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Review Article

Immunological Phenotypes of Premalignant Oral Lesions and the Immune Shifts with the Development of Head and Neck Cancer

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Abstract

Compared to other cancer types, squamous cell carcinomas of the head and neck (HNSCC) have been understudied.Studies in other cancer types have demonstrated immunological changes that occur with the development of cancer.However, few studies have looked at the immune changes that occur in premalignant lesions.HNSCC is often preceded by the appearance of premalignant oral lesions.However, information about the immune shifts that occur as a result of the premalignant oral lesions and following progression to HNSCC is sparse.This review aims to pull together studies with patients and animal models to summarize the multiplicities of immune activities that are associated with premalignant oral lesions and HSNCC.In general, the immune phenotype in premalignant oral lesions and regional lymph nodes is inflammatory and activated.However, development of HNSCC results in a shift to an immune inhibitory environment.

Keywords: Cytokines, Head and neck cancer, HNSCC, Immune, Inflammation, Oral cancer, Premalignant oral lesions

Overview of the Immune Influences on Premalignant Oral Lesions and Their Progression to Cancer

Despite advances in diagnosis and treatment, the 5-year survival rates for patients with head and neck squamous cell carcinoma (HNSCC) have not improved over 60% [1]. HNSCC is a highly aggressive disease that develops from the oral epithelium and its appearance is often preceded by premalignant oral lesions, most commonly leukoplakias [2]. Even with advanced treatments for premalignant oral lesions, about 30% progress to cancer [3]. Persistent infection with high-risk human Papillomaviruses (HPV) is associated with increased risk of oral cancer.Also associated with risk for HNSCC are alcohol consumption and tobacco.Each of these contributors to the development of epithelial dysplasia and progression to cancer are immune modulatory and complicate the immunological phenotype of oral tissues that are progressing to cancer [4-6].

The multifaceted aspects of the immune system have placed it into opposing roles in the development and progression of cancer (Table 1). On one hand, immune activation, and in particular inflammation, is considered to be among the contributors of cancer onset.Examples of this include associations between cancer and inflammation associated with obesity, inflammatory bowel disease and even oral irritation[7-11]. On the other hand, immune activation can also repress tumor development, as demonstrated through clinical immunotherapeutic trials using various iterations of cancer vaccines or other immune modulatory approaches.Immune protection against cancer is also demonstrated by the increased cancer development in immune compromised individuals such as the increased incidence of non-AIDS-defining cancers in patients with HIV infection [12-14]. These opposing capabilities of the immune system to promote or protect against cancer raise the question of its role in the development of oral lesions and progression to cancer.The answer to this question is highly fragmented, although there are more fragments that can be assembled to understand the immune status in overt HNSCC, as compared to the absence of information pertaining to the impact of the immune milieu on premalignant oral lesions.

The Immunological Environment of Premalignant Oral Lesions

Discussion of the immunological environment of premalignant oral lesions needs to focus not only on the epithelium undergoing transformation, but the myriad of associated cells that comprise the premalignant oral lesion.This includes immune modulatory cells such as endothelial cells of the expanding vasculature, the immune infiltrate consisting of a spectrum of cells further described below, smooth muscle cells and fibroblasts[2,15-17]. A prominent immunological impact of the development of the premalignant oral lesion is seen not only within the premalignant lesions, but throughout the oral cavity,within regional lymph nodes and, in some instances, in the circulation (Table 2). For example, compared to levels in the peripheral blood of healthy control patients,patients with premalignant oral lesions have an increased proportion of NK cells and activated B-cells [18]. Levels of the inflammatory cytokines interleukin (IL)-17 and IL-6 are increased in the peripheral blood of patients with premalignant oral lesions [19]. Other circulating inflammatory mediators whose levels are increased in patients with premalignant lesions are transforming growth factor-β(TGF-β) and C-reactive protein [20]. Also, levels of the inflammatory mediators IL-6 and tumor necrosis factor-α (TNF-α) have been shown to be elevated in the saliva of patients with premalignant oral lesions, although a separate study showed that salivary levels of the inflammatory mediator IL-8 not to be elevated [21,22]. Such studies raise the possibility of using salivary levels of select cytokines as biomarkers for oral carcinogenesis.Such immune reactivities to premalignant oral lesions can be triggered by the increased expression of some of

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Table 1: Opposing roles of immune system in development and progression of cancer.

