Review

HPV-induced recurrent laryngeal papillomatosis: rationale for adjuvant fatty acid therapy

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The course of human papilloma virus (HPV)-induced recurrent laryngeal papillomatosis (RLP) is variable and unpredictable. Some patients experience spontaneous remission, while others suffer from aggressive growth with dire consequences. Unfortunately, HPV DNA can persist in mucosa after treatment and can be reactivated under immunosuppressive conditions. For this reason, these benign tumors are notoriously recurrent. Better understanding of lipid-driven signaling pathways during tumorigenesis and immune responses in RLP patients can contribute to improve therapeutic approaches in an attempt to obviate this disease. Based on a mountain of evidence in the literature that concerns the immunomodulatory potential of certain FAs, it is clear that there is a rationale for adjuvant FA therapy (concurrent application) in the management of RLP. Of particular importance for immune surveillance is that the Th1 pathway in RLP is down-regulated and it is advocated that conjugated linoleic acid (CLA) and eicosapentaenoic acid (EPA) have the ability to restore the Th1/Th2 balance. Therefore, it is proposed that adjuvant FA therapy with CLA and EPA must be included in the therapeutical regime of RLP, since they are considered excellent anti-viral and anti-tumor agents to improve immune conditions and disease outcome. Immunocompetence plays a pivotal role in the clinical course of RLP and, hence, a new direction with adjuvant FA therapy may be the key to prevent recurrence of this disease.

Key Words: Benign tumors, laryngeal papillomatosis, therapeutic rationale, adjuvant fatty acid therapy, nutritional immunomodulation

INTRODUCTION

Human papilloma virus (HPV)-induced recurrent laryngeal papillomatosis (RLP) poses a risk of morbidity and mortality. Hoarseness is an early sign and airway obstruction a later life-threatening sign. Despite multiple treatment modalities, this disease is still hallmarked by recurrence that necessitates repeated surgery as the mainstay treatment. The severity of this disease varies due to unpredictability of clinical remissions and recurrences. The viruses involved (mostly HPV_6 and HPV_{11}) are held in a subclinical state in exposed individuals by a competent immune system, but are reactivated under immunosuppressive conditions and, hence, recurrence of RLP prevails, especially among young children.[1,2]

Lipid-driven membrane-to-nucleus signaling pathways are responsible for cellular changes that may have profound influences on cell growth that manifest in laryngeal papillomatosis and the immune defenses of patients with RLP. Both cellular and antibody (humoral) immune responses may be involved and the patient's immunocompetence may influence the clinical course of the disease. Among T lymphocytes, cytotoxic T lymphocytes (CD8+ cells) and T helper cells (CD4+ cells) play a central role in immune surveillance and virus elimination. Among T helper cells, a Th1/Th2 balance exist that regulates cytokine subsets for cell-to-cell communication and functional integration of the immune system. Of interest is that deficiency of the Th1 cytokine interleukin-2 (IL-2), responsible for lymphocyte clonal expansion and cyto toxic T lymphocyte function expression, can be up-regulated by immunomodulatory fatty acids (FAs).[3-7] This mini-review emphasizes the paramount importance and influence of fatty acids (FAs) on immune surveillance in RLP patients and how adjuvant FA therapy can be applied to improve immunocompetence. A body of research information that validates the beneficial use of specific FA agents in the therapeutic regimes of different tumor and cancer entities is discussed in support of our proposal for adjuvant FA therapy with conjugated linoleic acid (CLA) and eicosapentaenoic acid (EPA), with or without appropriate drugs after surgery, for the management of RLP.

