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IMMUNOMODULATION IN HUMANS CAUSED BY BETA-CAROTENE AND VITAMIN A

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ABSTRACT

Carotenoids and retinoids can stimulate some human immune responses. These include cytokine release with anti-tumor cell activity, increased natural killer cells and activated lymphocytes after both in vitro and in vivo treatment with beta carotene. Such stimulations seem only partly due to retinoids formed from carotenoid metabolism and may be due to effects caused by the structure of beta carotene. Changes in immune functions could explain in part the cancer resistance provided by high carotenoid or retinoid intakes in animals.

KEY WORDS: beta carotene, natural killer cells, activated lymphocytes, cancer.

INTRODUCTION

A variety of dietary components are possible inhibitors of human cancer initation or promotion (1,2). Two related groups include: (a) retinoids, particularly retinol or preformed vitamin A, and (b) carotenoids, provitamin A compounds. The latter group includes beta carotene which can be converted into retinol in vivo and others, like canthaxanthin, which cannot (3). However, all have immunomodulatory effects at physiological levels which may affect cancer growth.

Recently, great emphasis has been given to understanding the mechanisms of cancer prevention mediated by vitamin A and related compounds. This review article provides an immunology perspective on the actions of vitamin A, including modulation of T-lymphocyte helper cells, macrophages, Langerhans cells, and natural killer cells. The direct effects of vitamin A and related compounds on cancer cells and their toxicity, metabolism and deficiency are extensively reviewed elsewhere and are not discussed here (1,2).

[6]To Whom Correspondence Should be Directed

Retinoids, Carotenoids, and Cancer. During the past decade there has been increasing research which has documented a relationship between dietary retinoids, carotenoids, and cancer incidence (1-4). Both retinoid and carotenoid intakes have been inversely correlated with the incidence of certain cancers in humans, such as: adenocarcinomas, buccal cavity cancer, basal cell carcinoma, and lung, esophageal, and bladder cancers (1,2). Vitamin A deficiency increases the risk of cancer in animals and enhances the sensitivity of epithelial tissues to carcinogenesis by chemicals, irradiation, and viruses (5). Conversely, high intakes of vitamin A and related compounds may have a beneficial effect on the reduction of cancer risk.

Several modes of action have been proposed to account for the inhibitory effects of vitamin A on carcinogenesis: (a) interference with the interaction of the carcinogens or their active metabolites and the target site, (b) alteration of the metabolic pathway of carcinogen activation via inhibition of certain mixed function oxidases (1), (c) lysomal labilization and subsequent breakdown of premalignant cells (6), (d) induction of differentiation (7) or slowing of proliferation and (e) host immunomodulation with subsequent alteration of tumor growth (8,9).

Carotenoids, especially beta-carotene, appear to have a major inhibitory effect on cancer incidence. Epidemiological studies have demonstrated a positive correlation between beta-carotene intake and lower cancer risk (10-12). For example, serum beta-carotene levels were low in patients with gastrointestinal cancer in Israel, with cervical cancer in Japan, and with precancerous stomach lesions in Colombia (13). There may also be an association between low serum levels of beta-carotene and the risk of oral cancers and of squamous cell carcinomas of the lung (14,15). Thus, prospective trials are in progress to evaluate the prophylactic efficacy of beta-carotene in reducing overall cancer risk in humans (13) and animals (16).

The postulated anti-cancer mechanisms for carotenoids include the ones proposed for retinoids mentioned above (14). In addition, carotenoids can act as anti-oxidants by quenching free radicals (17,18). Modification of host immune defenses may also be an important activity of carotenoids which could play a role in their anti-cancer effects (17).

IMMUNOMODULATORY EFFECTS

T-lymphocytes. A variety of synthetic and naturally occurring retinoids stimulate cellular immune functions. Retinoic acid therapy caused enhanced cellular immune reactions and increased antigen recall reactions, while simultaneously improving the efficacy of dermatoses treatment (8). Retinoic acid at non-toxic concentrations increased the response of human T-lymphocytes (19) or thymocytes (20) to phyto-hemagglutinin (PHA), a T-cell mitogen, but not to concanavalin A (Con A) or pokeweed mitogen (PWM) (21). TPA-induced T-lymphocyte proliferation was also increased by retinoic acid given in vivo (22). We have recently shown that 13-cis retinoic acid increased the number of mature T-helper lymphocytes ($CD4^+$) in vitro (23) after incubation of peripheral blood mononuclear cells (PBMC) for 72 hours at low, clinically achievable concentrations (10^{-8}M). In addition, more numbers of helper cells showed expression of transferrin and interleukin-2 (IL-2) receptors which indicated increased numbers of activated T-helper cells (Fig. 1). In vivo experiments in oral leukoplakia patients taking 13-cis retinoic acid 30mg/kg/day for three months showed a 50% increase in numbers of T-helper cells, IL-2 receptor expression, and mitogenic response to phyto-hemoagglutinin (unpublished data). We found increased activation of lymphocytes and macrophages by increased percentage of cells with markers for these functions.