Immune contribution to cancer	Immune protection against cancer
Inflammation	Inflammation
Increased cancer in inflammation associated with obesity, oral irritation	Indication of failed immune anti-tumor attempt?
Immune inhibitory cell populations	Immunotherapy
Suppress immune anti-tumor defenses	Show potential of immune anti-tumor reactivity

Table 2: Inflammatory and immune stimulatory phenotype associated with premalignant oral lesions.

Premalignant lesion patient sample	4NQO mouse premalignant lesion model
Lesion tissue & blood	Lesions and regional lymph nodes
↑NK cells ↑CD8$^+$ granzyme b$^+$ T-cells ↑dendritic cells	↑Tc1 and Th1 T-cells
↑Inflammatory mediators	↑Inflammatory mediators
IL-6 IL-17 TGF-β TNF-α	IL-6 IL-17 IL-23 TGF-β TNF-α C-reactive protein CCL2 CCL3 CCL4 CCL5 PGE_2
↑Immune stimulatory cytokines	↑Immune stimulatory cytokines
IFN-γ IL-2	IFN-γ IL-2

the same tumor antigens on lesions as are prominent in HNSCC [23]. In fact, this tumor antigen expression on premalignant oral lesions can be used to stimulate immune reactivity by autologous blood lymphocytes.Among these tumor antigens are the mucinMUC-1 and epidermal growth factor receptor (EGFR).

Studies using a carcinogen-induced mouse premalignant oral lesion model that progresses to oral cancer have allowed more detailed assessments of the immunological changes that occur in the course of the development of lesions than would be allowed with patient specimens.Mice treated with the carcinogen 4-nitroquinoline 1-oxide (4NQO) in drinking water develop premalignant oral lesions predominantly on the tongue.These premalignant oral lesions progress to HNSCC.Studies with this model have shown prominent immune stimulation and increased cytokine production by the premalignant lesions as well as within regional lymph nodes [15,24]. Increased immune reactivity and, in particular, inflammation occur within both regional lymph nodes and premalignant oral lesion tissues of 4NQO-treated mice.The lymph nodes of these mice with premalignant oral lesions are enlarged, and the level and composition of the immune infiltrate within the lesions is increased.Also seen is an increase in conventional CD4$^+$ and CD8$^+$ T-cells that express markers for activation compared to what is seen in either healthy controls or HNSCC-bearing mice[15]. These mice with premalignant oral lesions have increased levels of Th1/Tc1 cells expressing interferon-γ (IFN-γ) and IL-2, and CD4$^+$Th17 cells producing the inflammatory cytokine IL-17.Heightened levels of cytokines and chemokines are also secreted by lymph node cells from 4NQO-treated mice with premalignant lesions.These include IFN-γ, IL-2, and members of the chemokine (C-C motif) ligand family CCL 5 (RANTES), CCL3 (macrophage inflammatory protein-1, MIP-1α) and CCL4 (MIP-1β) [15].

While few studies have examined the immunological milieu within the premalignant oral lesion tissues of patients, there have been reports indicating that, like that seen in the mouse models of premalignant oral lesions, inflammation and immune activation also occur in patients with lesions.Similar to the increases seen in levels of NK cells in the peripheral blood, NK cells are also increased within premalignant oral lesions [25]. An analysis of the immune infiltrate in leukoplakias with or without dysplasia showed an increased in numbers of CD8$^+$ T-cells within the epithelium of lesions with dysplasia as compared to levels in lesions without dysplasia or in HNSCC [26]. Also increased in these leukoplakias with dysplasia is the number of dendritic Langerhans cells, with prominent localization with infiltrating T-cells [25,26]. There have been demonstrations of increased levels of Th1 cytokines such as IL-2 and IFN-γ, as well as inflammatory cytokines IL-6 and IL-17within premalignant oral lesions [19]. A separate study comparing cytokine mRNA levels among premalignant oral lesions and healthy gingiva showed no statisticalincrease in TNF-α expression, but significant increases in expression of TGF-β and in select growth factors [27]. In contrast, TNF-α was shown to be expressed by immunohistochemistry throughout the epithelia of premalignant oral lesions, but only rarely in normal oral tissues [28]. Levels of CD8$^+$ T-cells expressing perforin or granzyme B are also increased in premalignant oral lesions compared to control tissue [29]. Half of the premalignant oral lesions examined expressed the inflammatory and pro-angiogenic chemokine C-X-C motif chemokine 12 (CXCL12, stromal cell-derived factor-1) and over a third expressed its C-X-C receptor, CXCR4 [30]. This CXCL12/CXCR4 axis could contribute not only to the inflammatory cell influx, but can also promotethe angiogenesis that is needed by the progressing lesion and subsequent cancer [31]. Expression levels of Toll-like receptors TLR4 and TLR9, which have an essential role in innate immunity activation, is increased in premalignant oral lesions compared to that in control normal mucosa, and the level of expression coincides with the magnitude of dysplasia [32].