CLINICAL COURSE OF RLP AND TREATMENT DIFFICULTIES

HPV-induced laryngeal papillomatosis remains a challenging disease for surgeons, since it can be notoriously recurrent and necessitates repeated laryngoscopy and surgical debulking to maintain a patent airway until the disease regresses spontaneously. Among potential complications, spread to the lungs is considered the most severe complication, owing to inaccessibility. Recurrence of this

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tumor is ascribed to the fact that HPV DNA can persist in adjacent, normal-appearing mucosa after surgical treatment. Several adjuvant therapies have been advocated in the past and among them are interferon, cidofovir, imiquimod, indole-3 carbonyl, ribavirin, and photodynamic therapy. Cidofovir is being used increasingly to treat benign RLP caused by HPV types 6 and 11, whilst imiquimod is also considered an extremely useful addition to the armamentarium of HPV therapies. As with surgical management, viral persistence occurs with these adjuvant therapies.[1,2] Failure of the immune system (both cellular and humoral components, to successfully control HPV-infected cells contributes to RLP and the immunocompetence of these patients may influence the clinical course of the disease. The potential use of HPV testing and vaccines to prevent or combat HPV infection holds the key to optimal management of this potentially devastating disease. Preclinical vaccine studies for papillomas based on oncogene peptides or proteins, DNA plasmids and different viral vectors are documented, all with shortcomings and benefits.[8-10] A clinical trial with HspE7, a wide spectrum vaccine that targets papillomas, reduced disease recurrence in laryngeal papillomas, but lacked a placebo group.[9] An appropriate vaccine for laryngeal papillomatosis is still awaited and, until then, it seems imperative to properly address cytotoxic T lymphocyte function.

LIPID AND IMMUNE STATUS OF RLP PATIENTS

From our preceding lipid studies with RLP patients,[11, 12] it is evident that enhanced dietary linoleic acid (LA) and saturated fatty acids (SFAs) are responsible for lipid driven signaling pathways during, respectively, tumorigenesis and immune responses. According to the literature, excessive dietary LA and SFA intakes are associated with inflammatory conditions and tumorigenesis, as well as Th1 inhibition and immunodeficiency.[13] Of particular importance is that transcription factors involved in these signaling pathways, including nuclear factor-kappa beta (NF-κβ) as the central mediator of the immune system, are targets that can be regulated with FA therapy and phytochemicals, such as indole-3 carbinol.[14-17] The importance of NF-κβ activity to orchestrate patient immunocompetence can not be underestimated. Feedback mechanisms exist, whereby, NF-κβ is activated by growth factors, cytokines, free radicals and oncogenes and, in turn, NF-κβ stimulates growth factors, cytokines and oncogenes (Fig 1).[18-20] Therefore, NF-kB controls proliferation, apoptosis and immunity, all crucial steps on which therapy is based. It is suggested that overlapping HPV expression (E6 protein of low risk HPV types 6 and 11) and NF-κβ in the cell nucleus has the potential to immortalize cells by degrading the tumor suppressor p53 oncogene, abrogating survival protein p21, and enhancing anti-apoptotic Bcl-2 in RLP patients.[21] It is also conceivable that prolonged disease conditions can eventually down-regulate cytokines and lymphocytes that may lead to immunodeficiency in RLP patients. Modulation of membrane FA compositions for manipulation of abnormal signaling pathways to prevent tumorigenesis and immunodeficiency is a therapeutic tool that is currently receiving renewed interest. In the case of RLP patients where, among other factors, NF-κβ and the anti-apoptotic