Beta-carotene (180 mg/day) given orally for two weeks to normal human volunteers increased the frequency or percentage of lymphocytes with $CD3^+$ (total T-cells) and $CD4^+$ (T-helper cells), but not $CD8^+$

(T-suppressor/cytotoxic) surface markers (24). We have shown in vitro that beta-carotene produced a significant increase in $CD4^+$ cells (23) and a dramatic increase in the percentage of natural killer cells among PBMC (Fig. 1). The increase in the expression of IL2-receptors was associated with

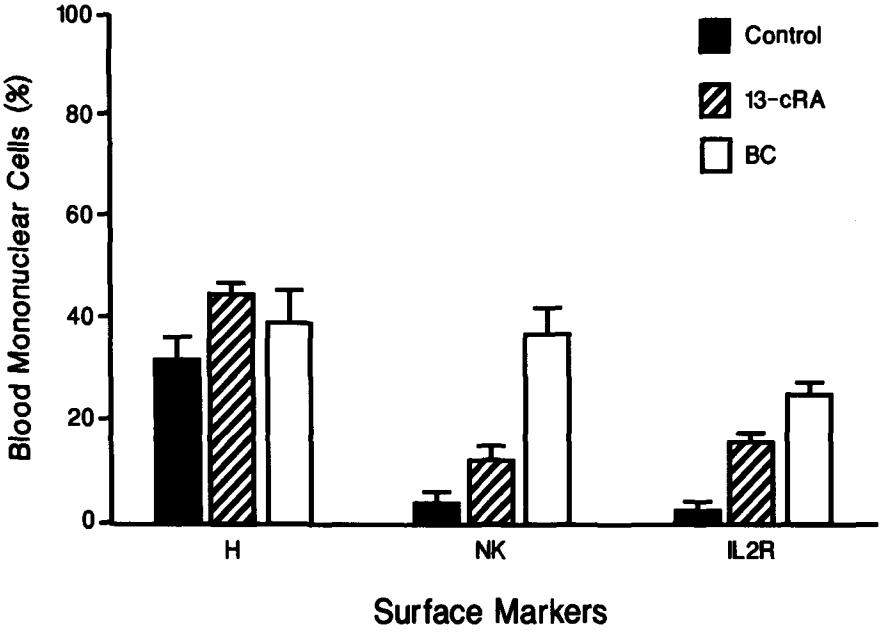


Fig. 1. Immunostimulation of peripheral blood mononuclear cells (PBMC) by 13-cis retinoic acid (13-cRA) and beta-carotene (BC). Purified human PBMC were incubated with either human 13-cRA or BC at 1×10^{-7}M for 72 hours in vitro and stained with monoclonal antibodies of T-helper cells (H), natural killer (NK) cells and interleukin 2 receptors (IL2R) to analyze in flow cytometer. Values were the mean percentages with standard deviation from three or more experiments using samples from 5-10 human blood donors.

increased NK and T-helper cells. Production of interferon by T-lymphocytes was increased by beta-carotene (25).

Similar immunostimulatory effects have been observed in animals given carotenoids. Canthaxanthin, provided as a supplement in the diet of mice at 1%, reduced the number of T-suppressor cells which were increased by ultraviolet irradiation (see Figure 3). Canthaxanthin also increased the percentage of T-helper cells four-fold, and enhanced lymphoid cell expression of activation markers (IL2-receptors) after 2 months of dietary supplementation in mice (Fig. 2). As canthaxanthin is not metabolized into retinol, this change was due to the carotenoid structure, rather than increased retinol in tissues. Both beta-carotene and canthaxanthin showed improvement in the response of rat lymphocytes to the mitogens in vivo (17).

Thus the overall effect of retinoids and carotenoids on T-lymphocytes appears to be stimulatory with increased responsiveness to mitogens, and an increase in the percentage of helper cells ($CD4^+$). However, the mechanisms involved, as well as the clinical relevance of these effects, remains to be determined. Some possible mechanisms involving T cell stimulation are described below.

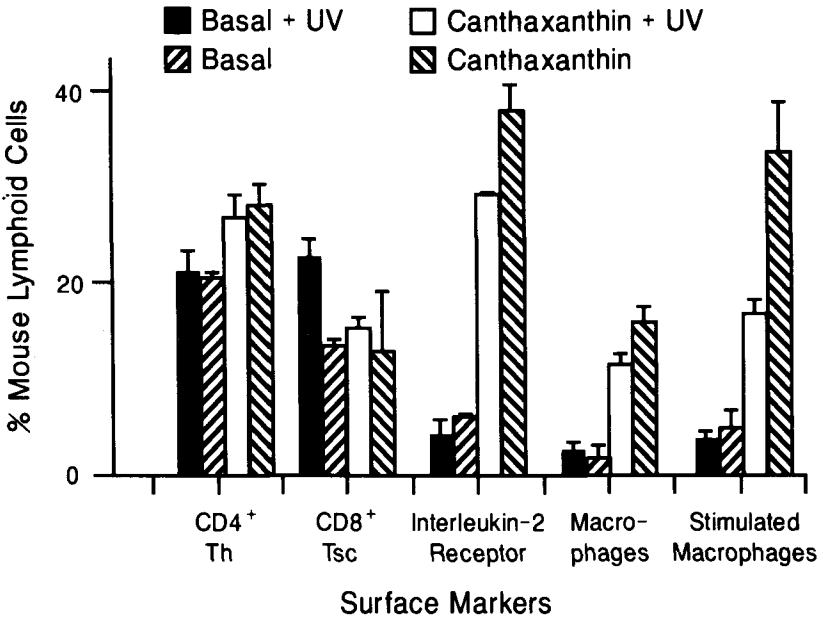


Fig. 2. Activation of mouse spleen cells by canthaxanthin after ultraviolet (UV) irradiation exposure. Mice were fed with dietary canthaxanthin (1% of diet) prior to UV exposure. After 20 weeks, spleen cells were collected and stained with various monoclonal antibodies to analyze in flow cytometer. Values were mean percentages with standard deviation from three or more experiments containing 5-8 mice. (Th - T-helper cells, TSC - T-suppressor cells). The mice received 4.6 $J/M^2/s$ with 80% in wavelength of 280-340 nm. The dorsa of the mice were shaved and they got five 30 minute exposures per week for 15 weeks.

