



RESEARCH ARTICLE

THE INFLUENCE OF THE MUCINS IN GENETIC BALANCE IN ORAL AND LARYNGEAL CANCER AND BY THEIR BIOCHEMICAL BEHAVIOUR A WORKING HYPOTHESIS FOR THEIR CARE

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ABSTRACT

Back Ground and Objectives: The most recent genetic research have identified key genes that may be promoting the formation of tumors of the oral cavity and larynx, regardless of external factors such as smoking and HPV. The aim of this paper is to verify whether the importance of the genetic factor is very dependent on the parameters affecting the oral defenses drop, mostly on mucins.

Study Material: Was conducting a review for 2015-2016 year with databases PUB MED, GENE, and HOME Genetic References, using key word and key stream "oral and laryngeal cancer genetic in 2015 and 2016 year to identify potential genes involved. The data were compared with the most recent review that also takes into account the two most important external causes smoking and HPV. According to a previous our study, have been identified, but also the incidence of other factors regarding the onset of oral cancer and larynx. The applicability and verification of these results even after a posterior effective bibliographic update has been tested on a sample of thirty laryngectomies patients, through the administration of a questionnaire

Results and Discussion: even if with some differences the type and the number of genes involved, are broadly similar to those identified in a recent review. Statistical analysis of the results obtained by processing the questionnaire, confirmed that the 1 smoke autoimmune disorders and certain environmental conditions and lifestyles, can inactivate and/or deprive the Mucinic Fraction.

To observe that the proportion of patients with laryngeal cancer presenting an autoimmune disease is higher than the contro group (0.012 with Fisher Exact test) and also versus to general population given in Italian (36% vs 1%) with p value < 0.001, with a test of proportions. Also during those same PCs smoking and the presence of an autoimmune disease are twonot associated risk factors (p = 0.1211 with fisher's exact test). Among all autoimmune conditions, according very recent epidemiological studies, diabetes, in the sample of laryngectomized patients is higher tha the control group, but with p value =0.195. The results also that xerostomia is in laryntomees group a sign very important were the p-value is 0.012 with large influence in men ,p-value = 0.054 indicate

Conclusions and Proposals: The etiology of cancer of the oral cavity and larynx is multifactorial. and seem to depend for different geographical areas, from food use/abuse, sexual mores and lifestyles and also by the increase in diabetes. The crucial protective function of mucins that altered in various carcinomas resulting in hyper expression, provides the original idea for a proposal to fight the tumor. You could use an oncogenic virus "attenuated" improved in capsid with the enzyme neuroaminidase, to delete the links-sialic acid mucin. Interrupting hyperexpressivity and consequently the process of angiogenesis, facilitating their entry into cells and the tumor suppressor p53, engineered viral DNA may then suppress carcinogenesis

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INTRODUCTION

Any research into cancer and therefore that purely genetic should be preceded by a careful examines epidemiological data with particular reference to their geographical distribution. In a recent paper we were analyzed the indices of incidence ASR taken from DataBase Globocan 2012 (IARC), pointing out that,

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for example, oral cancers have the highest values where there is very high the consume of the betel even with little consumption of alcohol and tobacco and low presence of the virus HPV. Also the presence of diseases like diabetes affects the onset of oral cancer and larynx as confirmed by epidemiological data (Suba et al., 2009) and by the results of our recent work, (Duca et al., 2015). These considerations not only statistics should direct research, in addition to the understanding of the genetic mechanisms that lead a cell to become cancerous, and perhaps even in the most urgent terms the adoption of preventive