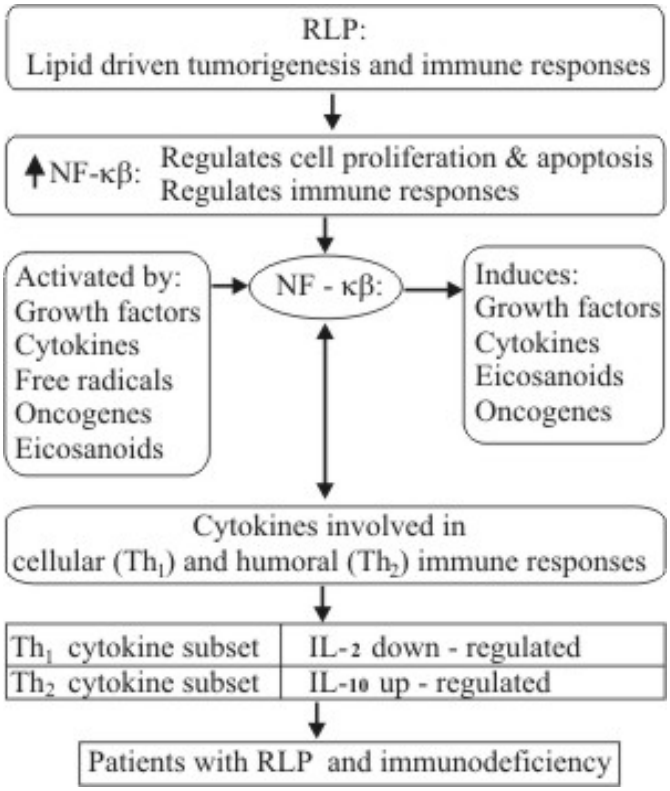

Figure 1. The diagram illustrates lipid drive tumorigenesis and immune responses by linoleic acid and saturated fatty acids, and the central role that NF-kB plays during these two main events. The cellular arm of the immune response plays an important role during recurrent laryngeal papillomatosis and the up-regulation of interleukin-2 (IL-2) and consequently also cytotoxic T cells (CD8+ cells) is suggested.

gene Bcl-2 are up-regulated,[21, 22] the beneficial therapeutic use of FA therapy needs to be evaluated.

THE IMPORTANCE OF IMMUNOCOMPETENCE TO COMBAT RLP

It is imperative to improve the immunocompetence of RLP patients, since immunodeficiency may hamper the clinical course of the disease. For immune surveillance (the body's ability to detect and destroy tumor cells) the cellular arm (Th1) of the immune response is important as Th1 pathways typically produce activation of cells that include cytotoxic T-lymphocytes. T lymphocytes produce cytokines and play a critical role in defining the type and magnitude of the immune response. Depending on the mode of activation, T-lymphocytes differentiate into either helper Th1 or Th2 cells (CD4+ cells), or become cytotoxic T lymphocytes (CD8+ cells). The Th1 cell produces primarily interleukin-2 (IL-2), interferon gamma (IFN-γ) and tumor necrosis factor -α (TNF-α), resulting in enhanced cell-mediated or cytotoxic responses. The Th2 cell produces IL-4, IL-5, IL-6 and IL-10, generating a humoral or anti-body-mediated immune response. According to available information, the HPV-11 E6 protein appears to be the dominant inducer of cytokine expression that favors cytokine Th1 responses in RLP.[23] Research confirmed that IL-2 expression is decreased, while IL-10 expression is increased in RLP patients.[5, 23] In the case of cell-mediated responses it became evident that CD8+ cells are potent mediators of viral clearance, but during chronic infections CD4+ cell help is required to sustain antiviral CD8+ cell activity for immune attack in RLP patients.[3,4] As far as the humoral response is concerned, deficiency of immature B cells and an imbalance between immunoglobulins (Ig) with enhanced IgE is implicated in RLP.[24] It is predicted that up-regulation of IL-2 and lymphocyte counts/function may improve the immunocompetence of RLP patients.

MODULATION OF IMMUNE SYSTEM BY SPECIFIC FATTY ACIDS

Clinically relevant to RLP patients are those FAs with anti-viral and immunomodulatory potential that are advocated to be useful in preventing and/or reversing some of the side effects of retroviral drugs. Among them, conjugated linoleic acid (CLA), derived from dairy products and ruminant meats, and eicosapentaenoic acid (EPA), derived from fish, and are highly acclaimed.[15,16,25,26] CLA (isomers of LA) protects against tumorigenesis, unlike LA that stimulates tumorigenesis, and is currently widely explored.[26] CLA has the potential to manipulate the AA cascade, modulate the immune system and ameliorate viral infection.[15] Although the safety and effectiveness of CLA for clinical use is already determined, there is still ongoing research to clarify the beneficial use of different isomers and their mixtures for specific conditions or diseases.[27] The anti-inflammatory role of EPA to manipulate the arachidonic acid (AA) cascade and to improve membrane FA compositions for normal cell function is well established.[16]