Of interest is that shifts in cytokine phenotypes in the patients' oral lesions do not always coincide with what's seen in the peripheral blood. While IL-17 and IL-6 levels are increased in both premalignant lesions and blood, levels of the Th1 cytokines IL-2 and IFN-γare increased only in the premalignant lesions, but not in the blood of patients with lesions [19]. However, the cytokine shifts in the regional lymph nodes coincide more closely with what is seen in the premalignant oral lesions.Thus, the cytokine phenotype within regional lymph nodes may be more representative of that within the premalignant oral lesions than the peripheral blood cytokine phenotype.Consistent with the immune activation seen in premalignant oral lesions, is a diminished level of the non-classicmajor histocompatibility class Ib antigen, which lessens its capacity to subvert immune responses [33]. The decline in this immune moderator could contribute to the increased immune reactivity seen in premalignant oral lesions.

The sources of the immune mediators that are produced within the premalignant lesions are multiple, including the lesion cells themselves.Immune mediators that are produced directly by the epithelium of premalignant lesions have been defined by establishing primary premalignant lesion cell cultures from tongue tissue of mice with carcinogen-induced lesions.These cultures produce high levels of pro-inflammatory and Th1-associated cytokines including granulocyte colony-stimulating factor (G-CSF), CCL5,

and CCL2 (monocyte chemotactic protein 1, MCP-1), with the levels produced being greater than those produced by primary HNSCC cultures established from mice whose lesions progressed to HNSCC [15,24]. Consistent with the increased production of inflammatory mediators was an increased production of prostaglandin E_2 (PGE_2) by premalignant lesion cells as compared to levels produced by HNSCC.IL-23, which is critical to the maintenance of IL-17 cells, is also produced in increased levels by premalignant oral lesion cells, suggesting this to be a route by which lesion cells may be stimulating the Th17 cell content [19]. These studies suggest that Th1/Tc1 and inflammatory immune reactivities are stimulated early prior to the appearance of HNSCC, during the premalignant lesion stages, and are more prominent than in HNSCC.

How Can A Small Premalignant Oral Lesion Cause Distant Immune Alterations?

One might ask- how can premalignant oral lesions that may be only a few millimeters in diameter cause significant immune alterations at distant sites?While premalignant lesion cells produce mediators that can alter immune reactivity, it is likely that much of the immunological skewing associated with premalignant oral lesions is the result of amplifications in cytokine cascades.For example, mediators from premalignant lesion cells can stimulate normal resting spleen cells to produce increased levels of Th1 and inflammatory cytokines, thus triggering greater reactivity than would be possible by the lesion cells alone [24]. This capacity is accentuated by the lesion production of chemokines that, in turn, stimulate an influx of immune cells that are then also exposed to the cytokine-triggering mediators produced by premalignant lesions [24,30]. As indicated above, these infiltrating cells include, but are not limited to, T-cells expressing markers of activations, skewed macrophages and neutrophils that are also recruited by chemokines, and activated endothelial cells associated with the premalignant lesions [15,17].

What is not often appreciated is the role of endothelial cells as immune regulatory cells.The development of premalignant oral lesions and their progression to cancer requires a healthy and increasing vasculature.The pro-inflammatory potential of endothelial cells, especially following stimulation, has been reasonably well described [34-36]. Because of their location, vascular endothelial cells have an intimate relationship with immune cells, which facilitates their recruitment of the immune infiltrate.Endothelial cells can secrete numerous immune suppressive as well as inflammatory products including vascular endothelial cell growth factor (VEGF), PGE_2, TGF-β, IL-6 and IL-10 [37,38]. In addition, endothelial cell-derived mediators can stimulate spleen cell production of pro-inflammatory cytokines such as IL-6, IL-9, IL-17, and TNF-α; production of the predominantly T-cell derived chemokine CCL5; and production of several predominantly monocyte-derived chemokines to include CXCL9 (monokine induced by γ-interferon, MIG) and CCL2 [39].