measures that safeguard the oral defenses as are the salivary mucins. In several recent articles, both epidemiological (Heather and Davies, 2014), and experimental, (Menicagli and Duca, 2014; Menicagli *et al.*, 2016), it has been assumed that this fraction of the salivary proteins, can be inactivated and / or precipitated by type of polyphenolic compounds present in concentrations more or less elevated in a wide consumption spices. In any case, genetic research, regardless of age-environmental parameters have made tremendous strides, showing almost definitively what are the main genes involved in the formation of oral cancers and larynx. In terms described above should, rather, probably, at least in most cases you should talk about genetic predisposition. In general, this "trend" is not autosomal dominant, and implies SNP mutations. (Erling Mellerup *et al.*, 2015) In a recent "Critical Report" appeared in Nature year 2016 (www.nature.com), have been identified nineteen genes, and having similar mutations present in the various types of oral cancer and larynx. The report by a diagram, has tried to correlate the frequency of mutations of the various genes, distinct mutations by type (missense, frameshift ... etc), the smoking status, the HPV status, with the appearance of anatomical sites of cancer interesting the oral cavity and larynx. The result of this detailed analysis, indicates that genes involved in the highest percentage of cases are p53 and CDKN2A, with missense mutations type. (70%), and there is not necessarily a predominant involvement in Smoking Status, and HPV Status. It 'so difficult with these data do not realize that so will establish cancer, must intervene more important mutations of those that appear sporadically and physiologically in life. More dangerous are those of hereditary type, especially compared to the p53 gene, such as that leading to the syndrome of Li-Fraumeni, responsible for numerous types of cancer and entails an increased risk, because the cells, having inherited the first mutation (loss dell'omozigosi, heterozygous for the healthy allele), only require the other, loss of Heterozygosity, (LOH), to eliminate the expression of p53 with the cellular control. Then loss in most of the gene mutations involved and found in the various tumor types, it must be in the presence of considerable environmental and / or pathological insults, because beginning the process of carcinogenesis which need in each case of the second mutation. With these various conditions are the objectives of this work. The first concerns the study, according to our new policy, of the literature, including for the year 2015-2016, in order to identify the genes involved in a relevant way, in the formation of oral cancer and larynx. Second goal, to try to correlate the consumption of alcohol and tobacco, with ASR indexes, and see if there is a definite bearing on them, the same principle will be adopted for the HPV virus, also investigating not only on environmental geo data, but also on anatomical sites where more it affects. The third objective was to continue the verification of the incidence of risk factors identified in our previous work, by administering the anamnestic questionnaire to other laryngectomees thirty patients, The fourth objective is that of proposing a methodology for the study through the formulation of a Flow-Sheet indicating the possible biochemical pathways that may interact with the proper functioning of the genes, for effect of the various risk factors taken into consideration by us in the study previous and to confirm the data obtained. The ultimate goal was to formulate, in purely theoretical terms, a

possible approach, genetic engineering, which could possibly impede the development of oral cancer and larynx.

MATERIALS AND METHODS

The bibliographic survey which aims to make a critical review of genetic influence, was set to ten Data Base in the Medline, setting the key word and key stream "oral and laryngeal cancer genetic 7or in 2015-2016 years". In terms of significatività, were chosen references present in greater numbers, for both types of cancer, and identified in the data base PubMed and Gene of these genes as potentially correlated with the development of tumors, the actual clinical findings were analyzed, placing them in the Data Base "Genetic Home References", that shows all identified cellular functions, and implications related to their mutations and / or defects in all diseases including those not carcinogenic. Having as a search engine, Google, have been researched the most recent data on alcohol consumption, (www.linkiesta.it 2013) and tobacco, (Second report on smoking WHO, 2008) (in WHO report 2013) way of building for oral cancer and larynx two tables, which compare these parameters with indexes ASR present for these diseases in the Data Base Globocan 2012. Also regarding the influence of HPV Virus, were obtained by extensive research until the year 2016 ii epidemiological data concerning both the spread of HPV virus relative to the head and neck, and its distribution in the different anatomical sites. In particular the results published in two separate "systematic reviews" were elaborated with their meta-analysis. The questionnaire proposed in our previous study, (Duca *et al.*, 2015), was again subjected to a population of thirty laryngectomees patients, and the results were processed using Fisher exact test, and the statistical risk was assessed by proportional test. the previous version in the questionnaire under the heading style and living conditions, they are grouped all those risk factors that include sexual habits, nutrition, food intolerance, physical activity, the conditions related to hormone function for the female sex.

RESULTS AND DISCUSSION

From the first survey of ten databases, it has emerged implications in forty-eight genes for oral cancer, and twenty-six for the laryngeal cancer, this genetic classification has been inserted into the database Genetic Home References, to identify to which of these mutations will is an actual clinical encounter. The result is shown in Table 1.

As can be seen, the genes identified as being most definitely involved in the carcinogenesis process, are almost all those listed in the report in Nature, and for leading in terms of appearance, or p53 and CDKN2A, also the frequencies of mutations are similar. Both genes are tumor suppressor genes, and are present in about 70% of cancer cases Neck and Head, but their mutations are implicated in the onset of various other tumors such as the bladder breast, and melanoma. This figure stems from the fact that their main role is in stopping the degenerative cellular process, with the other genes that generally act then cascade, but always after the genetic fault is present on both alleles.