B-lymphocytes. High dietary intakes or deficiencies of retinoids and carotenoids may be expected to alter immune functions of both B and T-cells either directly or through their interactions. Retinoic acid (10^{-7} M) in vitro increased the induction of antibody-producing human tonsillar B-lymphocytes sensitized to sheep red blood cells (SRBC), a T-cell dependent antigen (26). However, it inhibited B-cell transformation induced by Epstein-Barr virus, a T-independent antigen (19). While animal studies suggest that dietary retinoids enhance antibody production, similar data in humans is lacking.

Natural Killer Cells. In a mouse model, induction of cell-mediated cytotoxicity by NK cells to allogenic tumor cells was stimulated by low doses of retinoic acid while high doses were suppressive (27). In humans, NK cell activity was increased by retinoic acid (28) concomitant with suppressed tumor growth. Sidell et. al. (29) observed that NK cells collected from 4 of 10 donors showed a significant increase in cytotoxicity against K562 cells after exposure to retinoic acid. At high concentrations (10^{-5} M), retinoic acid had inhibitory effects on spontaneous and interferon-induced cytotoxicity of NK cells after prolonged periods of incubation (21,25). In our laboratory, we

have recently found that both beta carotene (Fig. 1), and canthaxanthin (Fig. 2) produced an increase in the percentage of NK cells after human PBMC were incubated with them for 3 days at clinically achievable concentrations in vitro (23). However, the effect of carotenoids on NK cells in humans needs further evaluation.

Monocytes/Macrophages. Mononuclear cells, especially monocytes (blood) and macrophages (tissues), have critical roles in host defense mechanisms and immunoregulation.

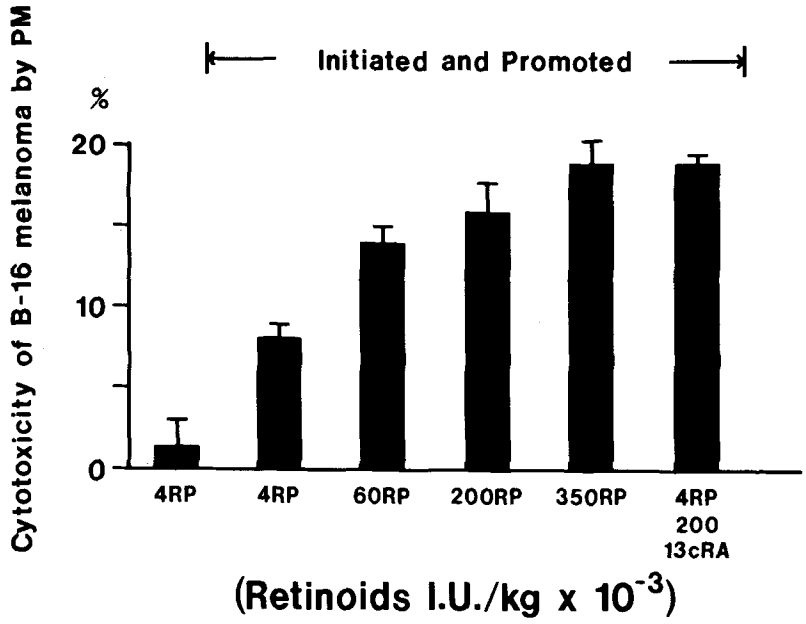


Fig. 3. Cytotoxicity of peritoneal macrophages (PM) after mice were fed with various concentrations of retinyl palmitate (RP). Skin tumors developed in mice following the initiation (DMBA) and promotion (TPA) processes. During the treatment with RP, PM were collected after 21 weeks and the cytotoxicity was measured against B-16 melanoma cells (47). The values were mean percentages with standard deviation of three or more experiments. Each contained 7 mice.

Retinoids affected the development and differentiation of human monocytes/macrophages in vitro including monocytic cell lines (1,7). Retinoic acid increased the growth of granulocyte/macrophage precursor cells, suggesting possible involvement in the early stages of differentiation by increasing the sensitivity to colony stimulating factor (30). Retinoic acid induced an increase in the phagocytic activity and surface marker expression on immature monocyte/macrophage human cell lines (31). At physiological levels (10^{-7}M), retinoic acid produced an increase in interleukin 1 (IL-1) production from PBMC[32] and increased their cytotoxicity to tumor cells in vitro (33). We (34) and others (35) have shown that retinoic acid induced activation of macrophages in mice (Fig. 3).

