4. ヘルパーT(CD4)およびサプレッサーT(CD8)細胞割合、CD4/CD8 比

ヘルパーT(CD4)細胞割合は、コントロール群と比較し 450 mg/kg α-Toc 添加食群において低い傾向を認めた。サプレッサーT(CD8)細胞割合については、コントロール群と各 VE 添加食群との間に有意な差異を認めなかった(図 5)。また、CD4/CD8比については、コントロール群と比較し 450 mg/kg α-Toc 添加食群においてやや低い傾向を認めた(図 6)。

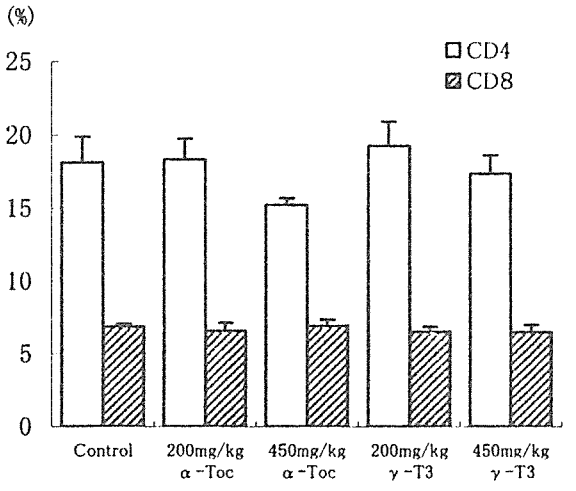

図 5 細胞割合

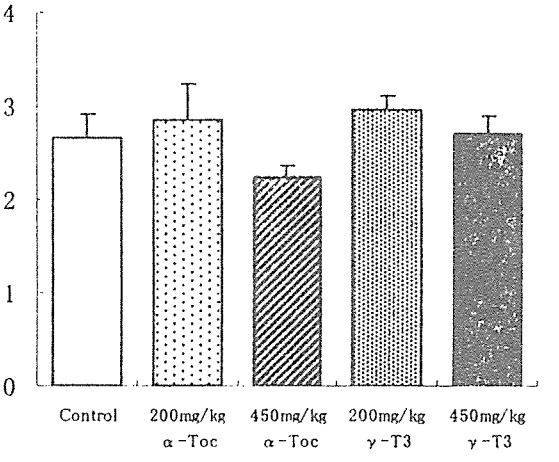

図 6 CD4／CD8 比

5. Con A 刺激に伴う脾臓リンパ球からの IL-4 産生

Con A 刺激に伴う脾臓リンパ球からの IL-4 産生は、コントロール群とα-Toc 添加食群との間に有意な差異を認めなかった。しかし、γ-T3 添加食群では IL-4 産生がコントロール群と比較し高い傾向を認めた(図7)。

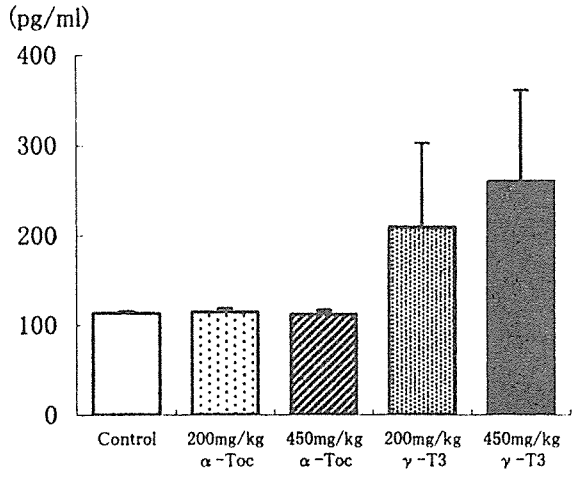

図 7 Con A 刺激に伴う脾臓リンパ球からの IL-4 産生

考察

本研究では、OVA 誘発食物アレルギーモデルマウスを用いて食物アレルギー発症に対する高 VE 食投与の影響について検討した。

その結果、食物アレルギー発症に伴い高値を示す血清総 IgE および OVA 特異的 IgE 濃度の上昇が、高 α-Toc 食摂取により抑制されることを認めた。このことは、鼻アレルギーモデルマウスを用いた Zheng らの知見[1]と一致する。また、今回はγ-T3 についても検討を行ったが、明らかな IgE 産生の抑制を認めなかった。図 8 に要約したように、IgE 産生に至るまでにはマクロファージ(MΦ)、ヘルパーT(Th)細胞、B 細胞ならびに形質細胞の関与が知られている。今回の研究では、α-Toc 添加食群において PHA および LPS 刺激に対する脾臓リンパ球幼若化能および Th 細胞割合の低下を認めた。このことから、高 α-Toc 食摂取により Th 細胞および B 細胞機能が低くなっているために IgE 産生が抑制されたものと考えられる。また、脾臓リンパ球からの IL-4 産生については、α-Toc の影響を認めなかったことから、IgE 産生の抑制とは関連しないことが示唆される。VE のアレルギー抑制機序として、α-Toc が直接的に IgE の産生を抑制すること[5]や犬の肥満細胞腫において *in vitro* の α-Toc 添加によりヒスタミンおよびプロスタグランジン D_2 (PGD_2) の放出が抑制されること[6]などが報告されている。今後さらにマスト細胞からのヒスタミン遊離など VE による抗アレルギー作用の詳細なメカニズムを解明していく必要がある。