Specific FAs, ligands for peroxisome proliferator-activated receptors (PPARs), drive tumor and immune signaling pathways and, interestingly, a new direction with PPAR target therapy is suggested.[28] However, it is argued that FA therapy, modulation of membrane FA compositions with those FAs that are ligands for specific PPAR family members to redirect signalling pathways, might be on the long term a more appropriate approach. At this point in time, a balance between PPARγ and PPARα, associated with cell proliferation and inflammatory conditions, and PPARδ/β, associated with apoptosis, is considered important. Research revealed that PPARδ/β has the ability to induce apoptosis, but when over-expressed it suppresses apoptosis. Based on laboratory studies, CLA and EPA can activate PPARγ and PPARα and, thereby, tilts the scale in favor of apoptosis.[29,30] In the case of RLP, high LA and palmitic acid (PA) levels are apparently responsible for, respectively, a mitogenetic driven stimulus and the apoptotic resistance of papilloma cells.[11,12] The potential of CLA and EPA to re-direct signaling pathways and, thereby, prevent RLP needs to be explored.

RATIONALE AND PROPOSAL FOR ADJUVANT FATTY ACID THERAPY

There is compelling evidence available from *in vitro* and *in vivo* studies that demonstrate the ability of CLA to modify immune responses and the impact it has on cytotoxic T lymphocytes to eliminate virus particles or to control/ ameliorate virus infection.[15] Important findings from a pig model with virally induced immunosuppression revealed the ability of CLA to stimulate the T-cell lymphocyte response and enhance cellular immunity by modulating phenotype and effector functions of CD8+ T-cells, involved in both adaptive and innate immunity.[3,4] It is also evident that two CLA isomers (*cis*-9, *trans*-11 and *trans*-10, *cis*-12) exert distinct effects on T lymphocyte populations and immunoglobulin subclasses.[15] Of importance is the fact that CLA has the potential to up-regulate IL-2 production and to improve cytotoxic T lymphocyte function, as well as the potential to down-regulate IgE and to improve B lymphocyte maturation.[15] Evidence for the efficacy and safety of CLA administration in humans is being steadily strengthened by results from animal toxicology tests, as well as clinical trials. Currently, mixtures (mostly 50:50) of CLA products (*cis*9, *trans*11-18:2) are used for inflammatory conditions.[15,27,31] Interestingly, CLA could be particularly beneficial for immunocompromised individuals who are slow to or low responders to vaccination.[15] A substantial body of work also indicates the immunomodulatory potential of n-3 PUFAs that improve quality of life in diseases currently considered to be Th1 or Th2 associated.[7] The impact of n-3 PUFAs lies in their ability to prevent inflammatory conditions and, thereby, modulate immune responses.[32,33] Interestingly, in vivo research revealed that dietary CLA-supplementation delayed the onset of inflammatory bowel disease by down-regulation of eicosanoids and up-regulation of PPARγ, whereas n-3 PUFAs accelerated colonic regeneration and clinical remission by activating PPARδβ.[34]

From the preceding information it is clear that there is a rationale for adjuvant FA therapy in the management of RLP. CLA and EPA, to prevent tumour growth, eliminate HPV particles or to control / ameliorate HPV infec-

tion and to improve immune defences is proposed. Adjuvant FA therapy, concurrent application to enhance antiviral drugs or alone to replace drugs, after surgery to improve immune defences and disease outcome is proposed.

