



Inflammatory Pathology of the Oral Cavity: Relevance in Oral Oncogenesis

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Abstract

Oral cancer is considered to be a growing public health problem and within head and neck cancer pathology, it is the most common. It is the 6th most common cancer in the world, corresponding to approximately 3% of all cancers.

Despite the dedication and investment in this pathology, the advances in diagnosis strategies and the development of early intervention programs and treatments, aimed to be more targeted, more effective and less aggressive, the global survival rate after 5 years has remained worldwide at approximately 50% over the last three decades. The evaluation of Quality of Life stands out in this context as a key indicator, along with survival.

We aim to review oral cancer etiology and discuss inflammation role in oral oncogenesis, considering its potential to modulate and amplify the impact of known risk factors. Additionally, we point out inflammation as predictive of poor prognosis in patients with oral cancer or at risk of developing it.

Articles were collected from the PubMed, Bon, Elsevier, Science Direct databases, considering mainly the last 5 years of publication (2015 to 2020). The indexing terms used were “oral oncology and risk factors”, “oral oncology and epidemiology” and “inflammation and oncogenesis”.

The role of the immune system and inflammation in the initiation, promotion and progression of oncologic pathology of the oral cavity has deserved maximum attention from the scientific community. It is clear that the presence of pro-inflammatory factors associated with immunosuppression are closely related to oral oncogenesis and poor prognosis. The chronic inflammation can contribute to modulate and amplify risk factors actions.

Chronic inflammatory pathology and microbioma of the oral cavity have relevance in oral oncology and can be used as biomarkers, signaling patients at higher risk. There is a whole potential knowledge that can contribute to a better understanding of oral oncogenesis and therefore making it easier both to identify individuals at risk and to achieve more targeted and focused treatment strategies for each cancer patient.

Keywords: Oral Cancer; Risk Factors; Etiology; Quality of Life; Inflammation; Prognosis

Abbreviations

DNA: Deoxyribonucleic Acid; EBV: Epstein Barr Virus; HPV: Human Papilloma Virus; PMN: Polymorphonuclear Neutrophils; QoL: Quality of Life; SCC: Squamous Cell Carcinoma; TAM: Tumor Associated Macrophages; TM: Tumor Microenvironment.

Introduction

In a public health context, oncological pathology is not a recent concern. It continues to mobilize increasing resources - whether human, social or economic - in an attempt to find solutions that

can smooth the path of the cancer patient and his/her caregivers and minimize the negative impacts on the individual, family and society [1-3].

The continuous research and constant reinvention remain the focus of medical science in order to support early diagnosis promotion, the study of how pathologies develop and the impact they have on society and on the quality of life (QoL) of both the patient and relatives. It is aimed to explore new forms of treatment and identify new etiological factors that may trigger, predispose or aggravate already known factors and that might be modified and controlled. There is thus a higher expectation of changing the epidemiological trend of oncology in recent decades [4-6].

In 2018, 18 million new cancer cases were diagnosed worldwide, the most frequent being lung and breast (each with 2.09 million cases), prostate (1.28 million cases) and there were 9 million deaths [7]. Also, in 2018, some 51,600 new cases of oral and pharyngeal cancer were diagnosed in the United States. Despite the dedication and investment in this pathology, the advances in diagnosis strategies and the development of early intervention programs and treatments (aimed to be more targeted, more effective and less aggressive), the global survival rate after 5 years has remained worldwide at approximately 50% over the last three decades. More specifically, survival after 5 years is only 40% in Portugal and even lower when only late diagnosed cases are considered, which contrasts with 47% of the European average. The evaluation of QoL stands out in this context as a key indicator, along with survival [8,9].

We aim to review oral cancer etiology and discuss inflammation role in oral oncogenesis, considering its potential to modulate and amplify the impact of known risk factors. Additionally, we point out inflammation as predictive of poor prognosis in patients with oral cancer or at risk of developing it.

Materials and Methods

Our research team works on prevention in oral oncology and health-related QoL assessment for 15 years. We formulated questions relating to the identification of risk factors and its interactions, prevalence of chronic inflammatory states in the oral cavity and preventive strategies for head and neck cancer.

