinogen level shows superior prognostic value than Epstein-Barr virus DNA load for stage IVA/B nasopharyngeal carcinoma patients in the intensity-modulated radiotherapy era. Oncotarget 7 (29):46242–46252

Lechner A, Schlößer HA, Thelen M, Wennhold K, Rothschild SI, Gilles R, Quaas A, Siefer OG, Huebbers CU, Cukuroglu E, Göke J, Hillmer A, Gathof B, Meyer MF, Klussmann JP, Shimabukuro-Vornhagen A, Theurich S, Beutner D, von Bergwelt-Baildon M (2019) Tumor-associated B cells and humoral immune response in head and neck squamous cell carcinoma. Onco Targets Ther 8:1535293

Li J, Wang J, Chen R, Bai Y, Lu X (2017) The prognostic value of tumor-infiltrating T lymphocytes in ovarian cancer. Oncotarget 8:15621–15631

Li B, Ren M, Zhou X, Han Q, Cheng L (2020) Targeting tumor-associated macrophages in head and neck squamous cell carcinoma. Oral Oncol 106:104723

Lupu M, Caruntu A, Caruntu C, Papagheorghe LML, Ilie MA, Voiculescu V, Boda D, Constantin C, Tanase C, Sifaki M, Drakoulis N, Mamoulakis C, Tzanakakis G, Neagu M, Spandidos DA, Izotov BN, Tsatsakis AM (2017) Neuroendocrine factors: the missing link in non-melanoma skin cancer (review). Oncol Rep 38 (3):1327–1340

Lupu M, Caruntu A, Caruntu C, Boda D, Moraru L, Voiculescu V, Bastian A (2018a) Non-invasive imaging of actinic cheilitis and squamous cell carcinoma of the lip. Mol Clin Oncol 8(5):640–646

Lupu M, Căruntu ANA, Moraru L, Voiculescu VM, Boda D, Tănase C, Căruntu C (2018b) Non-invasive imaging techniques for early diagnosis of radiation-induced squamous cell carcinoma of the lip. Romanian J Morphol Embryol 59:949–953

Lupu M, Caruntu A, Boda D, Caruntu C (2020) *In vivo* reflectance confocal microscopy-diagnostic criteria for actinic cheilitis and squamous cell carcinoma of the lip. J Clin Med 9(6):1987

Lyford-Pike S, Peng S, Young GD et al (2013) Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma. Cancer Res 73(6):1733–1741

Lyu H, Li M, Jiang Z, Liu Z, Wang X (2019) Correlate the TP53 mutation and the HRAS mutation with immune signatures in head and neck squamous cell cancer. Comput Struct Biotechnol J 17:1020–1030

Markowska J, Markowska A (1998) Spontaneous tumor regression. Ginekol Pol 69:39–44

Mazzaschi G, Madeddu D, Falco A, Bocchialini G, Goldoni M, Sogni F, Armani G, Lagrasta CA, Lorusso B, Mangiaracina C, Vilella R, Frati C, Alfieri R, Ampollini L, Veneziani M, Silini EM, Ardizzoni A, Urbanek K, Aversa F, Quaini F, Tiseo M (2018) Low PD-1 expression in cytotoxic CD8+ tumor-Infiltrating lymphocytes confers an immune-privileged tissue microenvironment in NSCLC with a prognostic and predictive value. Clin Cancer Res 24 (2):407–419

McGranahan N, Furness AJS, Rosenthal R et al (2016) Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science 351(6280):1463–1469

McManus JF (1958) Rudolf Virchow in 1858. Lab Investig 7:549–553

Mei Z, Huang J, Qiao B, Lam AK (2020) Immune checkpoint pathways in immunotherapy for head and neck squamous cell carcinoma. Int J Oral Sci 12(1):16

Miller JS, Lanier LL (2019) Natural killer cells in cancer immunotherapy. Annu Rev Cancer Biol 3:77–103