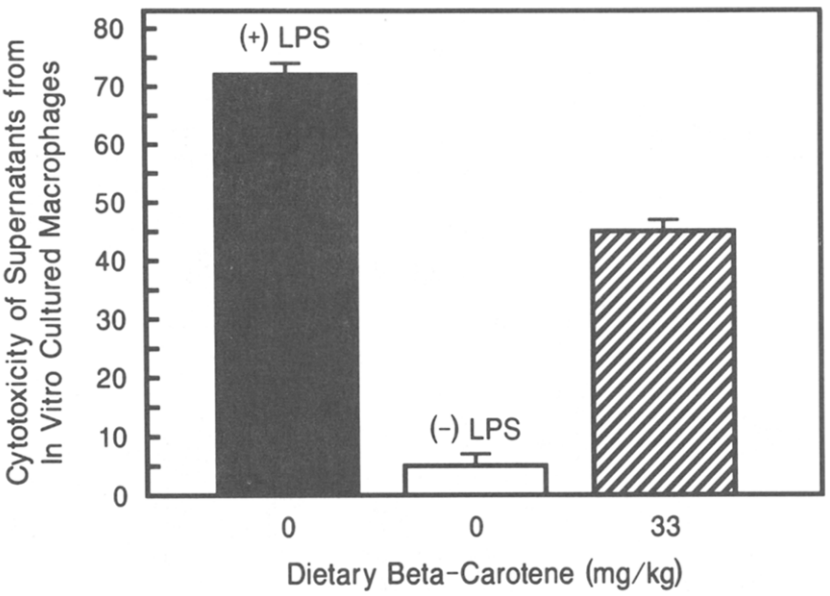
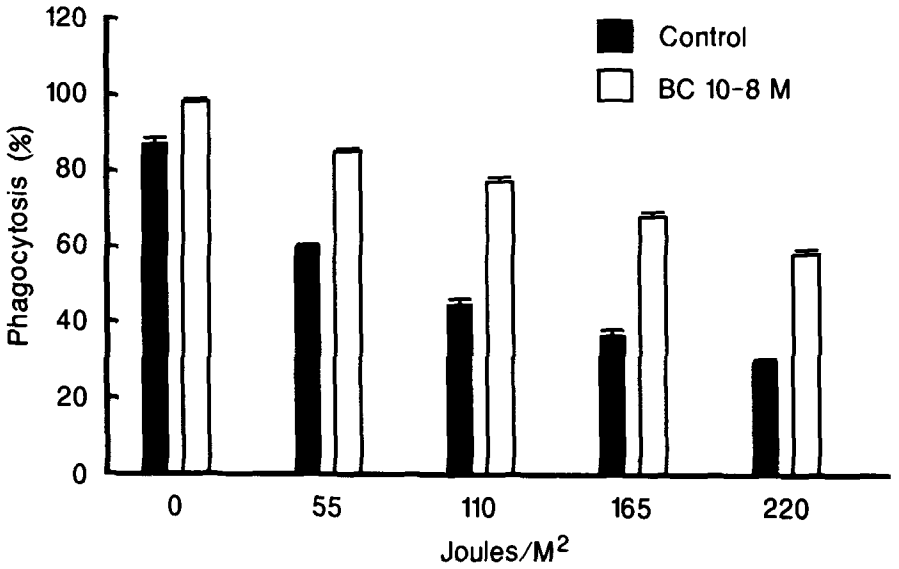


Fig. 4. Cytotoxic activity of supernatants from murine macrophages cultured in vitro with lipopolysaccharides (LPS) for 48 hours. The change in the percent of MTT dye incorporated by L929 tumor cells was assessed after 72 hour incubation with culture supernatants. All the values represent the mean and standard deviation of more than three replicate experiments (37). Mice fed BC and treated with LPS in vitro to get cytokine release as described for human cells (37).

Beta-carotene also enhanced antigen presentation by monocytes.[36] We have observed (37) that beta-carotene increased the ability of monocytes in vitro to produce a novel tumor cytotoxic factor (Fig. 4). It does not seem to be TNF, IL-I, IL-2, or interferon, and may play a role in host defense in vivo. Dietary beta carotene and canthaxanthin yielded mouse monocytes that released enhanced levels of cytotoxic activity in vitro for L-929 leukemia cells, without in vitro stimulation by carotenoids. In addition, the percentage of monocytes (Fig. 2) with markers of activation (Mac2) increased following consumption of a diet with 1% canthaxanthin for 2 months by mice (unpublished data). Recently, we and others have shown that beta-carotene protects against UV-B damage by preventing free radical action and by increasing phagocytosis (38) in vitro (37) (Fig. 5).

The above data suggests that retinoids and carotenoids might act by different pathways to stimulate monocytes. Retinoids appear to act at an early stage of the differentiation process and at early stages of the activation process by improved phagocytosis. On the other hand, carotenoids act at later stages of the activation process primarily as scavengers for oxygen radicals, enhancers of antigen presentation, and inducers for tumor cytocytic factors.



Fig, 5. Alterations of phagocytosis after treatment with ultraviolet irradiation (UV) and beta-carotene (BC) on human monocytes in vitro as described previously (38). Purified human monocytes were incubated with beta-carotene after UV exposure. Phagocytosis was determined using ^{51}Cr-labelled sheep red blood cells. Values are the mean percentages with standard deviations of three or more experiments containing several samples.