Table 1. Results in the questions on genetic influence in oral and laryngeal cancer formation. By genetic home references

Gene	Coded protein and functions	Diseases and Pathology
Tp53 17p13.1	P53-tumor suppressor	Breast, bladder, neck head squamous cancer and others cancers, li fraumen syndrome
Tp63 3q21	P63-transcription factor	Amylo-blepharonecrotodermal defect, neck head cancer
CDKN2A 9q21	p16-p14-tumor suppressor	Neck head squamous cancer, melanoma, breast pancreatic cancer
NOTCH1 9q34.3	Notch1-receptor for proliferation, differentiation, apoptosis	Adam-oliver syndrom, neck head cancer
PIK3CA 3Q26.3	P110 α -oxidative phosphorylation, cell division signal	Megaloencephalie capillary, malformation, colorectal cancer
HRAS 11P15.5	Hras-oncogenic and cell division	Costello syndrome, bladder, thyroid, kidney cancer
SAT1 Xp22.2	acetyltransferase family of polyamides metabolism, detoxification	Keratosis deculvans
CASPE2 p33-34	Family caspase /protease-, apoptosis	Autoimmune lymphoproliferative syndrome, breast neck head and lung cancer
FAT14 q35	tumor suppressor-catherins family-cells adesion	Many cancers
HLA/ABC6 p21.3	Human Leucocytes Antigen-MHC	Autoimmune Diseases
CYP1012 p22.2	P 450 Cytochrome family - metabolism of detoxification	Early -nonset, glaucoma, peters anomaly
XRCC3 14q32.3	RecA/ Rad 51-stability of chromosomes, DNA repair	Breast, melanoma, head and neck cancer
ADH4 q23	AlcoHol dehydrogenase - energy metabolism and sugar control	Alcohol dependence, diabetes
NOT2 12 22q12.1	Nuclear Erytroid Derived/transcription factor with Up-regulation of Oxidative sters	Diabetes, multi-sclerosis

Table 2.**- ASR INDEX FOR ORAL CANCER : INFLUENCE OF SMOKING AND ALCOHOL**

COUNTRY	ASR	SMOKING	ALCOHOL
PAPUA NEW GUINEA	25,4	+	+
MALDIVE	11,0	-	-
SHRY LANKA	10,3	+	-
BANGLADESH	10,1	+	-
PAKISTAN	9,9	+	-
UNGHERIA	9,7	++	+++
INDIA	7,6	+	+
PORTOGALLO	6,8	++	+++
SLOVACCHIA	6,5	+	++
AUSTRALIA	6,3	+	+
KAZAKISTAN	6,3	++	++
MYAMMAR	6,3	+	+
AZERBAIJAN	6,3	++	++
AFGANISTAN	6,3	++	.
KAMBOGIA	6,0	+	+
ITALIA	3,06	++	+

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Table 3.**-LARYNGEAL CANCER EPIDEMIOLOGY ASR INDEX**

COUNTRY	ASR 1	SMOKING	ALCOHOL	REFERENCES. 1-2-3
CUBA	7,6	+	+	1 GLOBOCAN IARC2012 2 OMS 2008 3 WWWLINKIESTA.IT 2013
HUNGARIA	6,4	++	+++	" "
IRAQ	5,6	+	-	
KAZAKISTAN	5,5	++	++	
UZBEKISTAN	5,5	++	++	
MOLDAVIA	5,3	++	+++	
ROMANIA	5,0	++	+++	
MONTENEGRO	5,0	++	+++	
BULGARIA	4,9	++	+	
CROAZIA	4,7	++	+++	
SIRIA	4,6	+	+	
PORTUGAL	4,6	++	+++	
TURKMENISTAN	4,5	+	++	
VENEZUELA	4,4	+	+	
POLONIA	4,3	++	++	
ITALY	3,2	++	++	Duca - Menicagli

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In Tables 2 and 3 are presented epidemiological data on the incidence of cancer in the world. relative to the oral cavity and larynx with dell"indice ASR values (Age Standardization Rate), which is the number of new cases standardized for age per one hundred thousand inhabitants., For countries with the highest incidence rate, indexes ASR, are compared with the relative consumption of alcohol and tobacco it is apparent from the analysis of these data it is difficult to establish an absolute correlation between the incidence of oral cancer and larynx with the two parameters taken into account that are considered the most dangerous ever along with the HPV virus. The signs, (-), (+), (++) , (+++), listed in the tables indicate in qualitative terms, the progressive increases in alcohol consumption and smoking.