以上、本研究により、高 α-Toc 食摂取により OVA 誘発食物アレルギー発症に伴う IgE 産生が抑制されることを認め、そのことが Th 細胞および B 細胞幼若化能および Th 細胞割合の低下と関連することが示唆された。

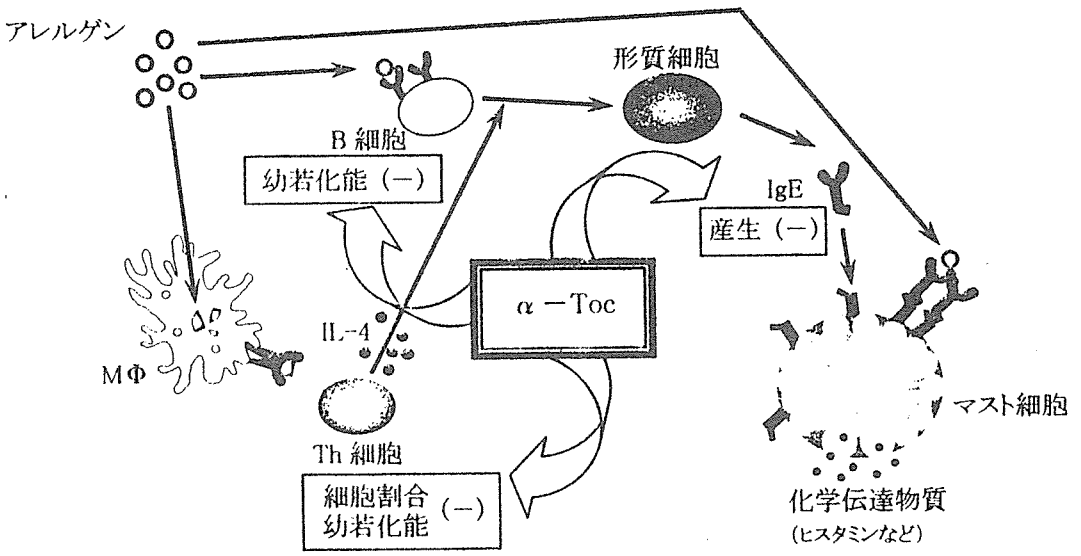

図 8 α-トコフェロールによる食物アレルギーの発症抑制メカニズム

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6) Gueck T., Aschenbach J. R. and Fuhrmann H., Influence of vitamin E on mast cell mediator release., *Vet. Dermatol*, 13, 301-305 (2002)

5

Nutrients to Stimulate Cellular Immunity: Role in Cancer Prevention and Therapy

Satoru Moriguchi,
Satoe Yamashita,
and Eiji Shimizu

Introduction

Nutrition plays an important role in two respects: one is the inhibitory factor for carcinogenesis via its immunoenhancing effects and the other is the determinant for prognosis of cancer patients. In this chapter, the relationship between the malnourished status of cancer patients and immune responses, and the beneficial effect of nutritional support using enteral and parenteral feeding are described first. The rest of this chapter discusses the immunomodulating action of each nutrient, such as fat, protein (amino acid), vitamins, and minerals, in cancer patients or animals with tumors. Finally, some foods that promote health are described in regard to their action on host immunity.

Nutritional Status in Cancer Patients and Immunity

Not only cancer itself but also conventional approaches to therapy for cancer such as chemotherapy, operative therapy, and radiation therapy are known to produce profound changes in host immunity. The effects of chemotherapy upon immune responses are related both to the dosage and duration of therapy and are readily reversible. Operative therapy likewise suppresses both humoral and cell-mediated immunity for 2 to 3 weeks, as manifested by in vitro and in vivo tests of these functions. And radiation therapy induces the decrease of host immune responses for more prolonged periods of time over 10 years. One of the factors inducing the decrease of host immunity following cancer and its therapies is malnutrition. Nutritional status affects both limbs of the immune system. Enteral and parenteral (intravenous hyperalimentation) nutrition are safe and effective methods for correcting deficits in cancer patients. In the malnourished gastric cancer patient, one week of pre- or postoperative parenteral nutrition significantly increased natural killer cell (NK) activity, T-helper proportion, T-helper/T-suppressor ratio, and total T lymphocyte count (Yan 1990). This evidence suggests that perioperative nutrition support can improve the immunocompetence of gastric cancer patients. The other study has shown that a marked depression of NK activity of peripheral blood mononuclear cells (PBMC) was observed in malnourished cancer patients with moderate protein-calories malnutrition, but

not in well-nourished cancer patients nor in the healthy controls (Villa et al. 1991). Although the decreased NK activity in this study was restored to normal by rIL-2, but not by α-rIFN, the ability to produce IL-2 in vitro in each cancer patient did not correlate with NK activity. This evidence suggests that malnutrition, rather than malignancy, plays a major role in the immune dysfunction of cancer patients. When compared with immune functions after operation in patients with esophageal or gastric cancer, ConA- and PHA-stimulated lymphocyte proliferation decreased significantly 7 days after esophagectomy, but was unchanged in the patients receiving gastrectomy (Tashiro et al. 1999). Since serum cortisol level was significantly increased in patients after surgery, stress response may induce in part the suppression of immune functions. In patients with hepatocellular carcinoma, the phagocytic and bactericidal activities of neutrophils and the percentage of NK cells were significantly reduced (Iida et al. 1999). In particular, the phagocytic and bactericidal activities of neutrophils were low in patients with poor nutritional status compared to those with a good nutritional status. Taken together, nutritional supplementation such as enteral and parenteral nutrition for malnourished cancer patients appears to be useful for preventing further decrease of host immune functions.