Miller JS, Soignier Y, Panoskaltsis-Mortari A, McNearney SA, Yun GH, Fautsch SK, McKenna D, Le C, Defor TE, Burns LJ, Orchard PJ, Blazar BR, Wagner JE, Slungaard A, Weisdorf DJ, Okazaki IJ, McGlave PB (2005) Successful adoptive transfer and *in vivo* expansion of human haploidentical NK cells in patients with cancer. Blood 105(8):3051–3057

Minetto P, Guolo F, Pesce S, Greppi M, Obino V, Ferretti E, Sivori S, Genova C, Lemoli RM, Marcenaro E (2019) Harnessing NK cells for cancer treatment. Front Immunol 10:2836

Mittal D, Gubin MM, Schreiber RD, Smyth MJ (2014) New insights into cancer immunoediting and its three component phases-elimination, equilibrium and escape. Curr Opin Immunol 27:16–25

Monisha J, Roy NK, Bordoloi D, Kumar A, Golla R, Kotoky J, Padmavathi G, Kunnumakkara AB (2017) Nuclear factor kappa B: a potential target to persecute head and neck cancer. Curr Drug Targets 18:232–253

Morgan RA, Dudley ME, Wunderlich JR, Hughes MS, Yang JC, Sherry RM, Royal RE, Topalian SL, Kammula US, Restifo NP, Zheng Z, Nahvi A, de Vries CR, Rogers-Freezer LJ, Mavroukakis SA, Rosenberg SA (2006) Cancer regression in patients after transfer of gentically engineered lymphocytes. Science 314(5796):126–129

Mosesson MW (2005) Fibrinogen and fibrin structure and functions. J Thromb Haemost 3(8):1894–1904

Nair S, Dhodapkar MV (2017) Natural killer T-cells in cancer immunotherapy. Front Immunol 8:1–27

Näsman A, Romanitan M, Nordfors C, Grün N, Johansson H, Hammarstedt L, Marklund L, Munck-Wikland E, Dalianis T, Ramqvist T (2012) Tumor infiltrating CD8+ and Foxp3+ lymphocytes correlate to clinical outcome and human papillomavirus (HPV) status in tonsillar cancer. PLoS One 7:1–8

National Cancer Institute (2015) Head and neck cancer. Lip and oral cavity cancer treatment (adult) (PDQ®) – Health Professional Version. https://www.cancer.gov/types/head-and-neck/hp/adult/lip-mouth-treatment-pdq. Accessed on 12 Jan 2021

Ndiaye C, Mena M, Alemany L, Arbyn M, Castellsagué X, Laporte L, Bosch FX, de Sanjosé S, Trottier H (2014) HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. Lancet Oncol 15:1319–1331

Neagu M, Caruntu C, Constantin C, Boda D, Zurac S, Spandidos DA, Tsatsakis AM (2016) Chemically induced skin carcinogenesis: updates in experimental models (review). Oncol Rep 35(5):2516–2528

Neagu M, Constantin C, Caruntu C, Dumitru C, Surcel M, Zurac S (2019) Inflammation: a key process in skin tumorigenesis (review). Oncol Lett 17(5):4068–4084

Nelson BH (2004) IL-2, regulatory T cells, and tolerance. J Immunol 172(7):3983–3988

Ngamphaiboon N, Chureemas T, Siripoon T, Arsa L, Trachu N, Jiarpinitnun C, Pattaranutaporn P, Sirachainan E, Larbcharoensub N (2019) Characteristics and impact of programmed death-ligand 1 expression, CD8+ tumor-infiltrating lymphocytes, and p16 status in head and neck squamous cell carcinoma. Med Oncol 36:21

NIH (2017) National Institutes of Health – National Cancer Institute. Cancer Stat Facts: Oral Cavity and Pharynx Cancer. https://seer.cancer.gov/statfacts/html/oralcav.html. Accessed on 10 Jan 2021