Langerhans Cells. Langerhans cells, antigen-presenting macrophage-like cells, have an important role in immune reactions in the skin. Ultraviolet irradiation decreased human Langerhans cell membrane markers such as ATPase staining, expression of OKT6 and HLA antigen (39) after vitamin A treatment for erythrokeratodermia variabilis (40). The surface markers were restored, including OKT6, HLA-Dr and ATPase staining after culturing for 48 hours in vitro (41). Retinol produced an increase in IL1 production and an increase in the density of OKT6, HLA-Dr and ATPase markers on human gingival Langerhans cells. Thus, retinoids seem to have immunostimulatory effects on Langerhans cells, which are important in antigen presentation to T-lymphocytes in the skin.

DISCUSSION

Interest in the potential mechanisms for the anti-cancer effect of retinoids and carotenoids has largely focused on their differentiating capabilities (1,2,4). Vitamin A has inhibitory capabilities against development of certain cancers (42,46), such as reducing the development of skin tumors due to chemical carcinogens (47,48). Vitamin A's marked immunomodulatory effects in animal systems may explain in part its significant

effects on cancer resistance (49,50). In this review we have attempted to highlight recent data on immunomodulation by vitamin A and related compounds (Table 1). These immune changes may play an important role in the anti-cancer effects of retinoids and carotenoids. Further laboratory and clinical studies are warranted in this regard to explain the relationship between immunomodulation and these compounds. We recognize that there are additional parameters which may influence immunomodulation including: (a) chronic deficiency problems; (b) the transportation and biosynthesis of these compounds through binding proteins (51), and (c) receptors for these compounds on various cells which function in cell modulation.

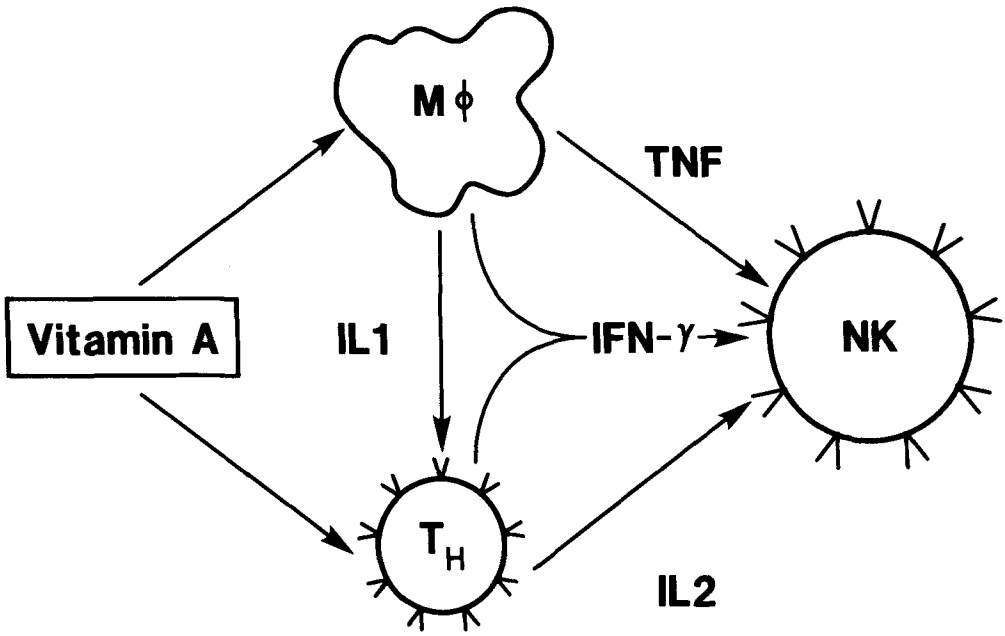


Fig. 6. Diagramatic representation of mechanisms for vitamin A actions on the components of the immune system.

Retinoids and carotenoids appear to have different effects on the immune system. Retinoids act on the differentiation processes of immune cells, increasing mitogenesis of lymphocytes and enhancing phagocytosis of monocytes/macrophages. Recent reports noted that retinoids activate protein kinase C (56), NK cells in vivo (57), and IL2 receptors activate human thymocytes (58). Carotenoids modify the release of some cytokine-like products after activation of lymphocytes and monocytes which may enhance immunosurviellance through activation of NK cells (Fig. 6). They also act as anti-oxidants reducing loss of immunological functions due to the immunotoxic effects of oxide radicals. Thus, it may be possible to exploit immunomodulatory effects of carotenoids for the treatment of specific diseases. For instance, beta-carotene increases NK cells and T-helper cell numbers. Restoring the number of these cells may be useful in acquired immunodeficiency syndromes such as (AIDS) where