It is a well-known fact that food restriction results in longer longevity than ad libitum feeding (Sheldon et al. 1995). Some previous animal studies have found that food restriction has a beneficial effect on the incidence of cancer. Using mice treated with 3-methylcholanthrene (MC), 40% dietary restriction caused a great inhibition of tumor incidence at 114 days after treatment(Konno et al. 1991). Since the optimum duration and degree of dietary restriction cause the enhancements of both splenic lymphocyte proliferation and phagocytic activity of alveolar macrophages in rats (Fig. 5.1), the decreased incidence of cancer may be related to the changes of host immune functions following dietary restriction. In fact, the above study has shown that dietary restriction causes a marked increase of the proportion of Thy1.2+, L3T4+T cells, and increased T cell responses against ConA and IL-2 in MC-treated diet-restricted mice. The increase of host immune functions might be one of the major causes for the reduction of tumor occurrence by dietary restriction. In conclusion, caution should be employed in the nutritional manipulation of malnourished cancer patients.

Role of Lipids in Cancer Prevention and Immunity

There is in vitro and in vivo evidence to suggest that dietary lipids play an important role in modulating immune functions. It is known that diets high in polyunsaturated fat, relative to diets high in saturated fat, are more immunosuppressive and are better promoters of tumorigenesis (Vitale and Broitman 1981). It has been also shown that rats fed diets high in lipid and cholesterol develop more 1,2-dimethylhydrazine (DMH)-induced bowel tumors than those fed diets low in lipid or without cholesterol. When rats were fed diets containing 20% safflower or coconut oil, with or without cholesterol (1%) and cholic acid (0.3%), for 35 weeks and concomitantly given DMH, the suppression of PHA response was observed in the polyunsaturated fat (safflower oil) diet group compared with the saturated fat (coconut oil) diet group (Kraus et al. 1987). And the addition of cholesterol to