Nordfors C, Grün N, Tertipis N, Ährlund-Richter A, Haeggblom L, Sivars L, Du J, Nyberg T, Marklund L, Munck-Wikland E, Näsman A, Ramqvist T, Dalianis T (2013) CD8+ and CD4+ tumour infiltrating lymphocytes in relation to human papillomavirus status and clinical outcome in tonsillar and base of tongue squamous cell carcinoma. Eur J Cancer 49(11):2522–2530

Oguejiofor K, Hall J, Slater C, Betts G, Hall G, Slevin N, Dovedi S, Stern PL, West CML (2015) Stromal infiltration of CD8 T-cells is associated with improved clinical outcome in HPV-positive oropharyngeal squamous carcinoma. Br J Cancer 113(6):886–893

Oguejiofor K, Galletta-Williams H, Dovedi SJ, Roberts DL, Stern PL, West CML (2017) Distinct patterns of infiltrating CD8+ T-cells in HPV+ and CD68 macrophages in HPV- oropharyngeal squamous cell carcinomas are associated with better clinical outcome but PD-L1 expression is not prognostic. Oncotarget 8:14416–14427

Old MO, Wise-Draper T, Wright CL, Kaur B, Teknos T (2016) The current status of oncolytic viral therapy for head and neck cancer. World J Otorhinolaryngol Neck Surg 2(2):84–89

Opitz JM (2016) Annals of morphology THEODOR BOVERI (1862–1915) to commemorate the centenary of his death and contributions to the Sutton–Boveri hypothesis. Am J Med Genet A 170:2803–2829

Ostroumov D, Fekete-Drimusz N, Saborowski M, Kühnel F, Woller N (2018) CD4 and CD8 T lymphocyte interplay in controlling tumor growth. Cell Mol Life Sci 75:689–713

Otsuka M, Egawa G, Kabashima K (2018) Uncovering the mysteries of Langerhans cells, inflammatory dendritic epidermal cells, and monocyte-derived Langerhans cell-like cells in the epidermis. Front Immunol 9:1768

Pan QX, Su ZJ, Zhang JH, Wang CR, Ke SY (2017) Glasgow Prognostic Score predicts prognosis of intrahepatic cholangiocarcinoma. Mol Clin Oncol 6 (4):566–574

Perdrix A, Najem A, Saussez S, Awada A, Journe F, Ghanem G, Krayem M (2017) PRIMA-1 and PRIMA-1Met (APR-246): from mutant/wild type p53 reactivation to unexpected mechanisms underlying their potent anti-tumor effect in combinatorial therapies. Cancers (Basel) 9:1–17

Pérez Sayáns M, Chamorro Petronacci CM, Lorenzo Pouso AI, Padín Iruegas E, Blanco Carrión A, Suárez Peñaranda JM, García García A (2019) Comprehensive genomic review of TCGA head and neck squamous cell carcinomas (HNSCC). J Clin Med 8:1896

Perri F, Pisconti S, Della VSG (2016) P53 mutations and cancer: a tight linkage. Ann Transl Med 4:2–5

Perri F, Ionna F, Longo F, Della Vittoria Scarpati G, De Angelis C, Ottaiano A, Botti G, Caponigro F (2020) Immune response against head and neck cancer: biological mechanisms and implication on therapy. Transl Oncol 13:262–274

Peter F, Wittekindt C, Finkensieper M, Kiehntopf M, Guntinas-Lichius O (2013) Prognostic impact of pretherapeutic laboratory values in head and neck cancer patients. J Cancer Res Clin Oncol 139(1):171–178

Pettersen JS, Fuentes-Duculan J, Suárez-Farĩas M, Pierson KC, Pitts-Kiefer A, Fan L, Belkin DA, Wang CQ, Bhuvanendran S, Johnson-Huang LM, Bluth MJ, Krueger JG, Lowes MA, Carucci JA (2011) Tumor-associated macrophages in the cutaneous SCC microenvironment are heterogeneously activated. J Invest Dermatol 131(6):1322–1330