While premalignant oral lesions may be small in relative size, their immunological impact can be highly prominent.This prominent impact is orchestrated by the dysplastic epithelium, and accentuated by soldiers in the cascade including the endothelium and infiltrating immune cells.Whether this escalation of immune reactivity is an attempt to mount an immune response to the developing malignancy or whether it contributed to the progression toward cancer is not certain, although these two possibilities are not necessarily mutually exclusive.What is certain is that if it is an attempt to eliminate the dysplastic epithelial cells, the attempt often times fails with the resulting emergence of HNSCC.

The Immunological Environment of HNSCC

While the immune phenotype of premalignant oral lesions is stimulated and inflammatory in nature, the immune phenotype of HNSCC is different as immune inhibitory mediators and suppressor cells become more prominent (Table 3). As for premalignant oral lesions, levels of $CD4^+$ and $CD8^+$ cells in patient HNSCC tissue specimens are increased compared to that seen in normal healthy oral tissue [40,41]. Also increased are levels of dendritic cells in HNSCC, with the dendritic cells co-localizing with the T-cell infiltrate [26]. There are, however, some region-specific differences.For example, levels of $CD8^+$ cells expressing perforin and granzyme B are increased in squamous carcinoma of the lip versus oral cavity [29]. Increases in the immune infiltrate and cytokines are also seen in HNSCC tissue and lymph nodes from the 4NQO HNSCC model compared to that seen in healthy control epithelium [15,19].

The increases in immune infiltration may give the perception of anti-tumor immune reactivity, but a prevailing inflammatory and immune inhibitory environment merges with the appearance of HNSCC.Inflammatory mediators whose levels are increased in the peripheral blood of HNSCC patients include IL-6, TGF-β and C-reactive protein, and increased levels of these mediators are associated with increased cancer aggressiveness and recurrence [20]. Some of these mediators, such as TGF-β and IL-6, have dual roles of being able to be both inflammatory and immune inhibitory. Levels of the pro-inflammatory mediator IL-8 have also been shown to be increased in the saliva of patients with HNSCC, although no association was seen between the levels of IL-8 and the cancer TNM stage [22].

The inhibitory immune environment within HNSCC as well as systemically in the HNSCC bearer is viewed as a major mechanism of immune evasion by the HNSCC. By secreting cytokines such as TGF-βand IL-10, HNSCC tumor cells promote a Th2-skewed response, which is associated with decreased antitumor efficacy [42,43]. This Th2-skewing is evident systemically as peripheral blood

Table 3: Shift to inhibitory phenotype in HNSCC.

HNSCC patient sample	4NQO mouse HNSCC model
Lesion tissue & blood	Lesions and regional lymph nodes
↑Th2/Tc2 ↑MDSC and $CD34^+$ cells ↑Treg ↑Th2-skewed dendritic cells	↑Th2/Tc2 ↑MDSC and $CD34^+$ cells ↑Treg ↑Th2-skewed dendritic cells ↑M2 macrophages
↑Inflammatory mediators	↑Inflammatory mediators
IL-1 IL-6 PGE_2 TNF-α TGF-β	IL-6 PGE_2 TNF-α TGF-β
↑Immune inhibitory mediators	↑Immune inhibitory cytokines
IL-6 IL-10 PGE_2 TGF-β	IL-6 IL-10 PGE_2 TGF-β

leukocytes isolated from HNSCC patients secrete abnormally high levels of Th2 cytokines [44,45]. Th2 cytokines include IL-10, whose levels are increased in HNSCC patients [46]. These studies also showed that select polymorphisms of plasma IL-10 are associated with more advanced disease.

Along with Th2-skewed cytokines, HNSCC tumor secretionof factors such as TGF-β function to directly inhibit cytotoxic T cell-mediated immunity and to recruit to the tumor site additional immunosuppressive cells, including myeloid-derived suppressor cells (MDSCs),the less mature $CD34^+$ progenitor cells, as well as M2-skewed macrophages [47,48]. Tumor-secreted granulocyte-macrophage colony-stimulating factor (GM-CSF) promotes MDSC and $CD34^+$ progenitor cells, and high levels of GM-CSF in HNSCC patients are associated with a poorer prognosis [49,50]. Once at the tumor site, these immunosuppressive cells facilitate tumor-promoting functions, resulting in increased tumor growth and angiogenesis.