An examination of these data it is clear that there is an absolute overlap, between the number of cases of cancer for the oral cavity and the larynx and the relative consumption of alcohol and smoking; in these terms just recently some epidemiological research (Suba et al., 2009), conducted in Hungaria, not a very sharp rise in oral cancer among non-smokers and non-drinkers, and in the absence of HPV infections, much to speak of "Morbus Hungaricus". Also, regarding the influence of HPV Virus, it is very important both to compare epidemiological data, summarizing 2016 concerning both the spread of HPV virus relative to the head and neck, and its distribution in various anatomical sites. In particular, we were drawn to findings published in two separate "systematic reviews" with its meta-analysis, (Gama et al., 2015; Laprise et al., 2015). And that also clarifies the spread in different geographical depending on the viral type.

Table 4.

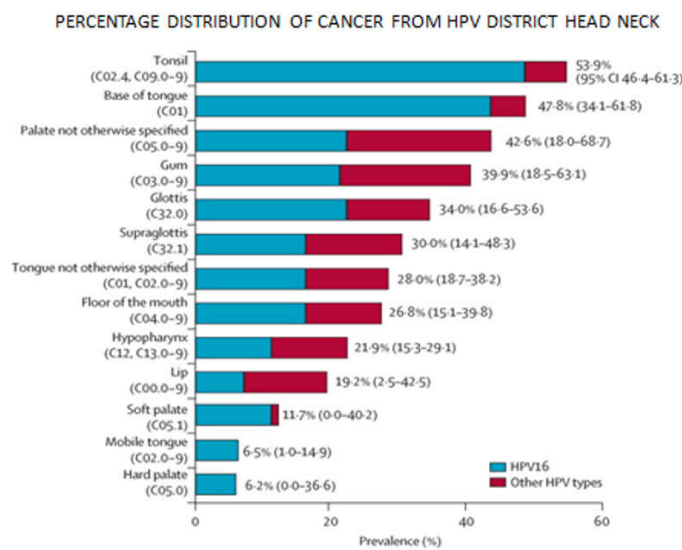


Table 5.

DISTRIBUTION GEO ANATOMIC OF THE CANCER FROM HPV AND TYPING

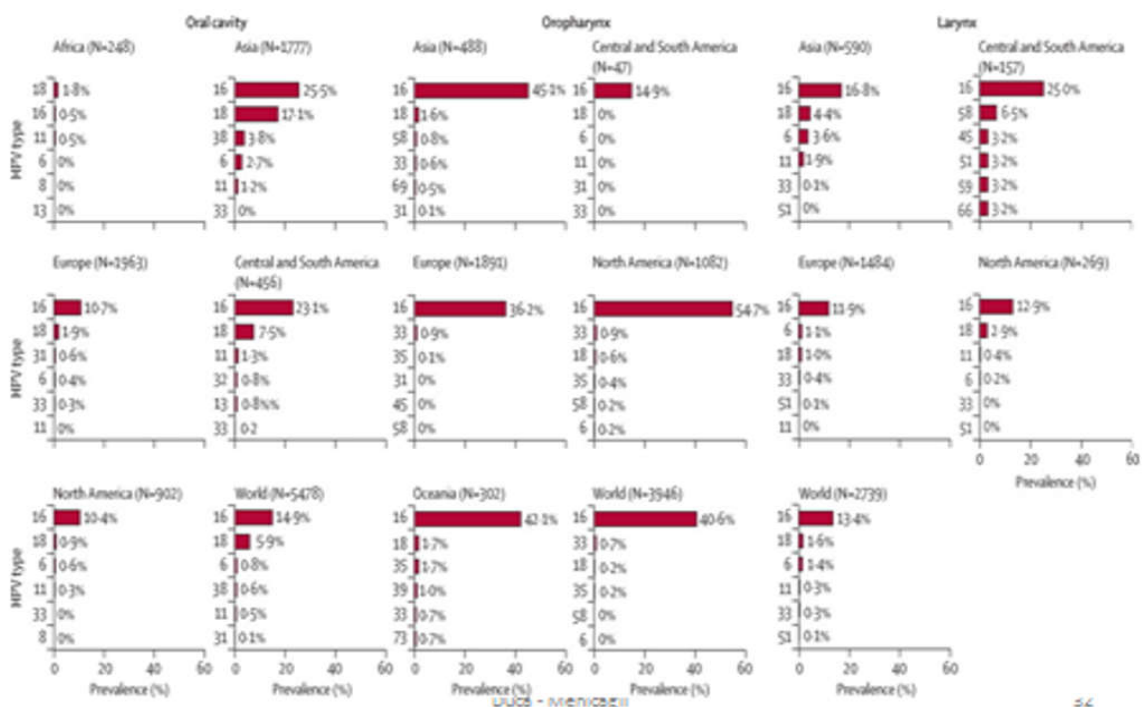




Table 6.