Pignon J, Bourhis J, Domenge C, Designe L (2001) Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-analysis of chemotherapy on head and neck cancer. Lancet 355(9208):949–955

Pilon-Thomas S, Kodumudi KN, El-Kenawi AE, Russell S, Weber AM, Luddy K, Damaghi M, Wojtkowiak JW, Mulé JJ, Ibrahim-Hashim A, Gillies RJ (2016) Neutralization of tumor acidity improves antitumor responses to immunotherapy. Cancer Res 76(6):1381–1390

Postow MA, Callahan MK, Wolchok JD (2015) Immune checkpoint blockade in cancer therapy. J Clin Oncol 33:1974–1982

Punyani SR, Sathawane RS (2013) Salivary level of interleukin-8 in oral precancer and oral squamous cell carcinoma. Clin Oral Investig 17(2):517–524

Quabius ES, Haag J, Kühnel A, Henry H, Hoffmann AS, Görögh T, Hedderich J, Evert M, Beule AG, Maune S, Knecht R, Óvári A, Durisin M, Hoppe F, Tribius S, Röcken C, Ambrosch P, Hoffmann M (2015) Geographical and anatomical influences on human papillomavirus prevalence diversity in head and neck squamous cell carcinoma in Germany. Int J Oncol 46:414–422

Quezada SA, Simpson TR, Peggs KS, Merghoub T, Vider J, Fan X, Blasberg R, Yagita H, Muranski P, Antony PA, Restifo NP, Allison JP (2010) Tumor-reactive CD4+ T-cells develop cytotoxic activity and eradicate large established melanoma after transfer into lymphopenic hosts. J Exp Med 207(3):637–650

Rao SK, Pavicevic Z, Du Z, Kim JG, Fan M, Jiao Y, Rosebush M, Samant S, Gu W, Pfeffer LM, Nosrat CA (2010) Pro-inflammatory genes as biomarkers and therapeutic targets in oral squamous cell carcinoma. J Biol Chem 285(42):32512–32521

Rettig EM, D'Souza G (2015) Epidemiology of head and neck cancer. Surg Oncol Clin N Am 24(3):379–396

Ribatti D (2017) The concept of immune surveillance against tumors. The first theories. Oncotarget 8 (4):7175–7180

Roh JL, Jang H, Kim EH, Shin D (2017) Targeting of the glutathione, thioredoxin, and Nrf2 antioxidant systems in head and neck cancer. Antioxidants Redox Signal 27 (2):106–114

Rooney MS, Shukla SA, Wu CJ, Getz G, Hacohen N (2015) Molecular and genetic properties of tumors associated with local immune cytolytic activity. Cell 160:48–61

Saijo M, Nakamura K, Masuyama H, Ida N, Haruma T, Kusumoto T, Seki N, Hiramatsu Y (2017) Glasgow Prognostic Score is a prognosis predictor for patients with endometrial cancer. Eur J Obstet Gynecol Reprod Biol 210:355–359

Sakaguchi S (2005) Naturally arising Foxp3-expressing CD25+ CD4+ regulatory T-cells in immunological tolerance to self and non-self. Nat Immunol 6 (4):345–352

Salama P, Phillips M, Grieu F, Morris M, Zeps N, Joseph D, Platell C, Iacopetta B (2009) Tumor-infiltrating FOXP3+ T regulatory cells show strong prognostic significance in colorectal cancer. J Clin Oncol 27(2):186–192

Sato J, Ohuchi M, Abe K, Satoh T, Abe T, Yamazaki Y, Satoh A, Notani KI, Kitagawa Y (2013) Correlation between salivary interleukin-6 levels and early locoregional recurrence in patients with oral squamous cell carcinoma: preliminary study. Head Neck 35 (6):889–894

