The Mysterious Chemo-Preventive Player in Oral Cavity: Retinoids

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Abstract

Vitamin A is considered as one of the essential micronutrients which are extensively associated with chemo-preventive and therapeutic modalities. Carcinogenesis is a complex disease where environmental and genetic factors act as a predisposing cause bringing about alterations in the overall cell microstructure. Possible role of Retinoid, which is a form of Vitamin A, has been recognized in suppressing breast cancer, lung carcinoma, cancer of the colon, prostate cancer, blood cancers and to some extent the cancers of the oral cavity. Retinoid is known to act through RAR/RXR receptors to form ligands and thereby affect the transcription process and controls angiogenesis, abnormal proliferation, and metastasis. Some varieties of leukemia have shown better results with Retinoid therapy. However its role in oral premalignant and malignant lesions are not much known. This review discusses the physiologic, epigenetic and molecular role of Retinoids in lesions of the oral cavity.

Keywords: *Retinoids, Oral Carcinoma, Chemopreventives.*

Introduction

Oral carcinoma is a major area of concern that has increased incidence and associated with a 5 years survival rate in 50% of patients.[1] Chemoprevention refers to the term that includes repairing and reversal of the cellular defects thereby preventing the initiation of disease and its further progression into a tumour. The rich source of Vitamin A is vegetables and animal products such as milk, eggs, cod liver oil, spinach, carrot, butter, etc. These are a precursor to retinol that consists of a retinoid molecule family. The extracted forms are retinol, retinal, pro-vitamin A like carotenoids and retinoic acid. Esterification of retinol takes place in the Liver and then it is distributed to the body parts through the bloodstream. Chemopreventive role of Retinoids was first identified by Sporn MB et al 1976.[2]

RXR or rexinoid receptoris a cell membrane receptor and its isoforms are α,β,γ. These isoforms allow swift movement of retinol in the cell as Retinoic Acid (RA). Similarly 9 cis RA, 13 cis RA and all TransRA(ATRA) are derivatives of retinoic acid. RA and Retinoic Acid Receptor (RAR) with α, β, γ isoformsbind together with hormone binding receptors causing gene transcription. Retinoid Acid Receptor β (RAR β) expression has shown alterations in leukemia,squamous cell carcinoma, breast carcinoma, etc.[3]

Immunomodulatory role of Retinoids: Vitamin A levels are maintained at a physiological level to protect the host from daily harmful stimuli thereby providing immunity. In autoimmune diseases the harmony between the T Helper cell (Th cells) and Regulatory T cell (Treg) population is disrupted.

(a) Th17 acts as a mediator for initiating autoimmune responses that help to protect the host from undesirable bacterial and fungal stimuli.

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(b) Treg, a member of the FOXP3+ family suppresses massive effector T cell activation by producing interleukins.[4,5] The role of RA is to directly influence FOXP3+ Treg cells in regulating the ratio between Treg and Th17 thereby preventing any untoward body's reaction to inflammatory responses. These changes cause improved resistance of the host towards the autoimmune disease.

(c) ATRA reduces anti-DNA antibodies. According to *Kinoshita K and Wasserfall C* et al, ATRA is used to treat autoimmune diseases like SLE and type 1 diabetes.[6,7] ATRA is also known to inhibit virus-induced T cell death in HIV positive patients. It down regulates the fasL production and alters the ratio of CD8+ and CD4+ T cells. [8,9]

(d) According to Gupta and Sansoni, et al. age-related changes can be due to a progressive increase in effector/cytotoxic CD8+ T cell population producing IL-2, IFN-γ and TNF α.[4,5]

However,a study by *Mecocci P*et al has shown that elevated levels of RA provide resistance to antigenic load in elderly patients.[10]

(e) T Lymphocytes that originate from thymus cells generate T Cell Receptors (TCRs) that carry an important signal for the maturation of T cell.[11] The survival of T lymphocyte depends upon antigen expression in acute diseases which increases IL-2 and BCL-XL expression and prevents apoptosis in the cell.[12,13]

Retinoids regulate healthy reserve of T lymphocyte by allowing maturation of normal cells and selective apoptosis of defective cells.

Retinoids act synergistically enhancing glucocorticoid-induced death and decreasing TCR–mediated death of thymocytes and T cell hybridomas.[14,15]

Tumor suppressionrole of Retinoids: Interaction of retinoid and its receptors downstream the proliferating tumor cells. They either undergo apoptosis or allow the abnormally proliferative cells to differentiate.

