

RRP Medical Reference Service

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Preface

The *RRP Medical Reference Service* is intended to be of potential interest to RRP patients/families seeking treatment, practitioners providing care, micro biological researchers as well as others interested in developing a comprehensive understanding of recurrent respiratory papillomatosis.

This issue focuses on a selection of references with abstracts from recent (2001 and later) RRP related publications. These listings are sorted in approximate reverse chronological order as indicated by the "Unique Identifier" numbers. Each listing is formatted as follows:

Journal or reference
Title
Language (if it is not specified assume article is in English)
Author(s)
Primary affiliation (when specified)
Abstract
Unique identifier

If copies of complete articles are desired, we suggest that you request a reprint from one of the authors. If you need assistance in this regard or if you have any other questions or comments please feel free to contact:

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RRPF Selected Articles and Abstracts

Gen Dent 2001 Jul-Aug;49(4):386-9; quiz 390-1

Analysis of HPV 16 and 18 by in situ hybridization in oral papilloma of HIV+ patients.

Paparotto Lopes SM, Meeks VI.

Department of Oral Medicine and Diagnostic Sciences, University of Maryland-Baltimore School of Dentistry, USA.

Human immunodeficiency virus (HIV) infection facilitates the development of other infections and lesions including oral papilloma, which has been associated with human papillomavirus (HPV). In analyzing the presence of HPV 16 and 18 by in situ hybridization in oral papillomas from five HIV+ male dental patients, HPV 16 and 18 were observed in 9 of 16 (52.2%) histopathologic specimens. All positive lesions occurred in heterosexual males admitting to oral sexual contact with a female partner (Pearson's correlation; $p = 0.0088$). These results suggest that oral sexual behavior may be a contributing factor in the presence of HPV 16 and 18 in oral papilloma.

Unique Identifier - 22011092

Eur J Gynaecol Oncol 2002;23(2):166-8

The prevalence of human papilloma virus DNA in women with mucopurulent endocervicitis.

Altuglu I, Terek MC, Ozacar T, Ozsaran AA, Bilgic A.

Department of Microbiology and Clinical Microbiology, Ege University Faculty of Medicine, Izmir, Turkey.

OBJECTIVE: The aim of the study was to determine the prevalence of human papillomavirus (HPV) infection in a group of patients with mucopurulent endocervicitis. **MATERIALS AND METHODS:** One hundred and forty-eight patients who came for their routine medical screening and were diagnosed with mucopurulent endocervicitis were enrolled in the study. HPV DNA was sought in cervical swab specimens placed in digene transport medium by use of the Digene Hybrid Capture assay. **RESULTS:** HPV infection was detected in 5.4% (8/148) of the patients with mucopurulent endocervicitis. The mean age of the patients was 36.4 \pm 8.2 (18-54) years. Approximately 40% (59/148) of the patients used intrauterine devices currently or in the past, while 16.2% (24/148) used combined oral contraceptives as the contraceptive method. HPV DNA was detected in eight patients: five had infections with

low-risk subtypes, one with high/intermediate risk subtypes and one with the combination of high- and low-risk subtypes. The mean age of the HPV infected patients was significantly lower than the HPV negative patients (28.2+/-6.3 versus 36.9+/-8.1 years, $p = 0.003$). Risk factors for HPV infection did not differ between the infected and uninfected groups.

CONCLUSION: HPV infection should be sought in patients with clinical evidence of mucopurulent endocervicitis even without risk factors for cervical neoplasia.

Unique Identifier - 22004362

Intervirology 2002;45(1):24-32

Evaluation of HBs, HBc, and frCP Virus-Like Particles for Expression of Human Papillomavirus 16 E7 Oncoprotein Epitopes.

Pumpens P, Razanskas R, Pushko P, Renhof R, Gusars I, Skrastina D, Ose V, Borisova G, Sominskaya I, Petrovskis I, Jansons J, Sasnauskas K.

Biomedical Research and Study Centre, University of Latvia, Riga, Latvia, Lithuania.

Objectives: In an attempt to develop virus-like particles (VLPs) as experimental vaccine against human papilloma virus (HPV)-induced tumours, the HPV16 E7 oncoprotein epitopes spanning amino acid (aa) residues 35-98 were expressed on three proteins capable of VLP formation: hepatitis B virus (HBV) surface (HBs) and core (HBc) antigens, and RNA phage fr coats (frCP). **Methods:** The profile of immunoglobulin isotypes induced in Balb/C mice after immunization with purified chimeric proteins was studied. **Results:** The HBs*-E7(35-54) protein expressing E7 residues 35-54 between residues 139 and 142 of the HBs carrier formed HBs-like particles in *Saccharomyces cerevisiae*. The HBcDelta-E7(35-98), but not the frCP-E7(35-98), ensured VLP formation in *Escherichia coli*. In Balb/C mice, the HBs*-E7(35-54) VLPs predominantly induced an anti-E7 antibody, but not anti-HBs carrier response, whereas the HBcDelta-E7(35-98) VLPs induced a lower anti-E7 compared to anti-HBc carrier response. The frCP-E7(35-98) protein elicited equally high antibody responses to both E7 and frCP carrier. Analysis of the immunoglobulin G isotype profile of the antibodies induced by the E7-carrying chimeras showed that the HBs and frCP derivatives were capable of eliciting the Th1 and Th2 subsets of T helper cells, whereas the HBc-derived chimeras elicited only the Th2 subset. **Conclusions:** The HBs and HBc, but not frCP carriers support an efficient outcome for VLPs carrying the HPV16 E7 epitopes. All chimeric proteins may be regarded as potential vaccine candidates.

Unique Identifier - 21935288

Arch Otolaryngol Head Neck Surg 2002 Apr;128(4):425-8

Powered instrumentation in the treatment of recurrent respiratory papillomatosis: an alternative to the carbon dioxide laser.

El-Bitar MA, Zalzal GH.

Children's National Medical Center, 111 Michigan Ave NW, Washington, DC 20010, USA.