Scheau C, Badarau IA, Mihai LG, Scheau AE, Costache DO, Constantin C, Calina D, Caruntu C, Costache RS, Caruntu A (2020) Cannabinoids in the pathophysiology of skin inflammation. Molecules 25(3):6522

Schiegnitz E, Kämmerer PW, Schön H, Blatt S, Berres M, Sagheb K, Al-Nawas B (2018) Proinflammatory cytokines as serum biomarker in oral carcinoma - a

prospective multi-biomarker approach. J Oral Pathol Med 38:42–49
Schumacher TN, Scheper W, Kvistborg P (2019) Cancer neoantigens. Annu Rev Immunol 37:173–200
Seifi S, Feizi F, Mehdizadeh M, Khafri S, Ahmadi B (2014) Evaluation of cytological alterations of oral mucosa in smokers and waterpipe users. Cell J 15 (4):302–309
Selby MJ, Engelhardt JJ, Quigley M, Henning KA, Chen T, Srinivasan M, Korman AJ (2013) Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T-cells. Cancer Immunol Res 1(1):32–42
Selzer E, Grah A, Heiduschka G, Kornek G, Thurnher D (2016) Pre-therapeutic fibrinogen levels are of prognostic significance in locally advanced head and neck cancer. Wien Klin Wochenschr 128(9–10):320–328
Shimizu S, Hiratsuka H, Koike K, Tsuchihashi K, Sonoda T, Ogi K, Miyakawa A, Kobayashi J, Kaneko T, Igarashi T, Hasegawa T, Miyazaki A (2019) Tumor-infiltrating CD8+ T-cell density is an independent prognostic marker for oral squamous cell carcinoma. Cancer Med 8(1):80–93
Simpson-Haidaris PJ, Rybarczyk B (2001) Tumors and fibrinogen. The role of fibrinogen as an extracellular matrix protein. Ann N Y Acad Sci 936:406–425
Smyth MJ, Dunn GP, Schreiber RD (2006) Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. Adv Immunol 90:1–50
Solomon I, Voiculescu VM, Caruntu C, Lupu M, Popa A, Ilie MA, Albulescu R, Caruntu A, Tanase C, Constantin C, Neagu M, Boda D (2018) Neuroendocrine factors and head and neck squamous cell carcinoma: an affair to remember. Dis Markers 2018:9787831
Spector ME, Bellile E, Amlani L, Zarins K, Smith J, Brenner JC, Rozek L, Nguyen A, Thomas D, McHugh JB, Taylor JMG, Wolf GT (2019) Prognostic value of tumor-infiltrating lymphocytes in head and neck squamous cell carcinoma. JAMA Otolaryngol Head Neck Surg 145(11):1012–1019
Spits H, Bernink JH, Lanier L (2016) NK cells and type 1 innate lymphoid cells: partners in host defense. Nat Immunol 17(7):758–764
Suwanpradid J, Holcomb ZE, MacLeod AS (2017) Emerging skin T-cell functions in response to environmental insults. J Invest Dermatol 137(2):288–294
Tafreshi NK, Lloyd MC, Bui MM, Gillies RJ, Morse DL (2014) Carbonic anhydrase IX as an imaging and therapeutic target for tumors and metastases. Subcell Biochem 75:221–254
Tai SF, Chien HT, Young CK, Tsao CK, de Pablo A, Fan KH, Liao CT, Wang HM, Kang CJ, Chang JT, Huang SF (2017) Roles of preoperative C-reactive protein are more relevant in buccal cancer than other subsites. World J Surg Oncol 15(1):47