Risk factor	Control group 20 men+ 10 women		Larynx group 24 men+ 6women			Fisher test p-value between control and larynx group
	M	Total M+W	M	W	Total M+W	
Age (for men ≥ 65 years, for women ≥ 60 years?)	15	21	18	4	22	1.000
Smoking	14	19	17	3	20	1.000
Alcohol	1	1	2	0	2	1.000
Cancer family	2	5	4	3	7	0.748
Xerostomia	1	1	7	2	9	0.012
Hypogeusia	1	1	4	2	6	0.103
Life style	7	10	8	1	9	1.000
Ab groups	4	7	4	3	7	1.000
Autoimmune diseases(diabetes)		1(1)	7(3)	2(2)	9(5)	0.012 (0.195)

- 1- Epidemiological data and the meta-analyses indicate most relevant in HPV only one of the problems for tumors of the oropharynx.
- 2- Data analysis and conclusions on the actual importance of the HPV virus are highly dependent on geographical areas in which the studies were conducted.
- 3- The burden of cancer from HPV is independent of the consumption of alcohol and/or tobacco.
4. The anatomical distribution of tumors in the presence of HPV poses an important question of etiological character.

There are many, have evidences of epidemiological data, than those provided by the most recent literature, from experiments conducted by researchers and by considerations so far undertaken on the role of genes, that environmental factors can be considered the true promoters of cancer. A clear demonstration of this evidence it is the clarified mechanism by which substances rich in polyphenols (Heather and Davies, 2014; Menicagli and Duca, 2014; Menicagli *et al.*, 2016) introduced for example with diet, can precipitate salivary proteins, depleting the oral cavity and larynx of its main natural defense: salivary mucins. It is clear that under these conditions, any chemical or physical agent carcinogenic present in food and smoke, is located in immediate contact with a gold-pharyngo-laryngeal mucosa discovery. This is also true for the HPV virus, which, statistically, propagates almost exclusively in anatomical points more unprotected Palatine and lingual tonsils. Were, is lack the mucin layer. The most relevant problem is the role of another risk factors, mostly arising

from age, nutrition, lack of physical activity, abuse of drugs and spices, and possible diseases, particularly diabetes presenting comorbidity in regard to these factors, it is important to note that there is certainly a biological indicator that can report a deterioration in education and/or in regular operation of the Mucosal layer that protects all epithelial cells of oral cavity proper function of this layer that has a well-defined replacement kinetic, focuses mainly on the fraction of the mucins. Under certain conditions, you can have a change in the short term, in other cases it may become chronic The alterations in the formation of mucins may be due to cellular biochemical changes (extra and intra). The most obvious intracellular alterations are due to changes that are not yet well defined and responsible for disorders such as sjogren's syndrome., but are meno importanti di quelle due to the action of endogenous and/or exogenous factors, episodic or chronic in anyway possible control chronic changes must be taken soot chemical-physical characteristics of the whole saliva such as ph; especially the conditions that lead to high acidity, and for pathological condition as diabetes. And in misura minore for others autoimmune diseases, and hormonal changes The consequences of these conditions are as final result an alteration of glycosilation process. The component that plays a key role in the process of glycosylation and salivary mucins work correctly is sialic acid the most recent surveys reveal in oral cancer and larynx altered the structure of salivary mucins and their percentage composition in sialic acid. (Mahmood, 2014; Chaudhury *et al.*, 2015) These conditions are, highlighted in the Flow-Sheet the history questionnaire, tested

in our previous work, and presented to a sample of thirty laryngectomees group and the results in Table 6.

Legend (diabetes)

Others Fisher tests

- 1) **only in men** : Xerostomia p-value=0.054, Hypogeusia p-value= 0.356
- 2) **only in women** : Xerostomia p-value=0.183, Hypogeusia p-value= 0.183
- 3) Value of autoimmune diseases in LARYNX Group vs Italia population incidence (1.5%): p-value \leq 0.001

The autoimmune find their apparent relationship with an altered salivation process for two fundamental principles:

- a- Effects related not only to the lack of saliva, but especially the quality of saliva itself, i.e. the spatial structure of mucinic layer which is also editable by the increase of IgA (for example as happens in conditions of diabetic disease manifests, see next slide)
- b- Changes of metabolic processes to autoanticorpali cells damage to structures such as histones and nucleosomes, which in turn act on formation of radicals, and increased concentration of sialic acid. (especially important in diseases like rheumatoid arthritis and SLE).