OBJECTIVE: To assess the advantages of powered instrumentation vs the carbon dioxide laser in treating patients with juvenile-onset recurrent respiratory papillomatosis. **DESIGN:** A retrospective study. **SETTING:** Tertiary care children's hospital. **PATIENTS:** Patients operated on for juvenile-onset recurrent respiratory papillomatosis between January 1, 1999, and December 31, 2000. Papillomas were excised using the microdebrider in one group and the carbon dioxide laser in the second group. **INTERVENTIONS:** Direct laryngoscopy and bronchoscopy, suspension microlaryngoscopy, and excision of papillomas by the carbon dioxide laser or the microdebrider. **MAIN OUTCOME MEASURES:** Operative time and postoperative complications. **RESULTS:** Seventy-three operations were performed (23 with the laser and 50 with the microdebrider). Sixteen patients were included, 10 with active disease and 5 with disease in remission; 1 was lost to follow-up. They had a mean age of 3.75 years, and the male-female ratio was 7:9. The patients presented mostly with hoarseness (13 [81%]). Four (25%) had soft tissue complications with the laser. The microdebrider was less time-consuming than the laser, although those treated with the microdebrider had more active disease. No factor could be used to measure treatment outcome due to disease variability. Those who were older, female, and African American tended to have less severe manifestations of disease. **CONCLUSIONS:** The microdebrider proved to be less time-consuming than the carbon dioxide laser when used in patients with juvenile-onset recurrent respiratory papillomatosis. Soft tissue complications were nonexistent. In addition to safety, the microdebrider is more appealing to the surgeon, anesthesiologist, and parents, especially because these children often need subsequent surgical procedures.

Unique Identifier - 21924447

Laryngorhinootologie 2002 Feb;81(2):118-21

[The tracheostomy-sphincter procedure - case report of a modified tracheostomy]

[Article in German]

Sauer JA, Sauer A, Werner JA.

Klinik für Hals-, Nasen- und Ohrenheilkunde, Philipps-Universität Marburg.

BACKGROUND: For an adequate speech production after tracheostomy patients are dependant on a temporary closure of the stoma. This closure can either be done manually or

by the use of various tracheostoma valves. The tracheostomy-sphincter procedure, which is introduced in this case, allows the voluntary constriction of the stoma. **METHODS:** This case describes the treatment of a paediatric patient with laryngeal stenosis. During tracheostomy formation, an artificial muscle-sphincter was created, using the sternohyoid muscle (strap muscle). **RESULTS:** Postoperative contractile movements were possible, which were improved by special exercises. After 3 months the complete closure of the tracheostoma was achieved. **CONCLUSIONS:** The establishment of a tracheostomy-sphincter can be carried out during tracheostomy and allows the patient to speak without the use of a device. Tracheobronchial secretions can be cleared via the pharynx by coughing.

Unique Identifier - 21912379

J Cutan Med Surg 2001 Jul-Aug;5(4):329-35

Tacrolimus in dermatology.

De Tran QH, Guay E, Chartier S, Tousignant J.

Centre Hospitalier de l'Universite de Montreal (CHUM), Campus Notre-Dame, 1560 Sherbrooke East, Montreal, Quebec, Canada H2L 4M1.

BACKGROUND: Tacrolimus (FK 506), a metabolite of the fungus *Streptomyces tsukubaensis*, is an anti-T-cell drug. It acts by inhibiting the production of IL-2, IL-3, IL-4, TNF α , and GM-CSF. More potent and with slightly less secondary effects than cyclosporine, it has been the object of considerable interest, especially in conditions that could benefit from the latter. **OBJECTIVE:** In psoriasis, a placebo-controlled double-blind study has shown oral tacrolimus at 0.1 mg/kg/day to be effective in controlling recalcitrant lesions. In human, small studies have reported tacrolimus ointment to be effective in controlling acute contact dermatitis. Short-term trials of topical tacrolimus in the treatment of atopic dermatitis have recently shown excellent results in both adults and children. In animal studies of hair growth disorders, topical tacrolimus induces anagen and protects from chemotherapy-induced alopecia. Animal studies with the ointment for the prevention of skin graft rejection, lupus dermatoses, and skin papilloma formation have also shown to be promising.

CONCLUSIONS: There are case reports of pyoderma gangrenosum, Sezary's syndrome, and Behcet's disease successfully treated with oral tacrolimus but, because of their small number, they remain anecdotal at this point.

Unique Identifier - 21904400

Cancer Immunol Immunother 2002 Apr;51(2):111-9

Immune response to E7 protein of human papillomavirus type 16 anchored on the cell surface.

Nemeckova S, Stranska R, Subrtova J, Kutinova L, Otahal P, Hainz P, Maresova L, Sroller V, Hamsikova E, Vonka V.

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To target the E7 protein of human papilloma virus 16 to the cell surface, a fusion gene was constructed. It encodes the signal peptide, part of the immunoglobulin (IgG)-like domain, the transmembrane anchor of vaccinia virus (VV) hemagglutinin (HA), and the complete E7-coding sequence. The fusion gene was expressed under the HA late promoter by a recombinant VV, designated VV-E7-HA. The E7-HA protein was displayed on the surface of cells infected with the recombinant virus and was more stable than unmodified E7. The biological properties of the VV-E7-HA virus were compared with those of a VV-E7 virus that expressed the unmodified E7 and with a VV expressing the Sig-E7-LAMP fusion protein. While the first two of these recombinants were based on VV strain Praha, the third was derived from the WR strain of VV. Infection of mice with the VV-E7-HA virus induced the formation of E7-specific antibodies with the predominance of the IgG2a isotype, whereas the other two viruses did not induce the formation of E7-specific antibodies. Unlike the other two viruses, VV-E7-HA did not induce a response of cytotoxic T lymphocytes or Th1 cells and did not protect mice against the growth of E7-expressing tumors. Thus, VV-E7-HA induced a differently polarized immune response to the E7 protein than the other two viruses.

Unique Identifier - 21900680

Gan To Kagaku Ryoho 2002 Feb;29 Suppl 1:176-93

A review of the natural history of cervical intraepithelial neoplasia.