Taipale K, Liikanen I, Juhila J, Karioja-Kallio A, Oksanen M, Turkki R, Linder N, Lundin J, Ristimäki A, Kanerva A, Koski A, Joensuu T, Vähä-Koskela M, Hemminki A (2015) T-cell subsets in peripheral blood and tumors of patients treated with oncolytic adenoviruses. Mol Ther 23(5):964–973
Tampa M, Caruntu C, Mitran M, Mitran C, Sarbu I, Rusu LC, Matei C, Constantin C, Neagu M, Georgescu SR (2018a) Markers of oral lichen planus malignant transformation. Dis Markers 2018:1959506
Tampa M, Mitran MI, Mitran CI, Sarbu MI, Matei C, Nicolae I, Caruntu A, Tocut SM, Popa MI, Caruntu C, Georgescu SR (2018b) Mediators of inflammation – a potential source of biomarkers in oral squamous cell carcinoma. J Immunol Res 2018:1061780
Tampa M, Mitran CI, Mitran MI, Nicolae I, Dumitru A, Matei C, Manolescu L, Popa GL, Caruntu C, Georgescu SR (2020) The ROLE OF BEta HPV types and HPV-associated inflammatory processes in cutaneous squamous cell carcinoma. J Immunol Res 2020:5701639
Taniguchi K, Karin M (2018) NF-κB, inflammation, immunity and cancer: coming of age. Nat Rev Immunol 18(5):309–324
Tezal M (2012) Interaction between chronic inflammation and oral HPV infection in the etiology of head and neck cancers. Int J Otolaryngol 2012:575242
Tezal M, Scannapieco FA, Wactawski-Wende J, Hyland A, Marshall JR, Rigual NR, Stoler DL (2012) Local inflammation and human papillomavirus status of head and neck cancers. Arch Otolaryngol Head Neck Surg 138(7):669–675
Thorsson V, Gibbs DL, Brown SD et al (2018) The immune landscape of cancer. Immunity 48 (4):812–830.e14
Trapani JA, Darcy PK (2017) Immunotherapy of cancer. Aust Fam Physician 46(4):194–199
Troiano G, Caponio VCA, Adipietro I, Tepedino M, Santoro R, Laino L, Lo Russo L, Cirillo N, Lo Muzio L (2019) Prognostic significance of CD68+ and CD163+ tumor associated macrophages in head and neck squamous cell carcinoma: a systematic review and meta-analysis. Oral Oncol 93:66–75
Vajdic CM, van Leeuwen MT (2009) Cancer incidence and risk factors after solid organ transplantation. Int J Cancer 125(8):1747–1754
van Pelt GW, Kjær-Frifeldt S, van Krieken JHJM, Al Dieri R, Morreau H, Tollenaar RAEM, Sørensen FB, Mesker WE (2018) Scoring the tumor-stroma ratio in colon cancer: procedure and recommendations. Virchows Arch 473(4):405–412
Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, Erfan J, Zabolotnyy D, Kienzer HR, Cupissol D, Peyrade F, Benasso M, Vynnychenko I, De Raucourt D, Bokemeyer C, Schueler A, Amellal N, Hitt R (2008) Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 359(11):1116–11127
Voiculescu V, Calenic B, Ghita M, Lupu M, Caruntu A, Moraru L, Voiculescu S, Ion A, Greabu M, Ishkitiev N, Caruntu C (2016) From normal skin to squamous cell carcinoma: a quest for novel biomarkers. Dis Markers 2016:4517492