Articles were collected from the PubMed, Bon, Elsevier, Science Direct databases, considering mainly the last 5 years of publication

(2015 to 2020). The indexing terms used were “oral oncology and risk factors”, “oral oncology and epidemiology” and “inflammation and oncogenesis”. We focus on a theoretical basis analysis. Qualitative and quantitative data processing techniques were used and each text was analyzed individually. Due to the limitations pointed out in the revised studies as well as the future perspectives suggested by their authors, several unanswered questions were identified. Perspectives for future research are therefore proposed which highlight the importance of prevention and early diagnosis strategies.

Results

Oral Oncology around the world: facts

Oral cancer is considered to be a growing public health problem and within head and neck cancer pathology, it is the most common. It is the 6th most common cancer in the world, corresponding to approximately 3% of all cancers [10]. All anatomical regions of the oral cavity may be involved: tongue, mouth floor, retromolar trigone, lip, hard palate/soft palate, jugal mucosa and gum. In an epidemiological context, the anatomical region of the nasopharynx, oropharynx and salivary gland tumors are sometimes presented together with the locations of the oral cavity [10].

Squamous cell carcinoma (SCC) is the most prevalent histological type in head and neck oncology, both in developing and developed countries [11,12]. Despite advances in diagnosis, surgical and oncologic treatment of SCC, the overall survival rate over 5 years has been maintained over the past three decades at approximately 50% [10]. According to the World Health Organization, there are an estimated 657,000 new cases of cancer of the oral cavity and pharynx and more than 330,000 deaths each year worldwide [10,12,13].

Oral oncology: from identification of risk factors to prevention strategies

Several risk factors are associated with oral oncogenesis, such as tobacco and alcohol consumption, as well as infection by several biological agents: Human Papilloma Virus (HPV), Cytomegalovirus, Epstein Barr Virus (EBV), Herpes, Candida and various bacteria. Multiple factors - from genetics to environmental factors such as sun exposure, exposure to harmful chemicals, nutritional factors, chronic oral cavity trauma or even literacy and health education - seem to contribute to oral oncogenesis. All these circumstances are associated with inflammatory states (acute and chronic), considered risk factors for oral oncogenesis and indicators of poor prognosis [14,15].

The identification of tobacco consumption, in its various forms, as the main risk factor for developing oral cancer has a history of decades. Tobacco consumption is related to 85% of all malignant head and neck tumors. Oncological pathology develops from the accumulation of mutations in genes involved in cell cycle regulation, angiogenesis, apoptosis, deoxyribonucleic acid (DNA) repair, among others. Approximately 30 to 70% of malignant head and neck tumors have a p53 gene mutation, a tumor suppressor gene, which has the overall function of preserving the integrity of the genome. The reported variability seems very much associated with ethnicity, geographical location and strongly associated with existing smoking habits. Mutations in the p53 gene can occur as a consequence of exposure to aromatic hydrocarbons, being the benzopyrene found in tobacco among the most carcinogenic. It is therefore not surprising that the risk of developing head and neck cancer pathology is 15 times higher for smokers than for non-smokers [16,17]. Premature deaths from tobacco-related oral cancer represent a considerable loss of productivity in developing countries. Furthermore, tobacco consumption is considered to be the second largest cause of death in the world, assuming that it can be the largest avoidable cause of death [18].

The consumption of tobacco combined with alcohol presents a synergistic result, being considered the greatest risk factor in oral carcinogenesis. Excessive alcohol consumption increases the risk of developing oral cancer [16,17]. In 2016, 2.8 million deaths worldwide were associated with alcohol consumption and this consumption contributed to approximately 10% of deaths at young

ages (15-49 years). Epidemiological data show chronic alcohol consumption as a significant risk factor for malignant tumors in several locations: oral cavity, pharynx, larynx, breast, liver, colorectal and lung, being responsible for 5% of all cancers. The association seems to be greater when related to the development of cancer in the oropharynx and hypopharynx than in the oral cavity and larynx [19-21]. The role of alcohol as a carcinogen is still under discussion - it acts as a co-carcinogen potentiating the carcinogenic effects of other chemicals, acting in the initiation and promotion phase. On the other hand, it is known that ethanol metabolism leads to the emergence of acetaldehyde and free radicals. Several studies show that aldehydes may be responsible for the co-carcinogenicity of alcohol, which, being mutagenic, leads to the inactivation of DNA repair processes, inducing mutations involved in tumor initiation. The consumption of alcohol can result in the exaggerated expression of oncogenes, contributing to the tumor promotion [21,22].

