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TONSILLAR ONCOGENESIS: CHRONIC TONSILLITIS AS AN INITIATOR AND COFACTOR OF OROPHARYNGEAL CANCER

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ABSTRACT

BACKGROUND

Oropharyngeal cancer represents a growing global public health problem and is predominantly characterized by a bimodal etiology associated either with exposure to tobacco and alcohol or with infection by human papillomavirus. At the same time, 15 to 25 percent of cases remain etiologically unexplained, indicating the presence of an additional pathogenetic mechanism. Chronic tonsillitis has traditionally been regarded as a background inflammatory condition without direct oncological significance; however, population based studies demonstrate a several fold increase in the risk of tonsillar cancer in such patients.

AIMS

The aim of this work is a conceptual analysis of the role of chronic tonsillitis in oropharyngeal oncogenesis and the formulation of an integrative pathogenetic hypothesis explaining the contribution of chronic inflammation, microbial dysbiosis, and viral synergism to the development of both HPV positive and HPV negative cancer.

METHODS

This study was conducted as a narrative review with a conceptual and analytical synthesis of epidemiological, experimental, and molecular literature relevant to chronic tonsillitis and oropharyngeal carcinogenesis. Literature selection involved a thematic and hypothesis driven selection of publications focusing on inflammation associated carcinogenesis, tonsillar microenvironmental alterations, microbial dysbiosis, immune evasion mechanisms, and interactions between bacterial inflammation and human papillomavirus. A formal systematic search protocol and quantitative data synthesis were not applied, as the primary objective was the development of an integrative pathogenetic model rather than estimation of effect sizes or prevalence.

RESULTS

Based on analysis of the literature, a three stage model of tonsillar oncogenesis is proposed. It includes initiation of malignant transformation driven by chronic inflammation, crypt hypoxia, and genotoxic stress; promotion of tumor growth through microbial dysbiosis involving Fusobacterium nucleatum and bacterially mediated immune evasion via the Fap2 TIGIT axis; and acceleration of oncogenesis through activation of viral oncogene transcription E6 and E7 via the NF kappa B pathway.

CONCLUSIONS

Chronic tonsillitis may be regarded as a potentially significant factor in the formation of an oncogenic microenvironment of the oropharynx and as a common pathogenetic element for both HPV positive and HPV negative forms of cancer. The proposed model provides a biological explanation for the epidemiological association between chronic tonsillitis and tonsillar cancer and for the observed reduction in tonsillar cancer risk after tonsillectomy, and it underscores the need for further experimental and clinical studies.

Keywords: oropharyngeal cancer, tonsillar oncogenesis, chronic tonsillitis, human papillomavirus, inflammation associated carcinogenesis, tonsillar microbiome, Fusobacterium nucleatum, immune evasion, tonsillectomy

INTRODUCTION

EPIDEMIOLOGICAL LANDSCAPE OF OROPHARYNGEAL CANCER

The incidence of oropharyngeal cancer (OPC) shows an alarming increase in many parts of the world [1]. Statistical data from Cancer Research UK [2] and studies by Chaturvedi et al. [3] confirm that this rise occurs against the background of declining tobacco consumption, indicating a shift in the etiological paradigm. According to projections, incidence rates continue to increase [4], reflecting an epidemic of human papillomavirus associated cancer, which now accounts for up to 80 percent of cases in developed countries [5, 6].

ETIOLOGICAL GAP

Despite the dominance of the HPV tobacco dichotomy, this model is incomplete. It is estimated that 15 to 25 percent of oropharyngeal cancer cases are not associated with any of the established risk factors [7]. This etiological gap points to the existence of a third and largely overlooked pathway of oncogenesis, likely related to the local tissue microenvironment.

CHRONIC TONSILLITIS AS A RISK FACTOR

In this context, chronic tonsillitis merits particular attention. It is not merely a recurrent infection but a persistent inflammatory condition characterized by profound structural alterations of the tonsillar crypts and the formation of stable biofilms [8]. A landmark population based study from Taiwan demonstrated a strong association, showing that patients diagnosed with chronic tonsillitis had an adjusted eightfold increased risk (OR 8.07) of subsequent tonsillar cancer [9].

INTERPRETATIVE CHALLENGE

The phenomenon of reverse causality must be considered. Early stages of endophytic growing cancer may clinically mimic chronic inflammation, leading to an apparent spike in risk during the first year after diagnosis. However, even after accounting for this diagnostic bias, the persistence of a strong association in long term follow up necessitates the search for fundamental biological mechanisms.