HNSCC tumor secretion of factors that are typically associated with a pro-inflammatory response harnesses these immune modulators to favor growth, angiogenesis and, paradoxically, immune escape. GM-CSF, TNF-α, IL-1 and PGE_2, which have traditional pro-inflammatory roles, are significantly increased in HNSCC tissues fromthe 4NQO carcinogenmouse model [51]. Many of these mediators are also produced by HNSCC cell lines established from patients with head and neck cancer [52]. Increased levels of PGE_2 are associated with invasion and angiogenesis in aggressive early-stage tumors [53]. Studies in other models have shown that PGE_2 also has inhibitory effects on granulocyte function and macrophage phagocytosis, IL-2 production by T cells, T-cell responsiveness to IL-2, and antigen-specific T cell responses [54-56]. Dendritic cells have also been shown to be impacted by PGE_2, as it inhibits their differentiation and alters the activity of Th1-associated dendritic cells to result in decreased IL-12 production and their increased promotion of Th2-skewed mature T-cells [57-59]. Blocking PGE_2 signaling reduces accumulation of MDSC and delays tumor growth [60]. A retrospective review of HNSCC patients taking cyclooxygenase inhibitors showed an increased survival over those not taking cyclooxygenase inhibitors following cancer treatment [61].

Other factors secreted by HNSCC tumors, such as the chemokine CCL2 (MCP-1), have been shown to contribute to immunosuppression at the tumor site by recruiting a population of M2-skewed tumor-associated macrophages secreting IL-10 and TGF-β [62]. The cytokine macrophage inhibitory factor could also contribute to the accumulation of these macrophages as levels of this mediator are increased within the tumors as well as in the inflammatory infiltrate [63]. By secreting a host of immune modulators, HNSCC tumors thwart an effective immune response and become increasingly difficult to treat.Combinations of cytokines, such as PGE_2 together with IL-6, can heighten the induction of immune inhibitory populations including Th2-skewed T-cells, M2-skewed macrophages, Treg and MDSC [64-66].

The developing HNSCC has prominent impacts on immune reactivity distal from the HNSCC site, with the phenotypes of both the distant and intratumoralreactivities being associated with patient outcomes [67-69]. Most studies involving the impact of HNSCC on patient immune status have assessed immune capabilities and phenotypes of patient peripheral blood.Peripheral blood lymphocytes have a reduced reactive capability to either proliferate or to release cytokines that evoke anti-tumor reactivity [70,71]. Circulating Treg cells from patients with advanced HNSCC were inhibitorier to the proliferation of effector T-cells than Treg from healthy controls or from patients without nodal involvement [72]. The activation status of peripheral blood $CD8^+$T-cells was reduced with increased cancer aggressiveness [73]. Thus, it is clear that the immune modulations in HNSCC patients can impact on clinical outcome [74,75].

Transition from Premalignant Lesions to HNSCC

While there have only been a few studies examining the immunological status of patients with premalignant oral lesions as well as those with HNSCC, they have shown a shift from an immune stimulatory or inflammatory environment to an immune suppressive phenotype.In most instances, however, these studies have not necessarily used the same immunological measurements and have certainly not tracked the same patients with premalignant oral lesions that subsequently develop HNSCC.Such analyses have more reliably been conducted in murine models where premalignant oral lesions progress to oral cancer.Nevertheless, the culmination of these studies has shown increased cellularity within regional lymph nodes, but differences in cellular and cytokines phenotypes, with a greater number of Treg, MDSC, Th2 cells, and M2 macrophages within HNSCC as compared to that seen in cervical lymph nodes or blood of those with premalignant lesions [15,19,24]. Contributing to the immune infiltrate within premalignant lesions and HNSCC is the increased expression of the chemokine CXCL12 in lesions and more so in HNSCC, which is capable of recruiting inflammatory and immune inhibitory cells such as macrophages, which can be skewed to become immune inhibitory M2 macrophages in the tumor environment [31,76]. The increased expression of select TLRs as premalignant lesions become more dysplastic and progress to HNSCC has led to suggestions that their role in activation of innate immunity could contribute to tumorigenesis [32]. An increased level of Th17 cells and Th1/Tc1 cells in mice with premalignant oral lesions compared to those with HNSCC suggests robust immune reactivity being attempted against the lesions, but which doesn't persist once HNSCCdevelops [15,19]. The simultaneous increase in expression of not only markers for activation, but also for exhaustion in mice with premalignant oral lesions could be an early indicator of a failing response against the lesions since they indicate that T-cells have been activated, but they are at the point their lifespan where, upon further stimulation, they will undergo programmed cell death rather than perform effector functions [15,77,78]. This suggests that the exhaustion is a reflection of a failed attempt to immunologically prevent the progression of premalignant oral lesions to cancer.This attempted, but failing, response is far less evident in HNSCC and, as HNSCC progresses, is instead replaced by pronounced levels of a broad myriad of immune inhibitory cells and their inhibitory cytokines [15,19,24]. Also, the levels and select polymorphisms of the Th2 cytokine IL-10 in patients with premalignant lesions were associated with increased risk of progression to HNSCC [46].