A third risk factor, viral biological agents, has been increasingly involved in oral oncogenesis. It seems such biological agents might be responsible for 5% of all malignant tumors, as identified in the United States of America and western countries. The HPV is related to an increased risk of head and neck SCC. The subtypes HPV 16 and HPV 18 are considered high risk and the subtypes HPV 6 and HPV 11 are considered low risk. HPV 16 is the predominant subtype found in the oral mucosa and has been the one most related to the group of oncologic pathologies [23].

Table 1 summarizes some of the scientific discussions regarding risk factors related to oral oncogenesis (2015-2020).

Risk Factor	Highlighted Evidence	Improvement strategy	Reference
Tobacco	There is a strong association between chewing tobacco and oral oncogenesis with differences depending on geographical location - India in the spotlight.	Smoking cessation measures and policies.	[24]
	Aetiology influences oncogenesis: it is different when occurs tobacco/alcohol association, the use of chewing tobacco or HPV infection.	Smoking cessation for smokers; research to understand the basis of oncogenesis by subgroups.	[17]
	Malignant tumors have different molecular expression and clinical-pathological behavior.	Margin for optimal diagnosis and treatment.	[17]
Alcohol	The risk of all causes of death, specifically cancer, increases with increased alcohol consumption; consumption that minimizes health loss is zero.	Control measures and policies on alcohol consumption.	[19]
	When alcohol consumption is associated with tobacco consumption or high-risk genotypes related to dehydrogenase, the potential for developing oral cancer increases dramatically.	Moderation in alcohol consumption;	[21]
	The risk is greater for heavy consumers for a short period of time than for light consumers for longer periods. After 20 years of cessation, the risk appears to be similar to those who have never consumed.	Special attention to young population.	[20]

Marijuana	Marijuana contains cannabinoids, immunosuppressants and potentially mutagenic chemicals. It alters the microbiota of the oral cavity and may be associated with cancer of the oral cavity and pharynx.	Suspend the consumption of Marijuana.	[25]
	Marijuana consumption has been associated with the development of periodontitis and increases the risk of oral cancer.	Tight control of periodontal disease in marijuana consumers.	[26]
Biological Factors	The oncoprotein HPV E6 (HPV infection) degrades p53 protein.	Vaccination for HPV.	[17]
	The EBV prevalence in various cancers and its ability to immortalize B cells identifies it as a carcinogenic co-factor that acts on the progression of the tumor.		[27]
Nutritional Factors	The identification of malnutrition high risk patients should be carried out at diagnosis (risk factor for poor prognosis) and nutritional support should be included in the treatment of the patient with oral cancer.	Healthy diet habits; nutritional support for oncologic patients.	[28]
	The pro-inflammatory potential of the diet is associated with increased oral and pharyngeal cancer.	Nutritional support for oncologic patients.	[29]
	Fruit and vegetable consumption are protective; betel chewing habits (popular in Asia) increase risk.		[30]
Occupational exposure	There is a strong association between the risk of oral cancer and exposure to occupational substances such as: formaldehyde, wood dust, asbestos, welding fumes, coal dust, oil, metals, leather dust, ionising radiation, among others.	Use of personal protective equipment; Respect for the rules of Hygiene and Safety at Work.	[31]
	Exposure to ionizing radiation increases the risk of oral and laryngeal cancer.	Close surveillance of all those exposed.	[32]
Prolonged sun exposure	Prolonged sun exposure is related to lip cancer.	Reduce unprotected sun exposure.	[30]
Chronic Trauma	Poor oral hygiene and chronic trauma induced by e.g. mal-adjusted prosthesis, fractured teeth or intra-oral piercing, increases the risk of oral cancer.	Diagnosis of chronic trauma and triggering factors removal; biopsy of suspected lesions.	[30]
Oral Microbiota and Oral Health	Several bacteria in the oral cavity have been identified as potential bacterial etiological agents in oral oncogenesis (<i>Porphyromonas gingivalis</i> , <i>Fusobacterium nucleatum</i> , <i>Treponema denticola</i> e <i>Streptococcus anginosus</i>).	Bacterial plaque control; control of oral cavity microbiota.	[33]
	There is an association between the development of oral cancer and the oral bacterial community, in particular to the bacteria associated with periodontitis (<i>Fusobacterium</i> , <i>Dialister</i> , <i>Peptostreptococcus</i> , <i>Filifactor</i> , <i>Peptococcus</i> , <i>Catonella</i> , <i>Parvimonas</i>).	Control of periodontal disease.	[34]
	Periodontal disease increases the risk of oral cancer.	Control of periodontal disease.	[35]