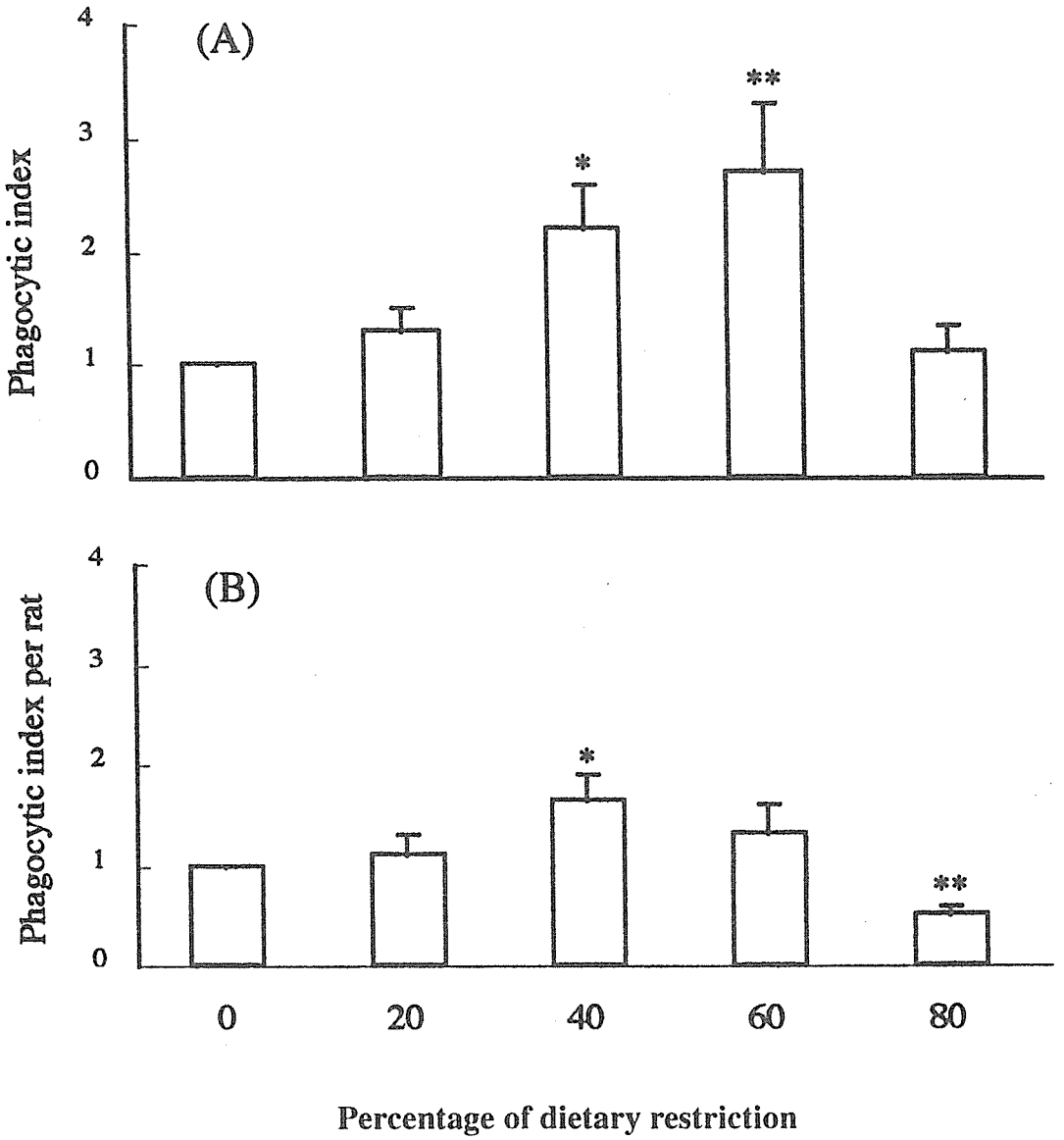

Figure 5.1. Phagocytic activity of alveolar macrophages (AM) (2 × 105) in rats (A) or AM per rat (B) fed mildly or moderately restricted diets (20 to 80% restriction to control) for 2 weeks. Phagocytic index was calculated by assigning 1 to phagocytic activity of control group and comparing this to phagocytic activity of other groups. Values are means ± SD of triplicate cultures; significantly different from controls (*P < 0.05, **P < 0.001). (Reproduced from J. Nutr. Sci. Vitaminol., 35; Moriguchi, S., Toba, M. and Kishino, Y., Effects of dietary restriction on cellular immunity in rats, 49–59. Copyright 1989, with permission from the Center for Academic Publications Japan)

either the polyunsaturated or saturated fat diet diminished PHA response, to a lesser degree, of T lymphocytes from rats fed these diets. However, natural killer (NK) cell activity was unaffected by either the difference of dietary fat or cholesterol. The other study has shown that the splenic lymphocyte transformation response induced by ConA, PHA, or pokeweed mitogen is significantly depressed in the rats fed 24% corn oil (vehicle-treat-

ed) and in the DMH-treated rats fed 5% fat compared with the vehicle-treated rats fed 5% fat (Locniskar et al. 1986). This study has also found that splenic NK cell cytotoxic activity was not significantly affected by dietary fat, DMH treatment, or tumor development. On the other hand, it has been found that corn oil administered by oral gavage retards mononuclear cell leukemia proliferation, which is mediated at least in part by enhancing immune competence (Hursting et al. 1994).

As described previously in this chapter, the beneficial effect of early postoperative enteral nutrition enriched with not only arginine and RNA but also omega-3 fatty acids was found in 78 patients undergoing curative operations for gastric or pancreatic cancer (Braga et al. 1996). Since prealbumin concentration, retinol-binding protein (RBP) concentration, delayed hypersensitivity responses, phagocytic ability of monocytes, and concentration of interleukin-2 (IL-2) receptors had recovered more in the patients receiving the enriched enteral solution, early enteral feeding is likely to induce the recovery of both their nutritional and immunological status quicker than those supported with standard enteral diet or total parenteral nutrition (TPN). The recent study has also shown that the supplementation of eicosapentaenoic acid (EPA) with soybean oil emulsion significantly improved the lymphocyte proliferation and natural killer cell activity compared with the group receiving only soybean oil emulsion (Furukawa et al. 1999). Furthermore, the other study was conducted to investigate the effect of immunological effects of three TPN regimens such as calories derived solely from glucose and a half of total calories derived from lipid emulsion (one as long-chain triglycerides and the other containing half the fat as long-chain triglycerides and a half as medium-chain triglycerides) in patients undergoing preoperative parenteral nutrition. This study has shown that NK activity and lymphokine-activated killer (LAK) activity were significantly higher after TPN with long-chain and middle-chain triglyceride solutions and a significant fall in LAK activity occurred after TPN with long-chain triglyceride solution (Fig. 5.2) (Sedman et al. 1991).The design of TPN regimens is also an important factor for cancer patients to improve or maintain their immune functions.