HYPOTHESIS FORMULATION

We propose that chronic tonsillitis acts as an independent driver of oncogenesis through a three stage model.

1. Initiation (inflammation). Genotoxic stress and crypt hypoxia.
2. Promotion (dysbiosis). Immune evasion mediated by bacterial checkpoints.
3. Acceleration (viral synergism). Bacterial activation of human papillomavirus oncogenes.

AIM AND RESEARCH OBJECTIVES

The aim of this work is a conceptual analysis of the role of chronic tonsillitis in oropharyngeal oncogenesis and the formulation of an integrative pathogenetic hypothesis explaining the contribution of chronic inflammation, microbial dysbiosis, and viral synergism to the development of both HPV positive and HPV negative cancer.

To achieve this aim, the following research objectives were defined.

To analyze epidemiological data indicating an association between chronic tonsillitis and an increased risk of tonsillar and oropharyngeal cancer.

To examine molecular and cellular mechanisms of chronic inflammation as an initiator of genotoxic stress in tonsillar tissue.

To summarize data on the role of oropharyngeal microbial dysbiosis and bacterially mediated immune evasion in the promotion of tumor growth.

To analyze mechanisms of interaction between bacterial inflammation and human papillomavirus in the context of viral oncogene activation.

To formulate a three stage model of tonsillar oncogenesis integrating inflammatory, microbiological, and viral factors.

METHODOLOGY OF THE REVIEW

This work was conducted as a narrative literature review with analytical and conceptual synthesis of data. The aim of the review was to integrate epidemiological, experimental, and molecular studies relevant to the role of chronic tonsillitis in oropharyngeal oncogenesis and to formulate a pathogenetic hypothesis.

Literature selection was performed in a targeted manner based on thematic and conceptual relevance. Publications addressing the following areas were analyzed: epidemiology of oropharyngeal and tonsillar cancer, chronic inflammation and carcinogenesis, the oropharyngeal microbiome and dysbiosis in chronic tonsillitis, immune mechanisms of tumor evasion, and molecular aspects of the interaction between bacterial inflammation and human papillomavirus.

The review included original experimental and clinical studies, population based cohort studies, and fundamental review articles from peer reviewed international journals. Priority was given to publications providing mechanistic data and concepts relevant to the construction of a pathogenetic model. A formal systematic literature search protocol and quantitative data synthesis were not applied, as the objective of the study was not to estimate the frequency or strength of associations but to provide a conceptual explanation of potential biological mechanisms.

RESULTS

ANALYSIS OR CONCEPTUAL FRAMEWORK

Components of the oncogenic field

Mechanism 1. Chronic inflammation as an initiator

Inflammation as a hallmark of cancer

The association between inflammation and cancer, first postulated by Rudolf Virchow in the nineteenth century [10], has now received molecular confirmation. In the seminal works of Coussens and Werb [11], as well as in contemporary reviews by Hanahan and Weinberg [12], inflammation has been codified as an enabling characteristic and as the seventh hallmark of cancer [13]. In contrast to acute inflammation, chronic tonsillitis represents a non resolving process that promotes carcinogenesis at all stages [14].

GENOTOXIC STRESS

The microenvironment of the palatine tonsils in chronic tonsillitis is characterized by increased levels of reactive oxygen and nitrogen species, predominantly produced by neutrophils [15]. These reactive molecules are associated with DNA damage in epithelial cells, including oxidative base modifications with the formation of 8 OHdG and the occurrence of DNA double strand breaks [16]. In the tonsillar epithelium under conditions of chronic inflammation, accumulation of such DNA damage has been documented, indicating tissue vulnerability in the setting of persistent oxidative stress [17, 18]. The proinflammatory cytokine milieu, particularly elevated IL 6 levels and TNF alpha signaling activity, promotes activation of cell survival pathways and reduces the elimination of genetically damaged cells through apoptosis [19].

NF kappa B and STAT3 signaling pathways

Chronic inflammation leads to the activation of key oncogenic signaling pathways.

1. NF kappa B exhibits sustained functional activation as a result of prolonged stimulation of Toll like receptors by bacterial components [20].
2. STAT3 represents a central oncogenic factor in head and neck cancer [21]. Its activation is mediated by

interleukin 6 signaling and establishes a self sustaining signaling loop that enhances cellular proliferation and survival [22].