It has been observed that expression of RAR-β is either lost or masked hence resulting in reduced intracellular binding of RA.[16,17]

Similarly, specific members of cytochrome (CYP 450) maintains the concentration of retinoic acids in the cell, for a specific period.

A link between RA signal and carcinogenesis may be established via the expression of enzymes of the CYP 26 superfamily. The anti-proliferative property of retinoids is diminished by the enhanced expression of CYP 26.Oxidative stress on the cell is prevented by extending the half-life of RA intra-cellularly, this is done by CYP 26 enzymes which help in preventing oncogenesis.[18]

Role of Retinoids in Apoptosis: Angiogenesis and neo-vascularization promote proliferation and metastasis of a tumor. Angiogenesis is a known predisposing factor to support the survival of neoplastic cells. It is present in all types of head and neck cancers with increased expression of VEGF. Anti-apoptotic activity of tumors can be associated with disrupted expression of NF-Kβ in carcinomas. Increased NF-Kβ expression is seen in bacterial or viral stimuli that lead to inflammation. Increase in NF-kβ expression means there is increasing resistance of the tumor to treatment. Retinoids act through the mitochondrial pathway to release cytochrome c into the cytosol which allows the caspase pathway to activate and cause apoptosis. According to Chen Z and Di Donato, et al, expression of NF-Kβ is seen due to phosphorylation of IKB (inhibitor of kappa beta) by IKB Kinase (IKK) which allows polyubiquitination and proteasome-dependent degradation of its inhibitors.[19] Then the entry of NF-Kβ into the nucleus permits various gene transcriptions to prevent apoptosis.

Anti-proliferative role of retinoids

Size, stage, size and type of tumor influences the fate and prognosis of a disease. Similarly Preferentially Expressed Antigen in Melanoma (PRAME),that is present in tumors is also expressed.PRAME can trigger cytotoxic T cell-mediated immune response in melanoma and other solid tumors like HNSCC. Usually PRAME is expressed weekly or negatively but in tumours its presence can be exponential. PRAME act as a co-repressor of the retinoid signaling pathway. Epping MT et al concluded that the direct mechanism of action of PRAME is unknown but it might prevent ligand-receptor activation of retinoids by acting as an antagonist that allows the growth of tumor cells and differentiation of malignant stem cells.[20] It also inhibits the action of retinoic acid thereby explains the failure of RA treatment in malignant and premalignant lesions in the literature.

Role of RA in the treatment of various conditions:

Oral Lichen Planus: Oral lichen planus is an autoimmune disease that affects the oral mucosa, nails, skin, and genital mucosa. There is a tendency for malignant transformation to SCC in about 1-2 % of affected patients.[21] Often characterized by the presence of inflammatory mediators like cytokines that interact between keratinocytes and T lymphocytes.[22] It is postulated that gene dysregulation is caused by aberrant productions of the cytokines and causes autoimmune reactions with basal cell apoptosis. Expression of (MHC) class II antigen, human leukocyte antigen DR and variable degree of epithelial thickness are features of lichen planus.[23] Vitamin A deficiency might favour the reprogramming of Treg cells into IL-17. RA treatment regulates Th 17 synthesis by inhibiting IL that further influences Treg cells to regulate peripheral tolerance.[24] The plasticity and phenotype of Treg cell production are maintained by RA which helps in controlling a disease. Cytokines production can also be influenced by local microenvironmental which may be controlled by introducing Vitamin A at early stages to reverse the pathogenesis.

Squamous cell carcinoma: Initiation, progression and metastasis of a complex multistep disease is influenced by genetics and environmental factors. Proliferation of stratified squamous epithelium is limited to the basal and parabasal layer and the maturation of the cell is the sequential process of terminal differentiation. In neoplastic lesions IL-8 and TGF β maintain angiogenesis. Retinoic acid treatment suppresses angiogenesis by neutralizing the IL 8 concentration in cancer cells.Retinoids inhibit the cell growth and GJIC- connected cells in HNSCC.[25]Retinoids exert their pleiotropic effects by binding to nuclear receptors in cells and causing inhibition of cell proliferation, modulation of cell differentiation and enhancement of apoptosis.[26,27]