What then triggers the shift from robust immune reactivity in the premalignant lesion environment to the immune suppressive

environment in HNSCC?Possibilities include the contribution of the inflammatory state that is so prominent in the premalignant oral lesion stage.Among the inflammatory mediators are PGE_2 and IL--6.These mediators can be produced by a multitude of cell types in the lesion and developing HNSCC environment, including epithelial cells, fibroblasts, and infiltrating immune cells and cancer cells [79]. Furthermore, the role of PGE_2 seems to shift during tumor progression whereas in the early stages of inflammation, PGE_2 promotes the infiltration of neutrophils, macrophages and mast cells [80-82]. However, $PGE_2$and IL-6 can also skew the immune infiltrate toward an immune inhibitory phenotype consisting of Th2 T-cells, M2 macrophages, Treg and MDSC, thereby contributing to the shift from an immune stimulatory to inhibitory environment [64-66,83,84]. Among the mediators whose levels are also increased in premalignant lesions and regional lymph nodes is TGF-β [19] Studies with a mouse skin carcinogenesis model showed that inhibition of TGF-β signaling lessened the level of inflammation that is associated with carcinogenesis, but increased premalignant progression to squamous cell carcinoma, raising the question of the pro-tumorigenic or anti-tumorigenic roles of inflammation [85].

TGF-β and IL-6 levels could be contributors to the increase levels of Th17 cells in premalignant oral lesions, whose phenotype is stabilized by IL-23, which is also in increased levels in premalignant lesions.However, IL-23 levels decline and TGF-β levels further increase in the HNSCC environment[19]. Since changing the balance to increased TGF-β levels while also reducing IL-23 levels favors skewing of T-cells toward suppressive Th2 cells, shifts in the levels of these mediators could be a cause of the decline in the Th17 cells that are seen in premalignant lesions to an increase in Th2 cells seen in HSNCC.The role of Th17 cells in tumor progression or protection from tumor is also controversial [86-88]. Th17 cell presence has been associated with improved prognosis in early stage ovarian cancer and malignant pleural effusions, as they promote a Th1 cytokine environment through the combined effect of IL-17 plus IFN-γ stimulation of CXCL9 and CXCL10 (interferon γ-induced protein 10, IP-10) to recruit effector T-cells [87,89]. Th17 cells have also been shown to have direct anti-proliferative and apoptosis-inducing effects toward HNSCC [86]. In other cancer scenarios, the presence of Th17 cells has been associated with increased cancer development [90]. These studies with Th17 cells and their plasticity to become Th2 cells suggest it may not be the cytokines per se that direct an inflammatory versus inhibitory environment, but the ratios of the cytokines may be equally important.

Overall, the diversity of the immune responses that are triggered by the premalignant oral lesion environment and the HNSCC environment is broad, reflecting attempts to eradicate the dysplastic cells, the failure of the immune eradiation, and the capture of immune reactivities by the emerging tumor to be subversive to anti-tumor immune defenses.Difficulties in deciphering, the aspects of the immunological components that are anti-tumorigenic versus pro-tumorigenic are compounded by the plasticity of immune cells and their phenotypic and functional shifts.A more thorough understanding of the roles of the immunological statesin the premalignant lesion versus HNSCC environments will allow targeted modulation of immune responsesto sustain the immunological attempt to eradicate the developing tumor.

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