Mechanism 2. Microbial dysbiosis as a promoter

Microbiome in chronic tonsillitis. Anaerobic shift

Chronic tonsillitis is associated with a fundamental shift in the tonsillar microbiota. In contrast to tonsillar hypertrophy, chronic tonsillitis is characterized by the predominance of obligate anaerobes, including Fusobacterium, Prevotella, and Parvimonas. This anaerobic shift transforms the local microbiome into an oncogenic consortium [23, 24].

Immune evasion. Fap2 TIGIT axis and tumor tropism

Seminal studies on the role of Fusobacterium nucleatum in colorectal cancer by Rubinstein et al. [25] and Kostic et al. [26] have demonstrated the ability of this bacterium to directly modulate the tumor microenvironment. In the work of Han YW [27], this microorganism was described as a co conspirator of oncogenesis. Given the documented dominance of this pathogen in tonsillar crypts in chronic tonsillitis [23], these mechanisms can be extrapolated to oropharyngeal cancer.

The principal promotional mechanism in tonsillar cancer is likely the formation of an immunosuppressive niche. A central role is played by Fusobacterium nucleatum, which uses its surface protein Fap2 as a bifunctional effector.

1. Tumor tropism. Fap2 binds to the carbohydrate antigen Gal GalNAc, which is overexpressed on the surface of malignant cells. This interaction explains the selective accumulation of Fusobacterium nucleatum within tumor tissue, functioning as a carbohydrate based homing signal [28].
2. Immune suppression. After anchoring to tumor cells, Fap2 interacts with the inhibitory receptor TIGIT expressed on natural killer cells and cytotoxic T lymphocytes [29].

This interaction functionally disables cytotoxic immune cells, creating a protective immunological niche around transformed cells. In addition, the microbiome associated with chronic tonsillitis promotes T cell exhaustion, as evidenced by high expression of the PD 1 marker [30, 31].

Mechanism 3. Viral synergism and barrier anatomy

CRYPT OCCLUSION AND HYPOXIA

In chronic tonsillitis, deep tonsillar crypts become occluded by massive biofilms and cellular debris [8]. This creates conditions of local hypoxia that are favorable for oncogenic anaerobic bacteria. Biofilms induce micro ulceration of the delicate reticular epithelium lining the crypts [32]. Through these micro ulcers, viruses such as human papillomavirus gain access to the basal membrane [33].

Molecular cascade of acceleration from LPS to NF kappa B to HPV

The microenvironment of chronic tonsillitis plays a decisive role in viral activation. Under normal conditions, human papillomavirus tends to suppress the activity of the cellular factor NF kappa B in order to maintain a latent phase. In chronic tonsillitis, however, a strong bacterial signal overcomes this viral suppression.

1. Gram negative bacteria such as Fusobacterium release lipopolysaccharide.
2. Lipopolysaccharide induces strong stimulation of the TLR4 receptor on epithelial cells [20, 34].
3. This leads to enforced nuclear translocation of the NF kappa B transcription factor.
4. Activated NF kappa B binds to the viral promoter region known as the long control region.
5. This event disrupts viral latency and results in a marked increase in transcription of the viral oncogenes E6 and E7 [35, 36].

Thus, bacterial inflammation acts as an external accelerator that promotes malignant transformation.

HYPOTHESIS FORMULATION. THREE STAGE MODEL

We propose an integrative model of tonsillar oncogenesis. Table 1 summarizes the proposed three stage model of tonsillar oncogenesis integrating inflammatory, microbiological, and viral mechanisms.

Table. 1 Three stage model of tonsillar oncogenesis in chronic tonsillitis with sources cited in the article

Stage	Process	Key factors	Main biological effect	Sources
Initiation	Chronic inflammation of tonsillar tissue	Persistent inflammation, crypt occlusion, hypoxia, ROS and RNS	DNA damage in epithelial cells, mutagenesis, reduced apoptosis	Virchow 1863 [10]; Coussens and Werb 2002 [11]; Hanahan and Weinberg 2011 [12]; Colotta et al. 2009 [13]; Korniluk et al. 2017 [14]; Azad et al. [15]; Marnett 2000 [16]; Tisch et al. [17]; Greten and Grivennikov 2019 [19]
Promotion	Microbial dysbiosis and immune evasion	Anaerobic microbiota, Fusobacterium nucleatum, biofilms	Survival and clonal expansion of transformed cells due to suppression of immune surveillance	Jensen et al. 2013 [23]; Teng et al. 2023 [24]; Rubinstein et al. 2013 [25]; Kostic et al. 2013 [26]; Han 2015 [27]; Abed et al. 2016 [28]; Gur et al. 2015 [29]; Geissler et al. 2017 [30]; Guo et al. 2024 [31]; Kostic et al. 2022 [32]
Acceleration	Bacterial viral synergism	Lipopolysaccharide, TLR4, NF kappa B, HPV	Activation of E6 and E7 oncogene transcription and acceleration of tumor growth	Stanley 2012 [33]; Yang et al. 2017 [34]; Wei et al. 2014 [35]; Acay et al. 2007 [36]