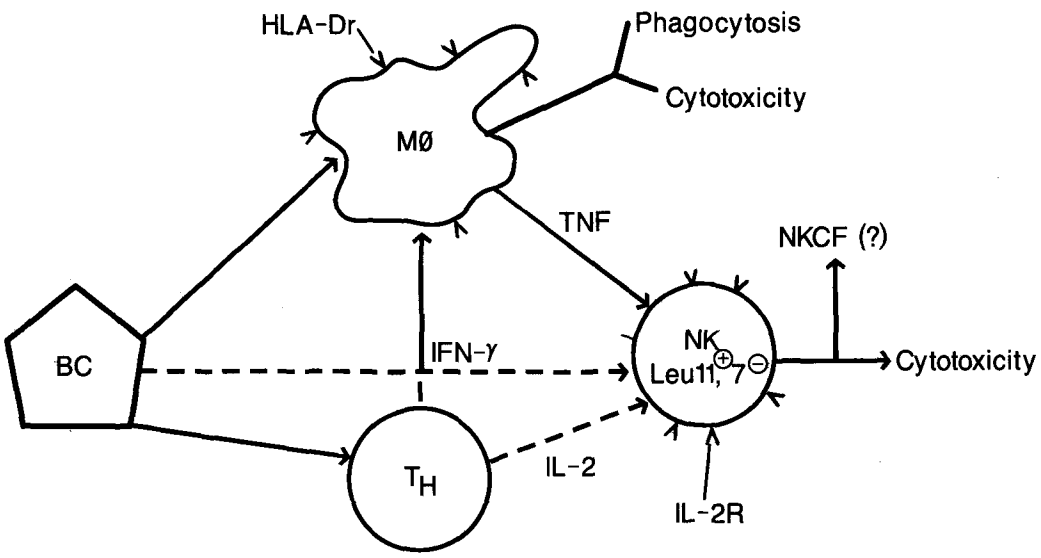


Fig. 7. Emphasis is placed on those potentially providing anti-cancer effects in pro-vitamin A compounds like beta carotene which may activate T-helper cells (TH) directly, or indirectly via interleukin 1 (IL1) produced by activated macrophages (Mo). Carotenoids seem to further extend the activation process to natural killer cells (NK) through elevation of one or more cytokines such as interleukin 2 (IL2), interferon-gamma (IFN-γ), and tumor necrosis factor (TNF).

immune cells are in low numbers and defective in nature (52). In vitro, vitamin A inhibited the replication of AIDS virus (53). Recently, it has been suggested that the AIDS virus persists in macrophages for long periods causing unresponsiveness to lymphokines and providing a favorable environment for enhancement of viral gene expression and dissemination. This may ultimately place the phagocytic system in a vulnerable situation and reduce its ability to protect against opportunistic infectious agents (54). We have shown that vitamin A elevated the percentages of helper cells and activated macrophages during murine retroviral infection in mice (Table 2) (55). Immunostimulation by vitamin A compounds was associated with enhanced survival time (55).

Clinical trials with carotenoids to stimulate activation of helper cells, macrophages and NK cells in AIDS patients would be of great interest due to their low toxicity. Thus immunomodulation may be an exciting tool to stimulate the cellular immune system and to understand the role of these dietary agents in cancer prevention.

TABLE 1

Immunomodulatory Effects of Vitamin A

Cell Type	Compounds	Function or Expression of Markers	Response	References
T-cells	Retinoids	1. $T_3^+ + T_6^-$ thymocyte maturation	increased	20
		2. Mitogenesis	increased	19,21,22
	Carotenoids	1. $CD4^+$ cells (helper)	increased	24
		2. Interferon production	increased	25
B-cells	Retinoids	1. T-dependent antibody production	increased	26
		2. T-independent	inhibited	26
Monocytes/Mo	Retinoids	1. Differentiation	occurred	30
		2. Surface Markers	increased	31
		3. Functions		
		a) Phagocytosis	increased	32,38,
		b) Chemotaxis	increased	32
		c) Cytotoxicity	increased	33,34,35,38
		4. Cytokins		
		a) Interleukin-1	increased	32
		b) Interferon	increased	19
		c) Macrophage inhibitory factor	decreased	19
		5. Enzymes		
		a) Lysozymes	increased	32
		b) Superoxide radicals	increased	32
	Carotenoids	1. HLA-Dr expression	increased	36
		2. Cytotoxicity	increased	37
		3. Phagocytosis	increased	38,
Langerhans Cells	Retinoids	1. OKT6 expression	increased	40,41
		2. HLA-Dr expression	increased	40,41
		3. ATPase staining	increased	40,41
		4. IL-1 production	increased	41
Natural Killer Cells	Retinoids	1. Cytotoxicity (at low concentrations)	increased	27,28,29
		2. IFN-induced cytotoxicity (at high concentrations)	inhibited	25,27

TABLE 2

Effects of dietary retinyl palmitate (RP, 120 units/gram diet) and canthaxanthin (CTX, 1% of diet) on the frequency of lymphocytes and macrophages (Mo) identified with surface markers and activation markers.

Treatment Groups	Percentages of Surface Markers on Spleenocytes				
	Helper cells (L3T4)	IL2-R	MO (Mac-1)	activated MO (Mac-2)	Ia antigen
virus	23.0 ± 2.6	6.3 ± 2.1	8.0 ± 1.0	5.6 ± 2	5.6 ± 5.0
virus + RP	23.0 ± 2.0	18.5 ± 0.5*	17.3 ± 3.0*	7.6 ± 1.1	15.6 ± 1.5*
virus + CTX	29.3 ± 2.5*	ND	39.0 ± 4.6*	9.7 ± 2.0	27.0 ± 4.0*

*Statistical analysis of student 't' test show P values less than 0.05.
ND = not determined, IL2-R = Interleukin 2 receptors.