Genetics and Heredity	Genetic polymorphisms associated with alcohol consumption need to be further studied to understand the susceptibility of consumers.	Cytogenetic and immunocytochemical control.	[20]
	Polymorphisms in the MDM2 gene (negative regulator of p53 gene activity), can increase susceptibility to cancer development.	Better understanding of the /Understand the mechanisms of genetic modification that are responsible for initiation.	[17]
	Tumour suppressor genes (APC, p53), proto-oncogenes (Myc), oncogene (Ras) and genes controlling normal cellular processes (EIF3E, GSTM1) are involved in oral oncogenesis.		[36]
	Mutations in proto-oncogenes VAV2 and IQGAP1 have been associated with family predisposition to develop oral cavity squamous cell carcinoma.		[37]
Age	Age over 45 increases risk.	Health education and surveillance.	[28,30]
Health Literacy	Poor oral health and oral cancer literacy makes it possible to identify particularly vulnerable sub-populations.	Health Education.	[38]
Inflammation and immune system disorders	Inflammation in the tumor microenvironment, whether intrinsically or extrinsically acquired, results in immunosuppression, increases the risk of malignant transformation, and stimulates progression and metastization.	Self-examination of the oral cavity; early diagnosis and control of inflammatory pathology of the oral cavity by health professionals.	[39]
	Immune system disorders increase the risk of oral cancer.	Cytogenetic and immunocytochemical control.	[30]

Table 1: Risk factors related to oral oncogenesis (2015-2020).

In the broad scientific discussion that we are currently witnessing, the various risk factors arise interlinked and inflammation seems to be the common denominator, standing out as the factor closely related to the initiation, promotion and progression of malignant neoplasms.

Inflammatory pathology of the oral cavity: its relevance in oral oncology

Relations between inflammation and the tumor microenvironment

Head and neck cancers are highly inflammatory in nature. Chronic inflammatory oral lesions show some degree of malignant potential in association with the development of SCC, including leukoplakia, erythroplasia, lichen planus and submucosal fibrosis. Metanalysis reveals a positive association between periodontal disease and risk of oral cancer, supporting the interaction of chronic inflammation and cancer progression. These risk factors imply that oral inflammation is an important component of oral SCC progression [15,40].

Although SCCs have always been considered as gene-related diseases, the molecular, genetic and immunoregulatory mechanisms of carcinogenesis remain unclear. As chronic inflammation is usually associated with worse prognosis, it is essential to understand how the tumor microenvironment (TM) is involved in the progression of SCC [15,41]. The interaction between tumors and their immunological microenvironment is complex and difficult to decipher [15]. TM, heavily influenced by chronic inflammation, has been shown to play a decisive prognostic role in the progression of oral cancer probably due to interference of the specific molecular microenvironment for cancer cells [15]. The inflammatory infiltrate, together with the inflammatory mediators, play an essential role in the formation of TM suitable for the expansion of tumor cells. The inflammation can be intrinsically derived from the tumor cells themselves - associated with the accumulation of mutations - or associated with several other factors such as viral infection, fungal or bacterial infection, autoimmune diseases, obesity, tobacco and alcohol consumption, exposure to asbestos, among others. Such mechanisms, intrinsic and extrinsic, both with inflammatory

potential occur in all phases of the tumor development, from oncogenesis to metastization, triggering mechanisms for tumor plasticity and progression [39,40,42]. Recent evidence indicates that oral tumors exist as a transformed complex of tumor cells, complexed with other cells that constitute the oral TM associated with SCC [43].