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Cervical Intraepithelial Neoplasia (CIN) is a premalignant lesion of cervical squamous cell carcinoma which over time may persist unchanged, regress to normal or a lesser grade of CIN, or progress to a higher grade of CIN or invasive carcinoma. Rates of progression correlate directly with the CIN grade. Human Papilloma Virus (HPV) detection is a significant determinant of CIN regardless of grade. Studies of risk factor profiles, cytogenetic abnormalities, cell proliferation indices, cell cycle and senescence control, oncogene and tumor suppressor gene expression, protein expression, and HPV status have been conducted to identify determinants of CIN I and CIN II/III and predictors of CIN I progression. Differences in these attributes suggest that CIN I is a sexually transmitted, productive HPV infection, whereas CIN II/III is a dysplastic lesion resulting from repeated exposure to a

sexually transmitted HPV and possibly an additional agent. HPV16 positivity and increased viral load in some earlier studies were predictive of prevalent CIN II/III. More recent studies with more sensitive HPV assays did not corroborate these findings. The role of cigarette smoking is controversial and requires additional study. Accumulating evidence suggests that high risk HPV DNA detection and persistence are predictive of CIN I progressing to CIN II/III. Other possibilities are persistence of a high risk HPV variant, altered cell immunity, and cigarette and oral contraceptive use. Possible biomarkers include aneuploidy, aneusomy of chromosomes 1 and 3, Ras and bcl-2 oncogene over expression, and cytokeratin 13 protein under-expression.

Unique Identifier - 21888001

Front Biosci 2002 Mar 1;7:e77-84

Clinical implications of human papillomavirus infection.

Sisk EA, Robertson ES.

University of Michigan Medical School, Ann Arbor, MI 48109-0934, USA.

Human papillomaviruses (HPV) are small DNA viruses associated with specific mucosal and epithelial lesions ranging from benign proliferative lesions to invasive carcinomas. Over 100 types of HPV have been identified, some of which are associated with benign lesions (low risk types) and others are associated with malignancies (high risk types). While the genome consists of 6 early genes and 2 late genes, the E6 and E7 genes have been most studied because they interact with p53 and Rb, respectively, thus contributing to the ability of HPV to mediate oncogenesis. Cervical carcinoma is the most common and most studied HPV-related malignancy. These lesions are thought to be originated from persistent high-risk type HPV infections which progress to well characterized precursor lesions and finally to carcinoma. This same HPV related progression has also been observed in other anogenital malignancies including anal, penile and vulvar carcinomas. Although the evidence is not as conclusive, HPV also likely plays a role in the development of a subset of squamous cell carcinomas of the head and neck as well as other cutaneous malignancies. While HPV infection is common, the progression to malignancy is relatively rare indicating a potential role for immune protection against persistent infection. This is supported by the fact that HPV infection and related malignancies are common in the immunosuppressed population. Thus, efforts have been placed on development of HPV vaccines to prevent and treat these common and diverse groups of HPV related malignancies.

Unique Identifier - 21850395

Gene Ther 2002 Jan;9(2):85-94

Immunization strategy against cervical cancer involving an alphavirus vector expressing high levels of a stable fusion protein of human papillomavirus 16 E6 and E7.

Daemen T, Regts J, Holtrop M, Wilschut J.

University of Groningen, Department of Medical Microbiology, Molecular Virology Section, Groningen, The Netherlands.

We are developing immunization strategies against cervical carcinoma and premalignant disease, based on the use of recombinant Semliki Forest virus (SFV) encoding the oncoproteins E6 and E7 from high-risk human papilloma viruses (HPV). Thus far, protein-based, as well as genetic immunization studies have demonstrated low to moderate cellular immune responses against E6 and E7. To improve these responses, we modified the structure and expression level of the E6 and E7 proteins produced by the SFV vector. Specifically, a construct was generated encoding a fusion protein of E6 and E7, while furthermore a translational enhancer was included (enhE6,7). Infection of cells with recombinant SFV-enhE6,7 resulted in the production of large amounts of the E6,7 fusion protein. The fusion protein was more stable than either one of the separate proteins. Immunization of mice with SFV-enhE6,7 resulted in strong, long-lasting HPV-specific cytotoxic T lymphocyte responses. Tumor challenge experiments in mice demonstrated that immunization with SFV-enhE6,7 resulted in prevention of tumor outgrowth and subsequent protection against tumor re-challenge.

Unique Identifier - 21846057

Pharmazie 2002 Jan;57(1):72-3

Investigations on topical formulations of clomiphene citrate for treatment of HPV lesions.

Cevher E, Sahin NO, Araman A.

Department of Pharmaceutical Technology, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey.

[No abstract available]

Unique Identifier - 21825554

Virology 1995 Apr 1;208(1):298-302

Tumor regression is associated with a specific immune response to the E2 protein of cottontail rabbit papillomavirus.

Selvakumar R, Ahmed R, Wettstein FO.

Department of Microbiology and Immunology School of Medicine, University of California, Los Angeles 90024-1747, USA.

Cottontail rabbit papillomavirus is the major papillomavirus animal model with which to study host-virus interactions. As with human papillomaviruses, papillomas may spontaneously regress, persist, or progress to carcinoma. Here we show that the majority (88%) of regressor rabbits had antibody to the nonstructural protein E2 compared to 29% in animals with persisting papilloma. The antibody response to other nonstructural viral proteins was the same for rabbits with regressing and persisting papilloma. The cellular immune response was measured by an in vitro proliferation assay. The responses to E6 and E7 were infrequent and similar in papilloma-bearing and in regressor rabbits and no rabbits responded to E1. In contrast, the response to E2 was more frequent in regressor rabbits. These data suggest that E2-specific immune responses may play a role in tumor regression.

Unique Identifier - 21820294

Ned Tijdschr Tandheelkd 1992 Dec;99(12):464-6

[Human papillomavirus and lesions of the oral mucosa]

[Article in Dutch]

Nauta JM, Burger MP, Kremer JF, Nikkels PG.

Kliniek voor Mondziekten, Kaakchirurgie en Bijzondere Tandheelkunde.

Recently there has been an increased interest in the possible role that viruses and especially the Human Papilloma virus (HPV) could play in the etiology of lesions of the oral mucosa. A distinction has to be made between the so-called low-risk types of the virus (HPV-2, 6, 11, 13 and 32) which can be found in benign oral mucosal lesions, and the high-risk type (HPV-16), which predominantly is found in malignant oral mucosal lesions.