Role of Protein or Amino Acids in Cancer Patients and Immunity

As described above, nutritional status is the most important determinant in the prognosis for cancer patients. It is well accepted that protein-calorie malnutrition impairs host immunity with particular detrimental effects on the T-cell system, resulting in increased opportunistic infection and increased morbidity and mortality in hospitalized patients including cancer patients (Daly et al. 1990). Levels of vitamins A and E, having a potent enhancing effect on host immune functions and being low in tumor bearing animals, decreased further when maintained in the restricted diet without soybean, but were raised to normal following addition of soybean in the diet (Mukhopadhyay et al. 1994). As soybean protein has high arginine content, the enhancing effect of soybean on immune functions in animals fed the restricted diet may be in part due to arginine. In fact, there are many reports showing that arginine has an immunoenhancing effects and an inhibitory

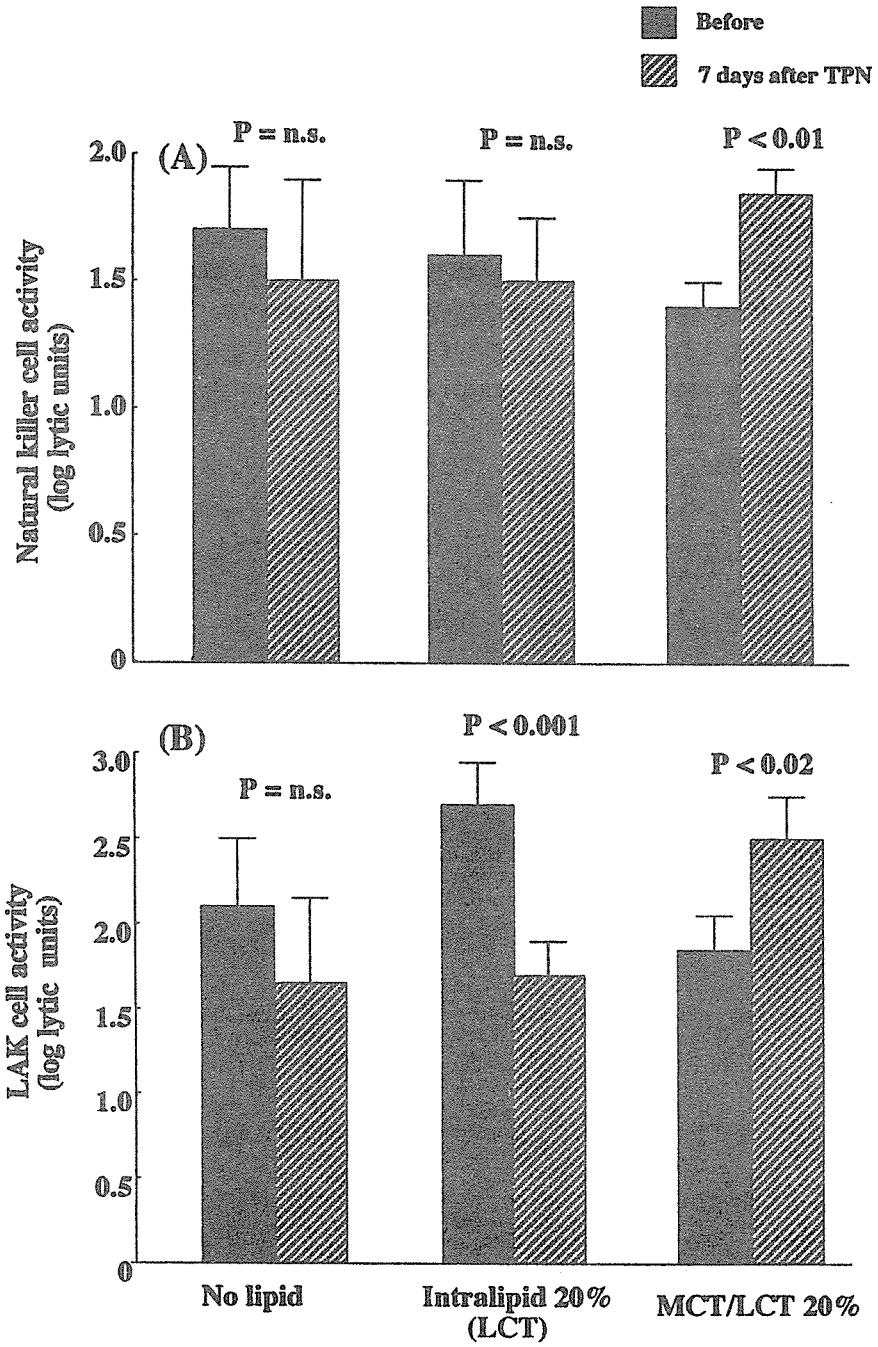

Figure 5.2. Changes in spontaneous natural killer cell activity (A) and the capacity to induce lymphokine-activated killer (LAK) cells in response to interleukin-2 (B) before and 7 days after total parenteral nutrition (TPN) with each of the three TPN regimens. Histograms denote means ± SEM of log-transformed data. MCT/LCT , medium-chain triglycerides/long-chain triglycerides. (Reproduced from Br. J. Sur, 78; Sedman, P. C., Somers, S. S., Ramsden, C. W., Brennan, T. G., and Guillou, P. J., Effects of different lipid emulsions on lymphocyte functions during total parenteral nutrition, 1396–1399. Copyright 1991, with permission from Butterworth-Heinemann Ltd.)