DISCUSSION

Based on a mountain of evidence in the literature (in vitro and in vivo animal and human studies) that FAs can inhibit cell proliferation, induce apoptosis, improve immune responses and even enhance the impact of other treatment modalities,[35-59] it is suffice to say that there is a rationale for adjuvant FA therapy in the management of different tumor and cancer entities. Depending on etiological causes and the clinical interventions required, there are those FAs advocated to: eliminate bacteria and viruses or ameliorate bacterial or viral infections; protect against smoke particles and oxidative stress, regulate and redirect enzymes where interference with essential fatty acid metabolism and enhanced fatty acid sytheses occurs, modulate membrane FA compositions and FA metabolism to prevent carcinogenesis; and regulate NF-κβ and Th1 / Th2 cytokine subsets to improve immunocompetence.[15,16,60]

Specific FA therapies can be included in the therapeutical regimes for different tumor and cancer entities, apart from the necessity to follow a healthy lifestyle, hallmarked by good nutrition with limitation on those environmental factors that might interfere with lipid metabolism. Previous studies done by us led to the construction of lipid models for keloids, laryngeal cancer and colorectal cancer that allowed a rationale for adjuvant FA therapeutic strategies, whether: systemically and locally with gamma-linolenic acid (GLA) and EPA to improve membrane FA compositions for normal signaling pathways as in the case of, respectively, keloid susceptible patients and normal wound healing after keloid excision;[61] neoadjuvant (before surgery) as in the case of early laryngeal cancer to prevent radioresistancy, based on the fact that GLA and EPA can down-regulate enhanced cyclooxygenas-2 (COX-2) and Bcl-2 activities that contribute to apoptotic resistance;[62] concurrent (during treatment) as in the case of colorectal cancer with CLA and EPA or GLA and EPA to prevent polyp growth or CLA and EPA to improve the immunocompetence of the patients for prevention of polyp recurrence after surgery[63] In the case of RLP, based on FA profiles reported,[11] the emphasis appears to be on improved immunocompetence and the prevention of tumor recurrence.

Considerable word has been done to demonstrate the beneficial use of FA therapy with GLA and EPA or lately CLA and EPA therapy.[49,54] Therapy with docosahexaenoic acid (DHA), widely researched for its apoptotic potential, raises the concern that it may have detrimental effects on lymphocytes.[64] The main concern regarding CLA therapy is currently clarification of appropriate mixtures of beneficial CLA specific isomer products to address specific conditions or diseases.[65,66]

CONLUSION

Currently, adjuvant treatment modalities for RLP are palliative at best and vaccines for optimal management are awaited. Clinical trials with adjuvant FA therapy with CLA and EPA after surgery, with or without drugs, to eliminate the virus and to improve patient well-being and disease outcome for RLP management need to be evaluated. The transition of experimental findings to clinical application is hampered by a lack of randomized clinical trials with long-term follow-up studies. Available research findings presented in this mini- review serve as a strong incentive for intervention trials that will test the effect of recommended adjuvant FA therapy in the management of RLP patients.

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AUTHOR DISCLOSURES

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人類乳突病毒誘導復發喉頭乳瘤：脂肪酸輔助治療之理論基礎

人類乳突病毒誘導復發喉頭乳瘤(RLP)的發生是多變的且不可預料的。有些病人的症狀會自動減輕，但有些病人則長出大瘤導致嚴重後果。不幸地，接受治療後，人類乳突病毒之 DNA 仍可持留在黏膜中且在免疫抑制的情況下，還會被活化。因此這些良性瘤會猖狂地不斷復發。了解 RLP 病人在致瘤過程和免疫反應中的脂質訊號路徑有助於改進此疾病的治療方法。既然脂肪酸的免疫調節功能已有佐證如山的文獻證據，顯然應用在 RLP 病人也是有合理的根據。在 RLP 中，Th1 路徑被向下調節，而共軛亞麻油酸(CLA)和二十碳五烯酸(EPA)被認為能夠恢復 Th1/Th2 的平衡。自從它們被認為是傑出的抗病毒和抗腫瘤劑而能改善免疫情況和疾病結果後，含有 CLA 和 EPA 的脂肪酸輔助治療就被提議包含在 RLP 的療程內。臨床上 RLP 病人的免疫能力扮演著一個重要的角色，因此以脂肪酸輔助治療的新方向可能成為預防疾病復發的重要關鍵。

關鍵字：良性瘤、喉頭乳瘤、治療理論基礎、脂肪酸輔助治療、營養免疫調控