Unique Identifier - 21686655

Otolaryngol Head Neck Surg 2002 Jan;126(1):79-80

Primary tracheal papillomatosis presenting as reactive airway disease.

Valentino J, Brame CB, Studtmann KE, Manaligod JM.

Division of Otolaryngology-Head and Neck Surgery, School of Medicine, University of Kentucky, Lexington, USA. jvale00@pop.uky.edu

No abstract available.

Unique Identifier - 21679827

Folia Histochem Cytobiol 2001;39 Suppl 2:193-4

PCNA and P53 expression in relation to clinicopathological features of oral papilloma.

Sulkowska M, Famulski W, Stasiak-Barmuta A, Kasacka I, Koda M, Chyczewski L, Sulkowski S.

Department of Clinical Pathology, Medical Academy, Bialystok, Poland.
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Although papilloma is the most frequent benign epithelial tumour of oral cavity, its biological potential for malignant transformation is still to be evaluated. The aim of the study was to correlate PCNA and P53 expression in 55 oral papillomas with some clinicopathological variables. The tissue samples were stained with H+E and by immunohistochemistry for PCNA and P53 protein. Staining patterns were assessed semiquantitatively and correlated with each other and grade of tumour epithelial dysplasia, tumour size, localization well patient age and sex. PCNA immunostaining was positive 43 (78%) oral papillomas. P53 immunohistochemical reaction was positive in 38 (69%) out of 55 epithelial tumours. Positive relationship between PCNA and P53 expression was observed as well as between PCNA immunostaining and grade of epithelial dysplasia. There was no statistically significant relationships between PCNA, P53 immunohistochemical positivity and papilloma size, site, patient age and sex. The results of this study suggest that immunohistochemical P53 overexpression is valuable marker of early neoplastic transformation and together with PCNA are presumed predictors for malignant transformation of oral papillomas.

Unique Identifier - 21678366

Cancer 2002 Jan 1;94(1):159-66

The effects of exogenous p53 overexpression on HPV-immortalized and carcinogen transformed oral keratinocytes.

Yoo GH, Washington J, Oliver J, Piechocki M, Kim H, Foster-Nora J, Shibuya TY, Wilson DR, Ensley JF.

Department of Otolaryngology-Head and Neck Surgery, Wayne State University, Detroit, Michigan 48201, USA. gyoo@med.wayne.edu

BACKGROUND: Overexpression of p53 in head and neck carcinoma cells has demonstrated tumor growth suppression using in vitro and in vivo models. The effects of exogenous overexpression of wild-type p53 on human papilloma virus (HPV)-immortalized and carcinogen transformed oral keratinocytes were determined. **METHODS:** The p53 gene was overexpressed in IHGK (immortalized human gingival keratinocyte), IHGKN [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, (NNK)]-carcinogen transformed keratinocytes, and two head and neck squamous carcinoma (HNSCC) cell lines, HN30 and HN12. The transfection efficiency, growth suppression, and inhibition of the cell cycle along with the induction of apoptosis were measured. **RESULTS:** Transfections with adenoviruses were more efficient for IHGK cells than for IHGKN, HN12, and HN30 cells. Inhibition of proliferation in all cell lines was proportional to the viral particle to cell (VPC) ratios. IHGK cells were more sensitive to p53 than IHGKN cells. HN12 cells were more suppressed than HN30 cells. HN12 were the most suppressed at 72 hours whereas HN30 cells were most suppressed at 24 hours. Expression of exogenous p53-induced G1 cell cycle arrest and p21 expression as VPC ratios increased in IHGK and IHGKN cell lines. Apoptosis also was induced in these cells by p53 as VPC increased. IHGK cells were more sensitive to p53-induced growth inhibition, cell cycle regulation, p21 expression and apoptosis than IHGKN cells. HN12 (mutated p53) cells were more sensitive to p53 overexpression than HN30 (wild-type p53) cells. Gene transfer and expression of exogenous p53 by using Ad-p53 demonstrates suppressive effects on HPV immortalized and carcinogen transformed oral keratinocytes. **CONCLUSIONS:** Cell cycle regulation by gene transfer is feasible in immortalized oral keratinocytes. Carcinogen transformed cells are less susceptible to the effects of p53 overexpression. Expression of exogenous p53 through p53 gene transfer can suppress HPV immortalization and carcinogen transformation in oral keratinocytes. The sensitivity of HNSCC cell lines to p53-induced cell cycle regulation and apoptosis is variable and dependent on the cell line and duration of exposure. In vitro results using p53 gene transfer must be validated in clinical studies with patients at risk for HNSCC.

UniqueIdentifier - 21673614

Zhonghua Kou Qiang Yi Xue Za Zhi 2001 Jan;36(1):34-6

[Study on the role of human papillomavirus in carcinogenesis of oral papillomas by in situ hybridization]

[Article in Chinese]

Bu J, Pang J, Bu R.

Department of Stomatology, General Hospital of PLA, Beijing 100853, China.

OBJECTIVE: To explore the role of human papillomavirus (HPV) infection on carcinogenesis of oral squamous cell papillomas (SCP). **METHODS:** By using digoxin labelled HPV 6/11 and HPV 16/18 probes, through hybridization in situ technique, the HPV DNA sequence in 30 cases of oral SCP were detected. **RESULTS:** Among them, 16 cases (53.3%) were positive for HPV 6/11 DNA. None of cases of SCP were positive for HPV 16/18 DNA. **CONCLUSION:** Our results show that the frequent finding of HPV 6/11 DNA in oral SCP had close association between oral papillomas and HPV 6/11 infection.

Unique Identifier - 21673024

Cancer Res 2002 Jan 15;62(2):472-9

Frequent detection of human papillomavirus 16 E2-specific T-helper immunity in healthy subjects.

de Jong A, van der Burg SH, Kwappenberg KM, van der Hulst JM, Franken KL, Geluk A, van Meijgaarden KE, Drijfhout JW, Kenter G, Vermeij P, Melief CJ, Offringa R.

Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, 2300 RC Leiden, the Netherlands.