Leukoplakia/Epithelial Dysplasia: The proliferation of basal and suprabasal cells of epithelium associated with a malignant transformation due to extrinsic factors such as tobacco products and with a high rate of proliferation as 43% are features of Leukoplakia. Ramaswamy G, et al. studied the association of intrinsic factors with leucoplakia, decreased plasma levels of vitamin A, B12, C, β carotene, and folic acid were found in patients with oral leukoplakia.[28]

Use of antioxidants like vitamin A block the generation of reactive oxygen species which further prevent normal cell to undergo genetic aberration thereby may revert the tissue to normal state.[29] Vitamin A supplementation and habit can control the variable degree of epithelial dysplasia. Meir, et al. observed that loss of RAR β mRNA as a result of hypermethylation in premalignant lesions may be restored by application of 13 cis RA. Vitamin A can exert its effects when initial signs and symptoms are noted, but once the disease process is advanced, no satisfactory results could be obtained solely. At present, further studies are still under research to estimate the effect of Vitamin A at the molecular level following treatment.

The molecular modification of vitamin A, aids a role in the expression of growth factors, differentiation of cells, immunity, reproduction and repair of epithelial tissue. In oral tissue, deficiency of endogenous vitamin A may cause defective tooth formation and hypo/ dyskeratosis of oral mucosa due to dysregulation caused during the development of dental lamina and oral ectoderm respectively.

Future Perspectives & Conclusions: This article attempts to review and present the chemotherapeutic effects of vitamin A and its analog as a preventive measure in oral premalignant lesions and oral cancer. Extensive research is being conducted to evaluate the usefulness of the molecule as a chemotherapeutic drug, though promising results are seen in leukemia and high-risk breast cancerous lesion but its usefulness in treating epithelial premalignant and malignant lesion is still under question. The effective use of chemoprevention may decrease the potential malignant transformation but it is yet to be authenticated by long term studies to analyze the effectiveness of retinoids following treatment. Moreover, we still stand deficient to identify the targeted receptor which maintains inter and intracellular homeostasis. Invent of targeted markers has given a promising scope to understand the molecular bases of Vitamin A therapy. Research should, therefore, focus on retinoid molecules that can delay the metabolism of RA inside the cell like RAMBA (Retinoic Acid Metabolism Blocking Agents). Validation of treatment to therapy must be viewed using the latest biomarkers to overcome undue exposure in resistant cases. More clinical studies are needed in this direction for treating epithelial malignancies using retinoids as a targeted epigenetic approach.