Macrophages associated with tumors

In recent years, several studies have found that macrophages comprise up to 50% of the mass of malignant solid tumors and play a decisive role in the infiltration of immune cells in the tumor [44,45]. Most tumor associated macrophages (TAM) are differentiated from monocytes derived from bone marrow. TAM exhibit great versatility as immune cells, as they produce several factors in TM that may promote or inhibit tumor progression [46]. It has been demonstrated that TAMs regulate cancer-related inflammation, immune response, matrix remodeling, and metastasizing capacity [47]. In addition, TAMs activate several molecular targets and signaling pathways related to the tumor formation process, including proliferation, apoptosis, invasion migration and angiogenesis. It was found that TAMs in SCC promote the formation of new tumors through the production of cytokines and pro-inflammatory factors that play a critical role in the various stages of malignant transformation, including growth, survival, invasion, angiogenesis and metastasis [43].

Unlike macrophages in non-cancerous tissues, TAMs are modified by the tumor, losing part of their phagocytic and effective antigen presentation capacity to T cells. Thus, TAMs present cellular plasticity in response to local microenvironmental stimuli. Macrophages are functionally heterogeneous cells, influenced by numerous signals present in TM that contributes to its instruction and polarization and therefore potentially influencing the development and progression of SCC. Furthermore, mitogen activated kinetic proteins can regulate inflammation and a wide range of cellular processes, including metabolism, proliferation, motility, apoptosis, survival, differentiation. Mitogen activated kinetic proteins play thus a crucial role in cellular growth and survival in several physiological and pathological processes, including innate processes and adaptive immune responses [15].

The role of Polymorphonuclear Neutrophils

Polymorphonuclear neutrophils (PMNs) are the most abundant leukocytes ($\pm 60\%$) in blood circulation and evolved as specialized cells capable of killing invading microorganisms. PMNs are present

on all mucosal surfaces and constantly migrate to the oral cavity to maintain balance [48].

In contrast to other members of the innate immune system, its potential for heterogeneity has not received much attention. Classically, PMNs are terminally differentiated cells in the blood and are considered a homogeneous population. PMNs exhibit unique properties, with a relatively short life span, absence of proliferative capacity, production capacity of reactive oxygen species and limited cytokine release capacity [49]. However, in the last decade, evidence on the phenotypic heterogeneity of peripheral circulation PMNs has emerged [50,51]. Subsets of PMNs were differentiated based on their phenotypic characteristics and their antimicrobial activity capacity [52]. Since the oral cavity consists of a combination of healthy oral tissue sites and stimulated oral tissue (e.g. sites with inflammation), the heterogeneity of PMNs therefore seems highly likely in the oral cavity [53]. In addition to the various states of activation in the tissue, the subsets of oral PMNs may also be different based on their migration route and access to the oral cavity (migration by chemotactic, mechanical or other sources such as tonsils [53]). It is still unclear whether different subsets are also associated with different functional responses.

The literature shows an unequivocal association between the inflammatory process and the initiation, promotion and progression phases in oncology. It is also clear the long way science has to go for a wider understanding of the mechanisms involved in both genesis and tumor progression that can thus be the result of unique, individual combinations. Such understanding is promising to optimize early diagnosis and therapeutic strategies, more focused on the uniqueness of each oncologic patient.

Discussion

This section discusses the relevance of inflammatory pathology of the oral cavity in the context of oral cancer.

Retrospective studies have evaluated histological diagnoses after biopsy of lesions present in the oral cavity. The results are diverse and the following stand out: epithelial hyperplasia/inflammatory fibrous hyperplasia (the most frequently diagnosed), fibroma, granuloma, ulcerative lesion, lichen planus/ lichenoid reaction, papilloma; keratosis, cyst, mucocellum, dysplastic lesion and squamous cell carcinoma (representing approximately 2% of the total histological results of biopsies performed) [54,55].

According to several authors, reactive hyperplastic lesions represent between 10.7%- 41.6% of the universe of oral pathology, analyzing the histological features of biopsies, Dutra and collaborators published in 2019 a study of 534 cases of reactive hyperplastic lesions, in a range of 2,400 records, corresponding to 22.5% of all diagnoses [54]. They represent a group of oral pathologies considered benign, which presents an exophytic shape and firm and fibrous consistency and results from a chronic inflammatory response to low intensity stimulus, which involves the constant repair of tissues. They include fibrous inflammatory hyperplasia (in 70% of all cases), fibromas and granulomas and are found preferentially in the gingiva/alveolar ridge, jugal mucosa, lip and tongue. They are associated with smoking habits, the use of poorly adjusted prostheses, trauma of the oral mucosa due to parafunctional habits, poor oral hygiene, fractured dental pieces, root remains or teeth that have sharp edges, the presence of brackets, implants or oral piercing [54,56,57]. These studies show that coexistence with lesions of an inflammatory nature of the oral cavity is a reality in the practice of Dentistry.