The incidence of genital human papillomavirus (HPV) infections is high in young, sexually active individuals. Most infections are cleared within 1 year after infection. The targets for the cellular immune response in this process of viral clearance remain to be identified, but the expression pattern of the E2 protein in early infection and low-grade cervical intraepithelial neoplasia renders this early protein a candidate antigen. Therefore, we studied the HPV16 E2-specific T-cell responses in more detail. Very strong proliferative responses against one or more peptide-epitopes derived from this antigen can be found in peripheral blood mononuclear cell cultures of approximately half of the healthy donors. Additional analysis revealed that at least a majority of these responses represent reactivity by memory CD4(+) T-helper (Th) 1-type cells capable of secreting IFN-gamma on antigenic stimulation. Interestingly, all of the E2 peptides against which strong responses were detected are clustered in the key functional domains of the E2 protein, which are conserved to considerable extent between HPV types. This suggests that HPV16 E2-specific Th memory

may be installed through encounter with HPV types other than HPV16. Indeed, one HPV16 E2-specific Th clone was found to cross-react against homologous peptides from other HPV types, but three other Th clones failed to show similar cross-reactivity. Therefore, part of the HPV16 E2-specific Th memory may relate to previous encounter of other HPV types, whereas the majority of the immune repertoire concerned is most likely established through infection with HPV16 itself. Our data are the first to reveal that the T-cell repertoire of healthy donors can contain particularly high frequencies of E2-specific memory Th cells and suggest that boosting of this immunity can be used for preventive and therapeutic vaccination against HPV-induced lesions.

Unique Identifier - 21668019

Ann N Y Acad Sci 2001 Dec;952:1-12

Genetic instability in epithelial tissues at risk for cancer.

Hittelman WN.

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Epithelial tumors develop through a multistep process driven by genomic instability frequently associated with etiologic agents such as prolonged tobacco smoke exposure or human papilloma virus (HPV) infection. The purpose of the studies reported here was to examine the nature of genomic instability in epithelial tissues at cancer risk in order to identify tissue genetic biomarkers that might be used to assess an individual's cancer risk and response to chemopreventive intervention. As part of several chemoprevention trials, biopsies were obtained from risk tissues (i.e., bronchial biopsies from chronic smokers, oral or laryngeal biopsies from individuals with premalignancy) and examined for chromosome instability using in situ hybridization. Nearly all biopsy specimens show evidence for chromosome instability throughout the exposed tissue. Increased chromosome instability was observed with histologic progression in the normal to tumor transition of head and neck squamous cell carcinomas. Chromosome instability was also seen in premalignant head and neck lesions, and high levels were associated with subsequent tumor development. In bronchial biopsies of current smokers, the level of ongoing chromosome instability correlated with smoking intensity (e.g., packs/day), whereas the chromosome index (average number of chromosome copies per cell) correlated with cumulative tobacco exposure (i.e., pack-years). Spatial chromosome analyses of the epithelium demonstrated multifocal clonal outgrowths. In former smokers, random chromosome instability was reduced; however, clonal populations appeared to persist for many years, perhaps accounting for continued lung cancer risk following smoking cessation.

Unique Identifier - 21653726

Chest Surg Clin N Am 2001 Nov;11(4):749-68

Bronchoscopic management of benign stenosis.

Shapshay SM, Valdez TA.

Department of Otolaryngology-Head and Neck Surgery, New England Medical Center, Tufts University School of Medicine, Boston, Massachusetts, USA.

In summary, the use of laser technology in the airway for the treatment of benign lesions has become a standard therapeutic modality for the airway endoscopist. It is extremely important that endoscopists be well acquainted with the laser soft tissue interactions of the laser being used and the safety precautions associated with each individual wavelength. They should be conversant with the indications and contraindications and have the ability to use adjuvant therapeutic modalities, such as stents and medications. As usual, patient selection is one of the key factors related to successful management.

Unique Identifier - 21639518

J Virol 2002 Feb;76(3):1533-6

Increased p50/p50 NF-kappaB activation in human papillomavirus type 6- or type 11-induced laryngeal papilloma tissue.

Vancurova I, Wu R, Miskolci V, Sun S.

Department of Pediatrics, Long Island Jewish Medical Center, New Hyde Park, New York, USA.

We have observed elevated NF-kappaB DNA-binding activity in nuclear extracts from human papillomavirus type 6- and 11-infected laryngeal papilloma tissues. The predominant DNA-binding species is the p50/p50 homodimer. The elevated NF-kappaB activity could be correlated with a reduced level of cytoplasmic IkappaBbeta and could be associated with the overexpression of p21(CIP1/WAF1) in papilloma cells. Increased NF-kappaB activity and cytoplasmic accumulation of p21(CIP1/WAF1) might counteract death-promoting effects elicited by overexpressed PTEN and reduced activation of Akt and STAT3 previously noted in these tissues.

Unique Identifier - 21635531

Vestn Otorinolaringol 2001;(6):33-7

[Immediate short- and long-term results of rehabilitation of children with laryngeal papillomatosis]

[Article in Russian]

Enin IP, Zaets VN, Iagoda NL, Karpov VP, Sivovolova NA, Morenko VM.

The authors review their 30-year experience with rehabilitation of children with laryngeal papillomatosis. A total of 212 patients at the age from 9 months to 15 years have been treated. Immediate, short- and long-term results of different combined surgical and conservative treatments are compared. The authors hold that the papillomatous tissue should be eliminated completely, therefore, during surgery under anesthesia endolaryngeal removal of the papillomas should be combined with monopolar coagulation of their residual tissues. The combined surgery should be immediately followed by etiopathogenetic conservative treatment. The highest effect was achieved with autoserum administration according to the scheme. In combined rehabilitation of such children local etiopathogenetic treatment is preferable.

Unique Identifier - 21618601

J Ethnopharmacol 2002 Jan;79(1):27-33

Tumour reducing and anticarcinogenic activity of *Acanthus ilicifolius* in mice.

Babu BH, Shylesh BS, Padikkala J.

Department of Biochemistry, Amala Cancer Research Centre, Amala Nagar, 680 553, Thrissur, India.