effect on tumor growth and metastasis. In vitro incubation with arginine induced threefold increase of NK cell activity of human PBL and 1.5-fold increase of human monocyte-mediated cytotoxicity (Fig. 5.3) (Moriguchi et al. 1987). Production of tumor cytotoxic factor from human monocytes also significantly increased after in vitro incubation with arginine. This evidence suggests that arginine action against tumor cells is due to not only the enhancement of host immune functions such as NK activity and human monocyte cytotoxicity but also to increased production of cytokines having the direct effect on tumor cells. Using arginine-enriched amino acids solution, growth and metastases of Yoshida sarcoma were suppressed (Tachibana et al. 1985). Since arginine supplementation enhanced the phagocytic activity of rat alveolar macrophages, the authors concluded that

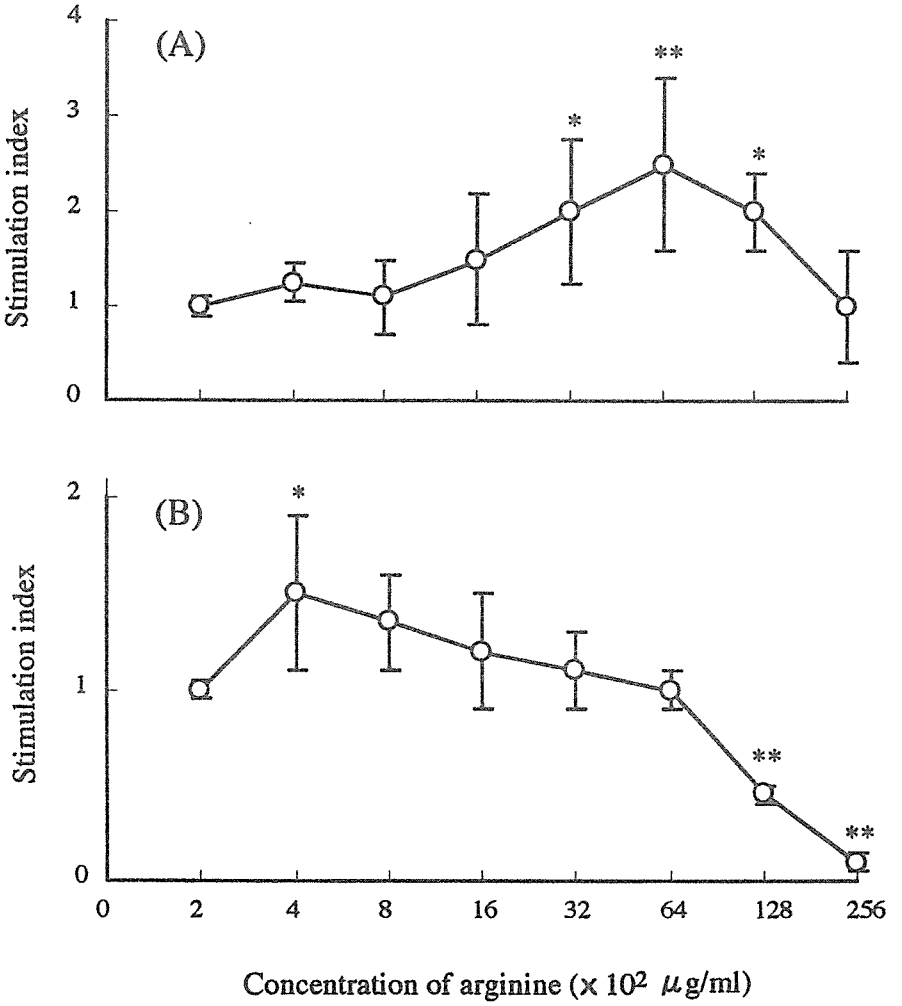

Figure 5.3. Natural killer (NK) cell activity (A) and monocyte cytotoxicity (B) after incubation with various concentrations of arginine for 48 hours. Bars are means ± SD of triplicate cultures and compared with that of control culture (2×10^2 μg/ml of arginine). NK activity and percent cytotoxicity of monocytes in control culture are 22.0 ± 1.6% and 11.0 ± 0.8 %, respectively; significantly different from control culture (*$P < 0.05$, **$P < 0.01$). (Reproduced from Nutr. Res., 7; Moriguchi, S., Mukai, K., Hiraoka, I., and Kishino, Y., Functional changes in human lymphocytes and monocytes after in vitro incubation with arginine, 719–729. Copyright 1987, with permission from Elsevier Science)

the suppressive effect of arginine-enriched solution on tumor growth and metastases may be due to its activation of the immunologic system. Some of the clinical studies and animal studies were designed to evaluate the effect of arginine plus other nutrients such as glutamine, RNA, omega-3 fatty acid, and ornithine 2-oxoglutarate on host immune response (Gianotti et al. 1999, Chuntrasakul et al. 1998, Kemen et al. 1995).

Supplemented diet or enteral diet has a beneficial effect on host immune functions. Recently, it has been found that arginine is a substrate for nitric oxide showing various physiological activities such as the regulation of arterial smooth muscle, blood pressure, and immune functions (Palmer et al. 1987, Haynes et al. 1993, Ding et al. 1988). On the other hand, it has been reported that the expression of adhesion molecule CD44 is closely associated with the degree of metastasis of tumors (Sikorska et al. 2002, Lakshmi et al. 1997). In fact, the higher metastatic B16 melanoma cells showed the higher expression of CD44 as shown in Figure 5.4 (Moriguchi et al. 2002). In addition, the expression of CD44 was significantly suppressed following in vitro incubation with SIN-1, spontaneously generating NO (Fig. 5.5), which resulted in the decreased lung metastases of B16 melanoma in mice fed the high arginine diet. These results suggest that arginine has an inhibitory effect on tumor growth and metastases via two different mechanisms, such as immunoenhancement and depressed expression of adhesion molecule CD44.