DISCUSSION

INTEGRATIVE MODEL

Chronic tonsillitis functions as a common denominator for both major oropharyngeal cancer phenotypes. In HPV negative disease, it provides mutagenic pressure and local immune protection that facilitate the survival and expansion of transformed clones. In HPV positive disease, it acts as a necessary co factor, offering a plausible explanation for why only a small fraction of HPV carriers ultimately develop cancer.

RESOLVING THE TONSILLECTOMY PARADOX. BIOLOGICAL INTERPRETATION

Available data suggest a dichotomy, namely a slight increase in systemic risk of certain other cancers after tonsillectomy [37] alongside a substantial reduction in the risk of tonsillar cancer itself, with an odds ratio of approximately 0.24 [38].

Authors such as Chen and Fakhry [38] have attributed the reduction in carcinoma risk to patient selection bias. An alternative biological interpretation can be proposed through the lens of tumor ecology. Tonsillectomy physically removes a unique anatomical substrate, the tonsillar crypt system. By eliminating this bioreactor where biofilms accumulate under hypoxic conditions and may serve as a reservoir for HPV persistence, surgery disrupts the carcinogenic sequence at the physical level. The pronounced protective effect can therefore be interpreted as a consequence of removing both the target tissue and the associated pathological microenvironment.

The present analysis addresses the stated research objectives in a coherent manner. First, the reviewed epidemiological evidence supports a persistent association between chronic tonsillitis and increased risk of tonsillar and oropharyngeal cancer. Second, synthesis of experimental and molecular studies indicates that chronic inflammation within tonsillar tissue generates conditions of genotoxic stress and dysregulated apoptosis that are

sufficient to initiate malignant transformation. Third, the assembled data support the role of microbial dysbiosis and bacterially mediated immune evasion as key mechanisms driving tumor promotion. Fourth, analysis of the interaction between bacterial inflammation and human papillomavirus provides a biologically plausible mechanism for acceleration of oncogenesis through activation of viral oncogenes. Taken together, these lines of evidence support an integrative three stage model of tonsillar oncogenesis that combines inflammatory, microbiological, and viral factors.

LIMITATIONS

This work has several limitations related to its design and scope. The article is presented as a narrative review and conceptual analysis and does not include original experimental or clinical data. Literature selection was purposeful and analytical rather than based on a formal systematic search protocol, which precludes quantitative assessment of the strength of the reported associations. The proposed mechanisms rely on extrapolation of findings from related fields of oncology, immunology, and microbiology and therefore require further experimental and clinical validation. The pathogenetic model presented does not aim to provide a definitive explanation for all cases of oropharyngeal cancer and should be regarded as a hypothesis intended to stimulate future research.

CONCLUSIONS

In accordance with the stated aim and research objectives, a conceptual analysis of data indicating the role of chronic tonsillitis in the formation of an oncogenic microenvironment of the oropharynx was performed. It is demonstrated that chronic inflammation, microbial dysbiosis, and bacterial viral synergism may jointly contribute to the initiation, promotion, and acceleration of tonsillar oncogenesis.

Based on the reviewed epidemiological and pathogenetic evidence, patients with refractory chronic tonsillitis and oropharyngeal dysbiosis should be regarded as a group at increased oncological risk. In this context, tonsillectomy may be reconsidered as a potential preventive measure against oncological disease through elimination of the anatomical substrate and pathological microenvironment that sustain carcinogenesis.

The presented conclusions are hypothetical in nature and emphasize the need for further experimental and clinical studies to validate the proposed model and to determine its practical significance.

DISCLOSURE

AUTHORS' CONTRIBUTIONS

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All authors have read and approved the final version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

Artificial intelligence tools were not used for data collection, data analysis, or interpretation of the results. Their use was limited exclusively to language editing and stylistic refinement of the manuscript text.

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