Alcoholic extract of *Acanthus ilicifolius* (250,500 mg/kg b wt) was found to be effective against tumour progression and carcinogen induced skin papilloma formation in mice. The extract was found to be cytotoxic towards lung fibroblast (L-929) cells in 72 h MTT assay and the concentration required for 50% cell death was 18 microg/ml. Oral administration of the extract (500 mg/kg b wt) reduced the tumour volume and administration of the same concentration increased the life span by 75% in ascites tumour (EAC cells) harbouring animals. The extract also significantly delayed the onset of dimethylbenzanthrazene DMBA/Croton oil induced skin papilloma in mice in a dose dependent manner.

Unique Identifier - 21611552

Pediatr Dermatol 2001 Sep-Oct;18(5):450-2

Treatment of human papilloma virus in a 6-month-old infant with imiquimod 5% cream.

Schaen L, Mercurio MG.

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A healthy female infant was diagnosed with genital warts at six months of age. She was the product of an uncomplicated vaginal delivery to a mother who was diagnosed with genital warts during the pregnancy, but did not undergo any treatment. The infant's warts were clinically resolved following a three week course of 5% imiquimod cream, an immunomodulating agent that has been demonstrated to be a potent inducer of several cytokines promoting an antiviral cell-mediated immune response.

Unique Identifier - 21603295

An Esp Pediatr 2001 Dec;55(6):558-60

[Recurrent respiratory papillomatosis: a cause of progressive respiratory distress]

[Article in Spanish]

Rojo Conejo P, Martin Puerto M, Mendoza Soto A, Malalana Martinez A, Villafruela Sanz M.

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A 5-year-old girl was brought to the emergency department because of respiratory distress of 3 months' evolution that had worsened over the previous 3 weeks. Cervical radiograph and cervical computerized axial tomography showed an endolaryngeal mass almost completely occluding the airway. Urgent laryngoscopy revealed an endolaryngeal fleshy mass, which was excised during the procedure. Histological diagnosis was laryngeal papilloma. Although infrequent in children, laryngeal papilloma is the most common laryngeal tumor in pediatrics. It is currently named juvenile onset recurrent respiratory papillomatosis. The human papilloma virus (HPV) causes the disease by vertical transmission from a mother with active or latent vulvar HPV infection.

Unique Identifier - 21587408

ORL J Otorhinolaryngol Relat Spec 2001 Nov-Dec;63(6):372-8

An initial assessment of the optical properties of human laryngeal tissue.

Mahlstedt K, Netz U, Schadel D, Eberle HG, Gross M.

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The optical properties of human laryngeal tissue have been examined over the whole wavelength range from 400 to 2,200 nm to facilitate the development of new laser applications. Tissue samples were taken from healthy vocal fold and from vocal fold of patients with papillomatosis and with chronic, nonspecific laryngitis. The transmission and scattering properties of the tissue samples were recorded with a computer-guided integrating-sphere system. From the measured data the optical properties were calculated by means of the inverse Monte Carlo simulation. In the 500- to 600-nm range papilloma tissues had a considerably higher absorption than healthy vocal fold. When applying the optical tissue properties as a possible influencing factor of the effectiveness of laser systems, laser applications at this wavelength range may be useful in the ablation of papilloma tissue.

Unique Identifier - 21570570

Am J Clin Dermatol 2001;2(4):239-51

Oral cancer. The importance of early diagnosis and treatment.

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Oral cancer is an important health issue. The WHO predicts a continuing worldwide increase in the number of patients with oral cancer, extending this trend well into the next several decades. In the US the projected number of new cases of oral and oropharyngeal cancer will exceed 31,000 per year. Mortality due to cancers in this region exceeds the annual death rate in the US caused by either cutaneous melanoma or cervical cancer. Significant agents involved in the etiology of oral cancer in Western countries include sunlight exposure, smoking and alcohol consumption. Use of the areca or betel nut in many cultures is a major etiological factor outside of the USA. Other etiologic factors associated with oral squamous cell carcinoma, but far less significant statistically, include syphilis and sideropenic dysphagia. Recently, strong evidence for an etiological relationship between human papilloma virus and a subset of head and neck cancers has been noted. It is generally accepted that most sporadic tumors are the result of a multi-step process of accumulated genetic alterations. These alterations affect epithelial cell behavior by way of loss of chromosomal heterozygosity which in turn leads to a series of events progressing to the ultimate stage of

invasive squamous cell carcinoma. The corresponding genetic alterations are reflected in clinical and microscopic pathology from hyperplasia through invasiveness. A wide range of mucosal alternations fall within the rubric of leukoplakia. Proliferative verrucous leukoplakia represents a relatively new type of leukoplakia that is separate from the more common or less innocuous form of this condition. Erythroplakia is particularly relevant considering its almost certain relationship with dysplasia or invasive carcinoma. Squamous cell carcinoma will develop from antecedent dysplastic oral mucosal lesions if an early diagnosis has not been made and treatment given. Early diagnosis within stages I and II correspond to a vastly improved 5-year survival rate when compared with more advanced stage III and IV lesions. Surgical management of this disease remains the mainstay of treatment. Other therapies include radiation and chemotherapy options that may be used adjunctively and palliatively. Following treatment, it is important to understand the significant risks of second primary cancers developing within the upper aerodigestive tract as a result of field cancerization. The most important message is that early detection of the asymptomatic early stage oral cancer translates in general terms to satisfactory clinical outcome and cure in most patients.

Unique Identifier - 21562033

Vestn Otorinolaringol 2001;(5):47-9

[Viferon treatment of recurrent respiratory papillomatosis in children]

[Article in Russian]

Nurmukhametov RKh, Onufrieva EK, Soldatskii IuL, Maslov IV, Tikhonenkova LP, Shchepin NV, Kol'tsov VD.

No abstract available.

Unique Identifier - 21556416

Eur J Med Res 2001 Oct 29;6(10):440-58

Virus infections and tumors of the oral mucosae. Symposium of the "Arbeitskreis Oralpathologie und Oralmedizin" and the "Arbeitsgemeinschaft Dermatologische Infektiologie der Deutschen Dermatologischen Gesellschaft", Rostock, July 6-7, 2001.

Gross G, Gundlach K, Reichart PA.