The prolonged use of total parenteral nutrition provokes mucosal atrophy of the small intestine (Grant and Snyder 1988), which is related to the lack of glutamine in standard currently available parenteral solutions. Because glutamine is poorly soluble and instable, it has been not generally used as one of the amino acids in parenteral nutrition. However, glutamine is a nutrient necessary for the intestinal mucosal metabolism as a major oxidative fuel. Alanylglutamine, glutamine-containing dipeptide, was found as a source of free glutamine in parenteral nutrition (Furst et al. 1989). On the other hand, although free glutamine is highly consumed by rapidly proliferating tumor cells, it was not clearly known whether tumor growth rate was increased by intravenous supplementation of alanylglutamine. In addition, it is known that glutamine is preferentially used for the provision of fuels in proliferating lymphocytes (Ardawi and Newsgolme 1982) and macrophages (Newsholme and Newsholme 1989). A study was undertaken and evaluated the changes of tumor volume and weight, and cellular immune response following the administration of an alanylglutamine-enriched solution. As a result, in vivo administration of alanylglutamine did not accelerate the growth of transplanted Yoshida sarcoma cells as measured by changes in the weight and volume (Kweon et al. 1991). And the addition of alanylglutamine to culture medium showed a significant increase in phagocytic activity of alveolar macrophages and in blastogenic response of splenocytes. These results suggest that alanylglutamine infusion does not stimulate tumor growth due to maintenance of some immunoenhancing effects by glutamine liberated from alanylglutamine in tumor-bearing hosts.

Role of Vitamins in Cancer Prevention and Immunity

Vitamin A is a nutrient having the most impact on both tumor incidence and growth and host immune system. Continuous administration of vitamin A and its derivatives

(retinoids) has been shown to prevent cancer of the skin (Verma et al. 1982), lung (Saffiotti et al. 1967), bladder (Moon et al. 1982), and breast (Moon et al. 1983) in experimental animals exposed to carcinogens. Epidemiological results also suggest that dietary retinoids may be chemopreventive to some forms of cancer in humans as well (Wald et al.