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References

1. Bodhade AS, Dive AM. Chemoprevention of premalignant and malignant lesions of oral cavity: Recent trends. Eur J Dent. 2013;7(2):246-50.
2. Sporn MB, Dunlop NM, Newton DL, Smith JM. Prevention of chemical carcinogenesis by vitamin A and its synthetic analogs (retinoids). Fed Proc. 1976;35(6):1332-8.
3. Bollag W, Holdener E. Retinoids in cancer prevention and therapy. Annals of Oncology.1992; 3:513-526. Ann Oncol. 1992;3(7):513-26.
4. Gupta S, Bi R, Su K, Yel L, Chiplunkar S, Gollapudi S. Characterization of naive, memory and effector CD8 T cells: effect of age. ExperimentalGerontology. 2004;39(4):545–550
5. Sansoni P, Vescovini R, Fagnoni F, Biasini C, Zanni F, Zanlari L, et al. The immune system in extreme longevity. Experimental Gerontology. 2008;43(2):61–65.
6. Kinoshita K, Kishimoto K, Shimazu H, Nozaki Y, Sugiyama M, Ikoma S, et al. Successful treatment with retinoids in patients with lupus nephritis. American Journal of Kidney Diseases. 2010;55(2):344–347.
7. Wasserfall C, Atkinson MA. Taking a daily vitamin to prevent type 1 diabetes? Diabetes. 2008;58(1):24–25.
8. Yang Y, Bailey J, Vacchio MS, Yarchoan R, Ashwell JD. Retinoic acid inhibition of ex vivo human immunodeficiency virus-associated apoptosis of peripheral blood cells. Proc. Natl. Acad. Sci. 1995;92(7):3051-3055.
9. Pohl J, LaFace D, Sands JF. Transcription of retinoic acid receptor genes in transgenic mice increases the CD8 T-cell subset. Mol Biol Rep. 1993;17(2):135-142.
10. Mecocci P, Polidori MC, Troiano L, Cherubini A, Cecchetti R, Pini G, et al. Plasma antioxidants and longevity: a study on healthy centenarians. Free Radical Biology and Medicine. 2000;28(8):1243–1248.
11. Szondy Z, Reichert U, Fesus L. Retinoic acids regulate apoptosis of T lymphocytes through an interplay between RAR and RXR receptors. Cell Death and Differentiation. 1998:5(1);4-10.
12. Duke RC, Cohen JJ. IL-2 addiction: withdrawal of growth factor activates a suicide program independent T Cells. Lymphokine Res. 1986;5(4):289-298.
13. Yang E and Korsmeyer SJ. Molecular thanatopsis: a discourse on the BCL-2 family and cell death. Blood 1996;88(2):386-401.
14. Iwata M, Mukai M, Nakay Y, Iseki R. Retinoic acid inhibits activation-induced apoptosis in T-cell hybridomas and thymocytes. J. Immunology. 1992;149:3002-3008.
15. Yang Y, Vacchio MS, Ashwell JD. 9-cis retinoic acid inhibits activation driven T-cell apoptosis: implications for retinoid X receptor involvement in thymocyte development. Proc. Natl. Acad. Sci. 1993;90(13):6170-6174.
16. Altucci L, Gronemeyer H. The promise of retinoids to fight against cancer. Nat Rev Cancer. 2001;1(3):181–193.
17. Freemantle SJ, Dragnev KH, Dmitrovsky E. The retinoic acid paradox in cancer chemoprevention. Journal of the National Cancer Institute. 2006;98(7):426–427.
18. Ross AC, Zolfaghari R. Cytochrome P450s in the Regulation of Cellular Retinoic Acid Metabolism. Annu Rev Nutr. 2011;31(1):65–87.
19. Chen Z, Hagler J, Palombella VJ, Melandri F, Scherer D, Ballard D,et al. Signal-induced site-specific phosphorylation targets I kappa B alpha to the ubiquitin-proteasome pathway. Genes & Dev. 1995;9(13):1586–1597.
20. Epping MT, Wang L, Edel MJ, Carlee L, Hernandez M, Bernards R. The human tumor antigen PRAME is a dominant repressor of retinoic acid receptor signaling.Cell. 2005;122(6):835-847.
21. Georgakopoulou EA, Achtari MD, Achtaris M, Foukas PG, Kotsinas A. Oral Lichen Planus as a Preneoplastic Inflammatory Model, Journal of Biomedicine and Biotechnology. 2012;2012:1-8.
22. Lu R, Zhang J, Sun W, Du G, Zhou G. Inflammation-related cytokines in oral lichen planus: an overview. J Oral Pathol Med. 2015;44(1):1–14.
23. Piattelli A, Carinci F, Iezzi G, Perrotti V, Goteri G, Fioroni M, et al: Oral lichen planus treated

with 13-cis-retinoic acid (isotretinoin): Effects on the apoptotic process. Clin Oral Investig. 2007;11(3):283-288.

24. Rudkin GH, Carlsen BT, Chung CY, et al. Retinoids inhibit squamous cell carcinoma growth and intercellular communication. J Surg Res. 2002;103(2):183–189.
25. Sidell N, Taga T, Hirano T, Kishimoto T, Saxon A. Retinoic acid-induced growth inhibition of a human myeloma cell line via down-regulation of IL-6 receptors. J Immunol 1991;146 (11) 3809-3814.
26. Horn V, Minucci S, Ogryzko VV, Adamson ED, Howard BH, Levin AA, Ozato K. RAR and RXR selective ligands cooperatively induce apoptosis and neuronal differentiation in P19 embryonal carcinoma cells. Fed Am Soc Exp Biol J. 1996;10:1071–1077.
27. Tejón G, Manríquez V, Calisto JD, Flores-Santibáñez F, Hidalgo Y, Crisóstomo N, et al. Vitamin A Impairs the Reprogramming of Tregs into IL-17-Producing Cells during Intestinal Inflammation. BioMed Research International. 2015;2015:1-8.
28. Rajendran R. Oral leukoplakia (leukokeratosis): Compilation of facts and figures. J Oral Maxillofac Pathol. 2004;8(2):58-68.
29. Gorsky M, Epstein JB. The Effect of Retinoids on Premalignant Oral Lesions Focus on topical therapy. Cancer. 2002;95(6):1258-64.