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The symposium on Virus Infections and Tumors of the Oral Mucosae was organized as a joint meeting of the Arbeitskreis Oralpathologie and Oralmedizin and the Arbeitsgemeinschaft Dermatologische Infektiologie (ADI) der Deutschen Dermatologischen Gesellschaft. The main topics of the meeting were herpes virus infections, human papillomavirus (HPV) infections and human immunodeficiency virus (HIV) infections of the oral mucosae. Clinically both diagnostic, differential diagnostic and therapeutic aspects of the virus-associated diseases were discussed in several presentations. Another important issue was the role of these viruses, particularly of HPVs, in the origin and development of oral cancer. Apparently besides smoking and alcohol other risk factors comprise high risk HPVs, immunodeficiency and possibly also genetic factors. Whether neonatal early infections may predispose children to a specific cancer risk in their future life is still at a level of discussion. Some arguments, however were shown that tonsillar carcinoma, which shows the highest prevalence of the high-risk HPV 16- DNA sequences between all oral cancer, is possibly an epidemiologically and etiologically distinct tumor. It is argued that this tumor is probably less dependent on classical carcinogens than other oral malignant tumors.

Unique Identifier - 21554916

Trop Doct 2001 Oct;31(4):195-7

Upper airway obstruction in Nigeria: an aetiological profile and review of the literature.

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The early history of tracheostomy and intubation suggested that upper airway obstruction had been in existence for a long time. A study of 80 patients with upper airway obstructions treated over a 10-year period between 1990 and 1999 was carried out to determine the aetiology and incidence. There were 65 (81%) males and 15 (19%) females with a sex ratio of 4.3:1 (M:F). The age ranged from 6 months to 70 years; with mean age of 27 years. Ninety-nine per cent were acquired causes and 1% were congenital. The commonest site of obstruction was in the larynx 81%. In children, the most common causes were laryngeal papilloma (16%) and foreign body (14%), while in adults, laryngeal carcinoma (24%) and direct laryngeal injuries (15%). The study revealed a wide range of causes of upper respiratory tract obstruction encountered in a developing tropical country. Health education and community awareness programmes should be supported. This would encourage early presentation, prompt referral to experts and earlier treatment with improved outcome.

Unique Identifier - 21530765

Clin Immunol 2001 Oct;101(1):94-9

Interaction of human papillomavirus type 11 E7 protein with TAP-1 results in the reduction of ATP-dependent peptide transport.

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Human papillomaviruses (HPVs) cause benign and malignant epithelial tumors of the respiratory and genital mucosa. We previously reported that recurrent respiratory papillomas caused by HPV 6/11 express low levels of antibody-detectable TAP-1, the protein that transports peptides into the endoplasmic reticulum for assembly and presentation by MHC Class I, and that the extent of TAP-1 immunostaining is inversely related to the frequency of disease recurrence. We have now determined a mechanism for the reduction in TAP-1 detection. Anti-TAP-1 antibody immunoprecipitated very low amounts of protein from papilloma cells. However, immunoprecipitation of calreticulin, another member of the MHC I assembly complex, coprecipitated TAP-1 at levels comparable to those of uninfected cells. Immunoprecipitation of an HPV-positive cell line with either anti-TAP-1 or anti-calreticulin coprecipitated HPV E7 protein. Finally, purified HPV 11 E7 protein inhibited ATP-dependent peptide transport in vitro. We propose that the interaction of E7 with TAP-1 prevents TAP-1 antibody detection and efficient peptide transport, resulting in poor presentation of viral antigen on HPV-infected cells and thus failure to mount an effective immune-mediated prevention of disease recurrence.

Unique Identifier - 21464572

Laryngoscope 2001 Sep;111(9):1639-44

CO(2) laser treatment in 244 patients with respiratory papillomas.

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OBJECTIVE: Respiratory papillomas (RP) tend to recur and the difficulty in eradicating the disease makes their treatment frustrating. Meticulous CO(2) laser excisions every 2 months has been the most effective treatment to date. This article analyzes the results of this plan in 244 patients with RP in the nose, nasopharynx, pharynx, hypopharynx, larynx, trachea, lung parenchyma, and skin. **METHODS:** Two hundred forty-four patients with recurrent RP were treated by the senior author with CO(2) laser excisions and, in some cases, podophyllum and alpha interferon. **Demographics,** initial distribution of papillomas, number of operations performed on each patient, and current results were evaluated. **RESULTS:** Careful laser

excisions of RPs every 2 months achieved "remission" of disease (no visible RP on indirect or often direct laryngoscopy 2 mo after last removal) in 37% of patients, "clearance" of the disease process (no RP clinically apparent for 3 y after last removal) in 6%, and "cure" (no clinical recurrence for 5 y after last removal) in 17%. Juvenile-onset RP tends to follow a more aggressive course than adult-onset RP. Four patients (1.6%) developed malignant transformation of their papillomas. Except for ones in lung parenchyma, RP in areas other than the true vocal cords tend to be cleared faster because aggressive removal does not cause hoarseness. Lung parenchyma RPs are eventually fatal because of pulmonary failure from abscesses and cysts resulting from a lack of effective treatment. CONCLUSION: Frequent and meticulously performed CO₂ laser excisions can achieve significant voice and airway improvement, and some clinical "cures." However, effective antiviral medicines and/or immunologic agents are needed to achieve true cures with elimination of all human papilloma virus 6 and 11 viruses.

Unique Identifier - 21453626

Laryngoscope 2001 Aug;111(8):1494-6

Powered instrument papilloma excision: an alternative to laser therapy for recurrent respiratory papilloma.

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No abstract available.

Unique Identifier - 21453597

Acta Anaesthesiol Scand 2001 Jul;45(6):790-2

Effects of changes in frequency and inspiratory time on arterial oxygenation and CO₂ elimination during high-frequency jet ventilation in a child with laryngotracheal papillomata.

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An 11-yr-old female without any pulmonary disorders underwent laser resections of laryngotracheal tumors using high-frequency jet ventilation (HFJV) 6 times over a period of

17 months at our institute. In this series of surgeries, we studied the effects on PaO₂ and PaCO₂ during HFJV of changes of either frequency or inspiratory time. Increasing the frequency from 100 to 400/min decreased the PaO₂ and increased the PaCO₂. Decreasing the inspiratory time from 30% to 20% increased the PaCO₂, although it did not affect the PaO₂. All the procedures were uneventfully carried out without critically impairing gas exchange during HFJV. In this patient with normal lung function, CO₂ elimination during HFJV appeared to be facilitated by either decreasing the frequency or increasing the inspiratory time. Arterial oxygen tension during HFJV was higher at lower frequencies.