These markers were detected by flow cytometer after 8 week post LP-BM5 murine leukemia virus infection. Results were presented with mean values and standard deviations of three or more experiments containing 5 mice/group. Modified from Watson et al. (55).

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REFERENCES

1. Lippman SM, Kessler JF, Meyskens FL Jr. Retinoids as preventive and therapeutic anticancer agents (Part I). Cancer Treatment Reports, 1987; 71:391-405.

2. Lippman SM, Kessler JF, Meyskens FL Jr. Retinoids as preventive and therapeutic anticancer agents (Part II). Cancer Treatment Reports, 1987; 71:493-515.

3. Heywood R, Palmer AK, Gresson RLL, Hummler H. The toxicity of beta-carotene. Toxicology, 1985; 36:91-100.

4. Sporn MB. Retinoids and suppression of carcinogenesis. Hospital Practice, 1983; 18:83-98.

5. Vyas D, Chandra RK. In: Nutrition, Disease Resistance and Immune Function. (Watson, R.R. ed.), 1984; p. 325-344, Mercell Dekker, New York.

6. Lotan R. Effects of vitamin A and its analogs on normal and neoplastic cells. Biochem Biophysical Acta, 1980; 605:33.

7. Trinchieri G, Rosen M, Perussia B. Retinoic acid cooperates with tumor necrosis factor and immune interferon in inducing differentiation and growth inhibition of the human promyelocytic leukemic cell line HL-60. Blood, 1987; 69:1218-1224.

8. Dennert G. In: Retinoids and the immune system: Immunostimulation by vitamin A. (Sporn, M.B. ed.), 1984; p. 273, Academic Press, Orlando.

9. Shapiro PE, Edelson RL. In: Retinoids: New trends in research and therapy (Saurat, J.H. ed.), 1985; p. 225, Basel, Karger.

10. Mathews-Roth MM. Antitumor activity of B-carotene, canthaxanthin, and phytoene. Oncology, 1982; 39:33-37.

11. Santamania L, Bianchi A, Arnaboldi A, Andreoni L, Bermond P. Dietary carotenoids block photocarcinogenic enhancement by benzo(a)pyrene and inhibits its carcinogenesis in dark. Experientia, 1983; 39:1043-1052.

12. Olson JA. Carotenoids, vitamin A and cancer. J Nutr, 1986; 116:1127-1130.

13. Ritenbaugh C. Carotenoids and cancer. Nutrition Today, 1987; 22:14-19.

14. Temple NJ, Basu TK. Does beta-carotene prevent cancer? A critical appraisal. Nutr Res, 1988; 8:685-701.

15. Menkes MS, Comstock GW, Vuillemier, JP, Helsin, KJ, Rider, AA, Brookmeyer, R. Serum beta-carotene, vitamins A and E, selenium, and the risk of lung cancer. N Engl J Med, 1986; 315:1250-1254.

16. Schwartz J, Shklar G. Regression of experimental oral carcinomas by local injection of beta carotene and canthaxanthin. Nutr Cancer, 1988; 11:35-40.

17. Krimsky NI, Deneke SM. Interaction of oxygen and oxy-radicals with carotenoids. JNCI, 1982; 69:205-210.

18. Bendich A, Shapiro SS. Effect of B-carotene and canthaxanthin on the immune responses of the rat. J Nutr, 1986; 116:2254-2262.

19. Soppi E, Terhi R, Soppi AM, Toivanen A, Jansen CT. Differential in vitro effects of etretitate and retinoic acid on the PHA and ConA induced transformation suppressor cell induction, and LMIF production. Intern J Immunol Pharmacol, 1982; 4:437-443.

20. Sidell N, Rieber P, Golub SH. Immunological aspects of retinoids in humans. Cell Immunol, 1984; 87:118-125.

21. Abb J, Deinhart F. Effects of retinoic acid on the human lymphocyte response to mitogens. Exper Cell Biol, 1980; 48:169-179.

22. Valone FH, Payan DG. Potentiation of mitogen-induced human T-lymphocyte activation by retinoic acid. Cancer Res, 1985; 45:4128-4131.

23. Prabhala RH, Maxey V, Hicks MJ, Watson RR. Enhancement of the expression of activation markers on human peripheral blood mononuclear cells by in vitro culture with retinoids and carotenoids. J Leuk Biol, 1989; 45:249-254.

24. Alexander M, Newmark H, Miller RG. Oral beta-carotene can increase the number of OKT4 + cells in human blood. Immunology Lett, 1985; 9:221-224.

25. Rhodes J, Stokes R. Interferon induced changes in monocyte membrane. Immunology, 1982; 45:531-536.

26. Sidell N, Famatiga E, Golub SH. Immunological aspects of retinoids in humans. Cell Immunol, 1984; 88:374-381.

27. Lotan R, Dennert G. Stimulatory effects of vitamin A analogs on induction of cell mediated cytotoxicity in vivo. Cancer Res, 1979; 39:55-58.

28. Goldfarb RH, Herberman RB. Natural killer cell reactivity. Immunology, 1981; 45:2129-2135.

29. Sidell N, Famatiga E, Shan H, Golub SH. Immunological aspects of retinoids in humans. III. J Biol Resp Mod, 1985; 4:240-245.

30. Tobler A, Dawson MI, Koeffler HP. Structure and function relationship in normal and leukemic hematopoiesis in vitro. J Clin Invest, 1986; 78:303-309.