Additionally, oral microbioma has received a lot of attention in the context of oral medicine. It is known that the binomial inflammation/infection is associated with 25% of all cancers, creating mutations in the DNA, such as 8-oxo-7,8-dihydro-2'-desoxyguanosine (8-oxodG) and 8-nitroguanine. Viruses like HPV, EBV or cytomegalovirus are associated with oral oncogenesis. Common bacteria in the oral cavity universe, especially associated with inflammatory/infectious periodontal disease - which include the periopathogens *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Treponema denticola* and *Streptococcus anginosus* - have been associated with the induction of chronic inflammation, inhibition of apoptosis, increased cell proliferation, suppression of the immune system and release of carcinogenic substances. Karpinski, in 2019 corroborates this association and indicates the bacteria *Streptococcus* sp., *Peptostreptococcus* sp., *Prevotella* sp., *Fusobacterium* sp., *Porphyromonas gingivalis*, and *Capnocytophaga gingivalis* as strongly associated with the development of oral cancer [58]. He points to the release of inflammatory chemical mediators as facilitators of proliferation, mutagenesis, oncogenic activation and angiogenesis [58-60]. This association is so important that the presence of oral bacteria has been indicated in recent decades as biomarkers of specific types of cancer: *Porphyromonas gingivalis* stands out in the signaling of gum cell carcinoma, or *Streptococcus intermedius*, *S. constellatus*, *S. oralis*, *S. mitis*, *S. sanguis*, *S. salivarius*, *Peptostreptococcus* sp., in the case of oral mucosa cancer [58,61,62].

The role of the immune system and immune cells in particular, in association with the secretion of chemical mediators of inflammation is not fully clarified, but has been linked to initiation, promotion and progression in oncology, and specifically to oral cancer.

Inflammatory cytokines such as interleukins -1 β (IL-1 β), IL-6, IL-17, IL-23, tumor necrosis factor alpha (TNF α) and matrix metalloproteinases such as MMP-8 and MMP-9 have been associated. Monocyte/macrophage inflammatory cells, neutrophils, fibroblasts and mast cells are also related. IL-1 β is associated to the stimulation of vascular endothelial growth factor production, promoting an inflammatory microenvironment, potentiating angiogenesis and tumor progression [58,63].

It is known that the inflammation associated with TM can have an intrinsic origin (mutated cells promote the recruitment of inflammatory cells) or extrinsic (infection, chronic trauma, autoimmune disease, obesity, tobacco or alcohol consumption, occupational exposure, among others). It seems clear that coexistence with pro-inflammatory factors as diverse as exposure to asbestos, nanomaterials or the presence of inflammatory pathology such as oral leukoplakia, promotes mutation and predisposes to oral cancer [39,59]. It has become clear that the topic stands out today in oncology.

There is still a long way to go, but the authors here reviewed agree that inflammation has the potential to modulate and amplify the impact of known risk factors. There is a whole potential knowledge that can contribute to a better understanding of oral oncogenesis and therefore making it easier both to identify individuals at risk and to achieve more targeted and focused treatment strategies for each cancer patient.

Conclusions

We highlight as conclusions of this work:

- The role of the immune system and inflammation in the initiation, promotion and progression of oncologic pathology of the oral cavity has deserved maximum attention from the scientific community. It is clear that the presence of pro-inflammatory factors associated with immunosuppression are closely related to oral oncogenesis and poor prognosis.
- The chronic inflammation can contribute to modulate and amplify risk factors actions.
- Chronic inflammatory pathology and microbioma of the oral cavity have relevance in oral oncology and can be used as biomarkers, signaling patients at higher risk.

- Participation of Oral Sciences in all phases of oncologic patient follow-up is crucial to modify epidemiological trends and optimize patients' and their relatives' QoL.

Conflict of Interest

The authors declare that there is no financial interest or conflict of interest.

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