Vomund S, Schäfer A, Parnham MJ, Brüne B, Von Knethen A (2017) Nrf2, the master regulator of anti-oxidative responses. Int J Mol Sci 18:1–19

Waldmann TA (2015) The shared and contrasting roles of IL2 and IL15 in the life and death of normal and neoplastic lymphocytes: implications for cancer therapy. Cancer Immunol Res 3:219–227

Wang YF, Chang SY, Tai SK, Li WY, Wang LS (2002) Clinical significance of interleukin-6 and interleukin-6 receptor expressions in oral squamous cell carcinoma. Head Neck 24(9):850–858

Wang C, Dickie J, Sutavani RV, Pointer C, Thomas GJ, Savelyeva N (2018) Targeting head and neck cancer by vaccination. Front Immunol 9:1–12

Wang J, Sun H, Zeng Q, Guo XJ, Wang H, Liu HH, Dong ZY (2019) HPV-positive status associated with inflamed immune microenvironment and improved response to anti-PD-1 therapy in head and neck squamous cell carcinoma. Sci Rep 9(1):13404

Ward MJ, Thirdborough SM, Mellows T, Riley C, Harris S, Suchak K, Webb A, Hampton C, Patel NN, Randall CJ, Cox HJ, Jogai S, Primrose J, Piper K, Ottensmeier CH, King EV, Thomas GJ (2014) Tumour-infiltrating lymphocytes predict for outcome in HPV-positive oropharyngeal cancer. Br J Cancer 110(2):489–500

Weidhaas JB, Harris J, Schaue D, Chen AM, Chin R, Axelrod R, El-Naggar AK, Singh AK, Galloway TJ, Raben D, Wang D, Matthiesen C, Avizonis VN, Manon RR, Yumen O, Nguyen-Tan PF, Trotti A, Skinner H, Zhang Q, Ferris RL, Sidransky D, Chung CH (2017) The KRAS-variant and cetuximab response in head and neck squamous cell cancer a secondary analysis of a randomized clinical trial. JAMA Oncol 3 (4):483–491

Wellenstein MD, de Visser KE (2018) Cancer-cell-intrinsic mechanisms shaping the tumor immune landscape. Immunity 48:399–416

Wiegand S, Zimmermann A, Wilhelm T, Werner JA (2015) Survival after distant metastasis in head and neck cancer. Anticancer Res 35(10):5499–5502

Wondergem NE, Nauta IH, Muijlwijk T, Leemans CR, van de Ven R (2020) The immune microenvironment in head and neck squamous cell carcinoma: on subsets and subsites. Curr Oncol Rep 22(8):81

Wright TI, Spencer JM, Flowers FP (2006) Chemoprevention of nonmelanoma skin cancer. J Am Acad Dermatol 54(6):933–946

Wu S, Zhu W, Thompson P, Hannun YA (2018) Evaluating intrinsic and non-intrinsic cancer risk factors. Nat Commun 9(1):3490

Xia A, Zhang Y, Xu J, Yin T, Lu XJ (2019) T cell dysfunction in Cancer immunity and immunotherapy. Front Immunol 10:1719

Xu WY, Zhang HH, Yang XB, Bai Y, Lin JZ, Long JY, Xiong JP, Zhang JW, Sang XT, Zhao HT (2018) Prognostic significance of combined preoperative fibrinogen and CA199 in gallbladder cancer patients. World J Gastroenterol 24:1451–1463

Yan M, Xu Q, Zhang P, Zhou XJ, Zhang ZY, Chen WT (2010) Correlation of NF-κB signal pathway with tumor metastasis of human head and neck squamous cell carcinoma. BMC Cancer 10:437

Yang S, Zhao K, Ding X, Jiang H, Lu H (2019) Prognostic significance of hematological markers for patients with nasopharyngeal carcinoma: a meta-analysis. J Cancer 10(11):2568–2577

Zhang JM, An J (2007) Cytokines, inflammation, and pain. Int Anesthesiol Clin 45(2):27–37

Zhang Y, Cao J, Deng Y, Huang Y, Li R, Lin G, Dong M, Huang Z (2020) Pretreatment plasma fibrinogen level as a prognostic biomarker for patients with lung cancer. Clinics (Sao Paulo) 75:e993

Zheng Y, Chaudhry A, Kas A, DeRoos P, Kim JM, Chu TT, Corcoran L, Treuting P, Klein U, Rudensky AY (2009) Regulatory T-cell suppressor program co-opts transcription factor IRF4 to control TH2 responses. Nature 458(7236):351–356