31. Ohta M, Furukawa Y, Ide C, Akiyama N, Utakoji T, Miura Y, Saito M. Establishment and characterization of four human monocyte leuckemic cell lines with capabilities of monocyte-macrophage linease differentiation and constitutive productive of IL-1. Cancer Res, 1986; 46:3067-3074.

32. Treschel V, Eveguoz V, Fleisch H. Carotenoid dose level, and protection against UVB skin tumors. Biochem J, 1985; 230:239-344.

33. Moriguchi S, Kohge M, Kishino Y, Watson RR In vitro effect of retinol and 13-cis retinoic acid on cytotoxicity of human monocytes. Nutr Res, 1988; 8:255-264.

34. Moriguchi S, Werner L, Watson RR. High dietary vitamin A (retinyl palmitate) and cellular immune functions in mice. Immunology, 1985; 56:169-177.

35. Katz DR, Drzymala M, Turton JA, Hicks RM, Hunt R, Palmer L, Malkovsky M. Regulation of accessory cell function by retinoids in murine immune responses. Brit J Exper Path, 1987; 68:343-350.

36. Gruner S, Volk AD, Falck P, Baehr RV. The influence of phagocytic stimuli on the expression of HLA-Dr antigens; role of reactive oxygen intermediates. Europ J Immunol, 1986; 16:212-215.

37. Abril ER, Rybski JA, Scuderi P, Watson RR Beta-carotene stimulates human leukocytes to secrete a novel cytokine. J Leuk Biol, 1989; 45:255-261.

38. Schoen DJ, Watson RR. Prevention of UV irradiation induced suppression of monocyte functions by retinoids and carotenoids in vitro. Photochem Photobiol, 1988; 48:659-663.

39. Koulu L, Christer JJ, Viander M. Effect of UVA and UVB irradiation on human epidermal Langerhans cell membrane markers defined by ATPase activity and monoclonal antibodies (OKT6 and anti-Ia). Photodermatology, 1985; 2:339-346.

40. Van der Schroeff JG, Ruiter DJ, Bots GTAM. Epidermal Langerhans cells in erythrokekratoderma variables. Arch Dermat Res, 1982; 274:339-348.

41. Walsh JJ, Seymore GJ, Powell RN. The in vitro effects of retinol on human gingival epithelium. J Invest Dermatol, 1985; 85:501-506.

42. Meyskens FL, Jr. In: Vitamins, Nutrition and Cancer (Prasad, A. ed.), 1984; p. 266, Basel, Karger.

43. Hennekeng CH. Micronutrients and cancer prevention, N Engl J Med, 1986; 315:1288-1289.

44. Sporn MB, Roberts AB. Role of retinoids in differentiation and carcinogenesis. Cancer Res, 1983; 43:3034-3040.

45. Goodman DS. In: Retinoids (Sporn, M.B., Roberts, A.B., and Goodman, D.S., eds.), 1984; p. 41, Academic Press, New York.

46. Ames BN. Dietary carcinogens and anticarcinogens. Science, 1983; 221:1256-1262.

47. Gensler HL, Watson RR, Moriguchi S, Bowden GT. Effects of dietary retinyl palmitate or 13-cis retinoic promotion of tumors in mouse skin. Cancer Res, 1987; 47:967-970.

48. Verma AK, Duvick L, Ali M. Modulation of mouse skin tumor promotion by dietary 13-cis RA and DFMO. Carcinogenesis, 1986; 7:1019-1023.

49. Watson RR, Rybski JA. Immunological response modification by vitamin A and other retinoids. in Nutrition and Immunology (Chandra, R., ed), 1988; pp. 87-99, Alan R. Liss, New York.

50. Malkovsky M, Edwards AJ, Hunt R, Palmer L, Medawar PB. T-cell mediated enhancement of host-versus-graft reactivity in mice fed a diet enriched with vitamin A acetate. Nature (London), 1983; 302:338-340.

51. Goodman DS, Huang HS, Shiraton T. Mechanism of biosynthesis of vitamin A from carotenoids. Biol Chem, 1966; 241:1929-1932.

52. Spickett GP, Dalgleish AG. Cellular immunology of HIV-infection. Clin Exper Immunol, 1988; 71:1-7.

53. Nakashima H, Harader S, Yamamoto N. Effect of retinoic acid on the replication of human AIDS virus in HIV-1^+ MT-4 cells. Med Microbiol Immunol, 1987; 176:189-198.

54. Roy S, Wainberg MA. Role of mononuclear phagocyte system in the development of AIDS. J Leuk Biol, 1988; 43:91-97.

55. Watson RR, Yahya MD, Danban HR, Prabhala RH. Enhanced survival by vitamin A supplementation during murine retrovirus infection. Life Sci, 1988; 43: xii-xvii.

56. Isakov N. Regulation of T-cell-derived protein kinase activity by vitamin A derivatives. Cell Immunol, 1988; 115:288-298.

57. McKerrow KJ, Mackie RM, Lesko MJ, Pearson C. The effect of oral retinoid therapy on the normal human immune system. Brit J Dermatol, 1988; 119:313-320.

58. Sideh N, Ransdell F. Retinoic acid upregulates interleukin-2 receptors on activated human thymocytes. Cell Immunology, 1988; 115:299-309.

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