Unique Identifier - 21314822

Biochem Biophys Res Commun 2001 Mar 30;282(2):409-15

Vitamin C augments chemotherapeutic response of cervical carcinoma HeLa cells by stabilizing P53.

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Human Papilloma Virus (HPV) is associated in most instances with cervical cancer. The HPV oncoproteins target P53 protein for degradation, leading to deregulation of cell cycle. We investigated whether stabilization of P53 in cervical cancer cells, by downregulating HPV transcription would restore the apoptotic ability of these cells. Our findings show that vitamin C downregulates the redox sensitive transcription factor AP-1 and decreases one of its transcription targets HPV E6, and stabilizes P53. This was associated with an increase in Bax and decrease in Bcl-2 and telomerase activity. Accumulation of P53 and its target gene bax then sensitized HeLa cells to cell-cycle arrest, cell death/apoptosis induced by cisplatin, and etoposide. Increasing drug sensitivity of cervical carcinoma cells by stabilizing P53 using vitamin C is a novel approach and has potential clinical relevance.

Unique Identifier - 21294747

Eur Respir J 2001 Apr;17(4):830-1

Successful treatment of severe respiratory papillomatosis with intravenous cidofovir and interferon alpha-2b.

Armbruster C, Kreuzer A, Vorbach H, Huber M, Armbruster C.

Second Medical Dept/Pumologisches Zentrum.

In contrast to uncomplicated juvenile laryngeal papillomas which may regress spontaneously,

papillomatosis involving pulmonary parenchyma is associated with a poor outcome. This report represents the case of a 34 yr-old female in whom respiratory papillomatosis resulted in voice problems and recurrent pneumonias due to bronchial obstruction. A computed tomographic scan of the chest showed worsening bilateral round cavitating consolidations. Bronchoscopy revealed polypoid lesions of the right vocal cord and the midtrachea which were confirmed as squamous papillomatosis by histology. Interferon (IFN)alpha-2b treatment was inefficient as was cidofovir monotherapy on a maintenance basis. Six months of IFN-alpha-2b and cidofovir in combination led to a complete macroscopic disappearance of the laryngeal lesions and to an impressive regression of the tracheal papillomas and of the intrapulmonary consolidations. These data provide support that severe respiratory papillomatosis can be safely treated by interferon alpha-2b and cidofovir in combination. Probably the same mechanisms as in ribavirin plus interferon alpha-2b, in the treatment of patients with chronic hepatitis C, are responsible for the therapeutic success in this case.

Unique Identifier - 21293927

Lin Chuang Er Bi Yan Hou Ke Za Zhi 1998 Aug;12(8):349-52

[The study of PCNA expression and AgNORs counting adult-onset laryngeal papilloma]

[Article in Chinese]

Wang T, Wang D.

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Avidin-Biotin-peroxidase Complex technique (ABC) and silver staining technique were used to study the relationship between proliferative activity and the biological status of adult-onset laryngeal papilloma. The proliferating index of PCNA positive cells was closely related to AgNORs count. The two indices were significantly different among these groups ($P < 0.05$). CONCLUSION: PCNA expression and AgNORs count are useful in distinguishing between benign and malignant laryngeal neoplasms, monitoring premalignancy and observing tumor biological activity.

Unique Identifier - 21161686

Lin Chuang Er Bi Yan Hou Ke Za Zhi 1998 May;12(5):211-3

[Ultrastructural pathologic research on the adult laryngeal papilloma]

[Article in Chinese]

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In this paper, the ultrastructural features of laryngeal papillomas of 9 cases of adult patients were investigated by means of SEM. It showed that the polypoid surface of the papilloma is easily recognized; the surface cells are covered by microvilli of different size and shape; and the epithelium is bordered by an irregular and continuous basement membrane. In some areas, there is pseudopodium of basal cells stretching into connective tissue. The structure of interface between basement membrane and connective tissue varies with aggravation of tumor cell atypia. The significant variation of structural of basement membrane and semidesmosomes suggests the possibility of malignant change.

Unique Identifier - 21031594

Int J Cancer 2001 Jan 1;91(1):8-21

Retinoic acid (RA) receptor transcriptional activation correlates with inhibition of 12-O-tetradecanoylphorbol-13-acetate-induced ornithine decarboxylase (ODC) activity by retinoids: a potential role for trans-RA-induced ZBP-89 in ODC inhibition.

Dawson MI, Park JH, Chen G, Chao W, Dousman L, Waleh N, Hobbs PD, Jong L, Toll L, Zhang X, Gu J, Agadir A, Merchant JL, Bai L, Verma AK, Thacher SM, Chandraratna RA, Shroot B, Hill DL.

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Evaluation of retinoic acid receptor (RAR) subtype-selective alpha and gamma agonists and antagonists and a retinoid X receptor (RXR) class-selective agonist for efficacy at inhibiting both induction of ornithine decarboxylase (ODC) by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) in mouse epidermis and rat tracheal epithelial cells and the appearance of papillomas in mouse epidermis treated in the 2-stage tumor initiation-promotion model indicated that (i) RXR class-selective transcriptional agonists, such as MM11246, were not involved in ODC inhibition; (ii) RAR-selective agonists that induce gene transcription from RA-responsive elements (RAREs) were active at low concentrations; (iii) RAR-selective antagonists that bind RARs and inhibit AP-1 activation on the collagenase promoter but do not activate RAREs to induce gene transcription were less effective inhibitors; and (iv) RARgamma-selective retinoid agonists were more effective

inhibitors of TPA-induced ODC activity than RARalpha-selective agonists. These results suggest that RARE activation has a more important role in inhibition of ODC activity than RXR activation or AP-1 inhibition and that RARgamma-selective agonists would be the most useful inhibitors of epithelial cell proliferation induced by tumor promoters. The natural retinoid all-trans-RA induced expression of transcription factor ZBP-89, which represses activation of the GC box in the ODC promoter by the transcription factor Sp1.

Unique Identifier - 21024129

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