For diabetes question the possible explanation may result by altered sIgA production., with the alteration of salivary mucins structure Significantly higher s-IgA levels occurred with xerostomia and denture stomatitis in diabetic patients. In addition, s-IgA was significantly higher in patients with uncontrolled diabetes compared to those with controlled diabete, (Kakoei *et al.*, 2015). Interesting is also that limited to our sample, but nonetheless in accordance with epidemiological data, in the group of the laryngectomees, globocan 2012 "the incidence of cancer is much higher in men than women. Past research questioned the protective role of hormones in the development of tumors of the oral cavity and larynx. Was detected, on the basis of epidemiological data, which in the absence of risk factors such as alcohol and smoking, above a certain age (70 years), the incidence of cancer related to the oral cavity was higher in women. The latest research, (Purshotam, 2014) however, underscore how the endocrine microenvironment may actually be an important element, in addition to traditional risk factors like smoking, HPV infections and alcohol, in the process of tumor formation. It has been shown in fact sex hormone receptors are also expressed in the oral cavity, larynx and lungs, as well as in the sexual organs and that they play a vital role in the expression of some genes involved in complex mechanism that leads to cancer. Also alcoholic patients with chronic liver disease have altered metabolism of sex hormones involving testosterone and estrogen. Certain salivary gland tumors are similar to breast cancer.

Conclusions and Proposals

The etiology of cancer of the oral cavity and larynx is multifactorial. Oral tumors seem to depend, at least in a large

geographical area, from environmental factors/behavioral (betel). For tumors of the larynx can identify five main risk factors: sex, smoking, age, autoimmune disorders and xerostomia to man and women. In all cases it is possible to speculate that the triggering event tumor risk factor, it is made possible by a weakening of the protective layer resulting from qualitative and quantitative variation of salivary mucins. The mucins found as components of mucus gel layers at mucosal surfaces throughout the body play roles in protection as part of the defensive barrier on an organ and tissue specific basis. The human MUC gene family codes up to 20 known proteins, which can be divided into secreted and membrane-associated forms each with a typical protein domain structure. The secreted mucins are adapted to cross link in order to allow the formation of the extended mucin networks found in the secreted mucus gels. The membrane-associated mucins possess membrane specific domains which enable their various biological functions as part of the glycosylation. All mucins are highly O-glycosylated and this is tissue specific and linked with specific biological functions at these locations, (Gibbins, 2013). Mucin biology is dynamic and the processes of degradation and turnover are well integrated with biosynthesis to maintain a continuous mucosal protection against all external aggressive forces. Interaction of mucins with microflora plays an important role in normal function. Mucins are modified in a variety of diseases and this may be due to aberrant mucin peptide or glycosylation.

Major conclusions

- Mucins represent a family of glycoprotein having fundamental roles in mucosal protection and communication with external environment.

To this scientifically irrefutable data, must be added the fact also true that in many forms of cancer, and this is also the case for those of the oral cavity and larynx, their overexpression

Proposal

Sialic acids have a pivotal functional impact in many biological interactions such as virus attachment, cellular adhesion, regulation of proliferation, and apoptosis. A common modification of sialic acids is O-acetylation. O-Acetylated sialic acids occur in bacteria and parasites and are also receptor determinants for a number of viruses. The severing of ties between sialic acid and protein cores of mucins, allows in many cases, to the weakening of the mucosal layer virus entry. Certain viruses such as Influenza type A, penetrates the host mucus by cleaving sialic acids with neuraminidase. This allows the virus to enter host cells, and fulfill the lytic cycle. Contrary to what the cellular binding of VLPs (HPV 38) was sensitive to trypsin but not to sialidase, N-glycosidase, or octyl-beta-D-glycopyranoside treatment, suggesting that a cell surface protein is involved in the VLP binding. With this in mind, you can propose a new methodology scientifically, a working hypothesis unproven that covers the following steps:

- a Extraction-purification-activation of blood-borne attack on the neuraminidase and reference sites-decreased angiogenesis

- b Engineering of an oncogenic virus (hvp 6.11), with Tp53 and CDKN2A
- c Infection of canee cells, and viral DNA inclusion, with the activation of the two tumor suppressor genes

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