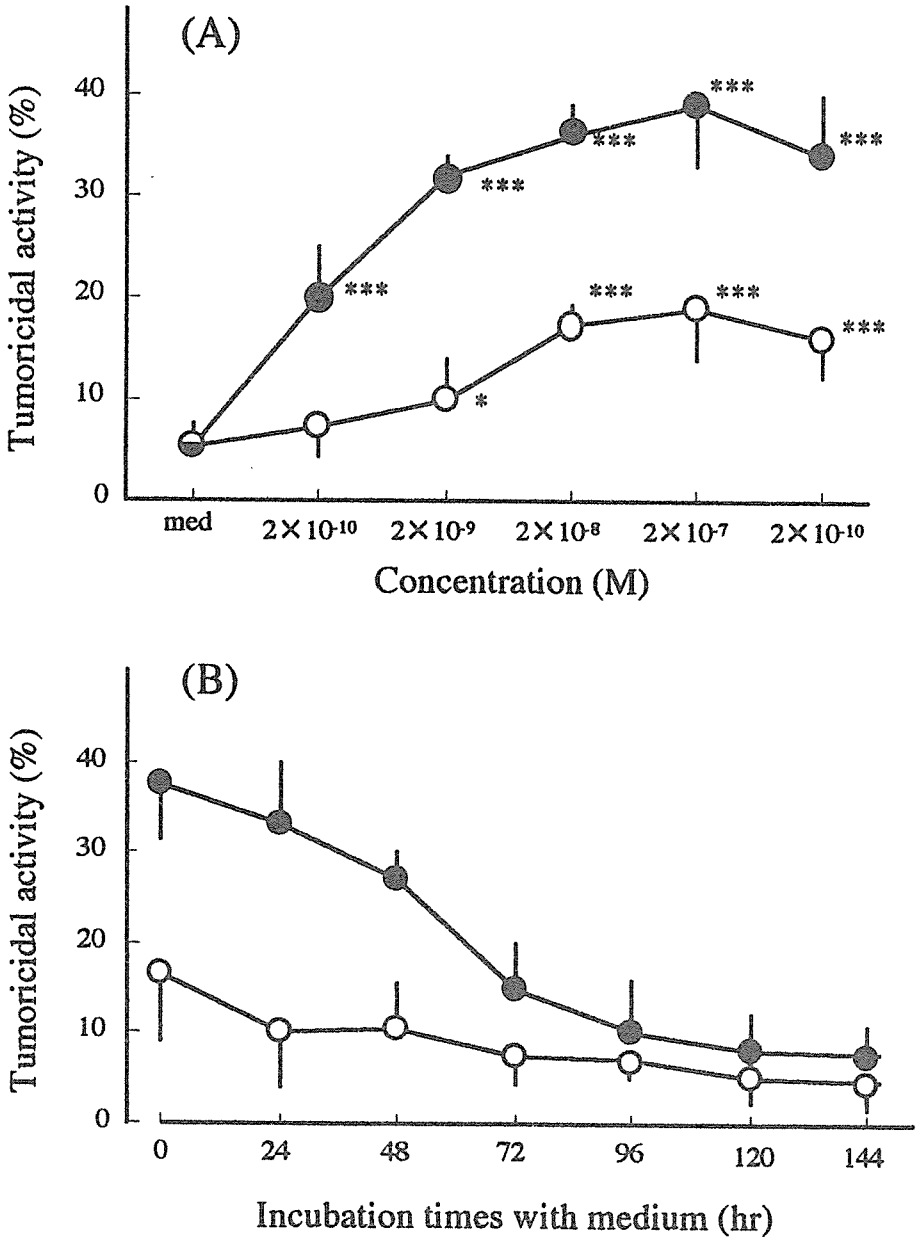

Figure 5.4. Tumoricidal activity of human monocytes treated in vitro with various concentrations (2×10^{-10} to 2×10^{-6} M) of beta-carotene or beta-carotene encapsulated in liposomes for 24 hours (A) and maintenance of the tumoricidal state of human monocytes after in vitro incubation with 2×10^{-7} M of beta-carotene or beta-carotene encapsulated in liposomes (B). Values are means ± SD for triplicate cultures; significantly different from cultures with medium containing 0.2% ethanol (*P < 0.05, ***P < 0.001). (Reproduced from Nutr. Res., 10; Moriguchi, S., and Kishino, Y ., In vitro activation of tumoricidal properties of human monocytes by beta-carotene encapsulated in liposomes, 837–846. Copyright 1990, with permission from Elsevier Science)

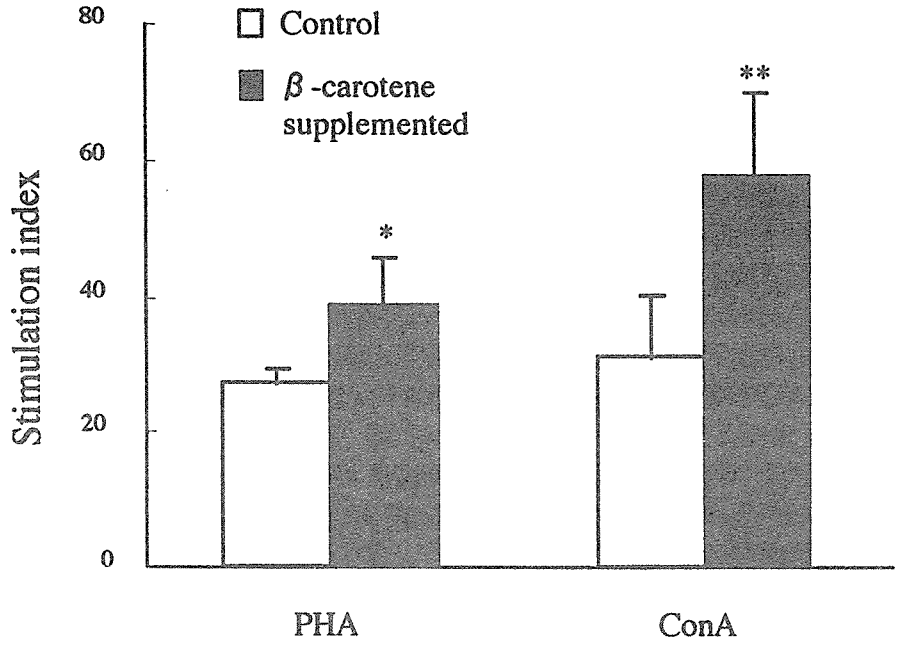

Figure 5.5. Proliferation of peripheral blood lymphocytes with PHA or ConA in control and beta-carotene supplemented subjects. Values are means ± SD; significantly different from control subjects (*P < 0.05, **P < 0.01). (Reproduced from Nutr. Res., 16; Moriguchi, S., Okishima, N., Sumida, S., Okamura, K., Doi, T., and Kishino, Y., Beta-carotene supplementation enhances lymphocyte proliferation with mitogens in human peripheral blood lymphocytes, 211–218. Copyright 1996, with permission from Elsevier Science)

1980, Kark et al. 1981). However, the toxicity of vitamin A precludes its use as a form of cancer prevention. The development of new vitamin A derivatives having low toxicity and high chemopreventive activity is required. The effect of selected doses of dietary retinyl palmitate and 13-*cis*-retinoic acid has been measured by using mouse skin papilloma promotion by 12-*O*-tetradecanoylphorbol-13-acetate (TPA). Dietary retinyl palmitate yields a dose-dependent inhibition of the number and weight of tumors, whereas dietary 13-*cis*-retinoic acid resulted in a decrease of weight but not in number of tumors (Gensler et al. 1987). This result suggests that retinyl palmitate inhibits both incidence and growth of tumors, whereas 13-*cis*-retinoid acid inhibits not the incidence of tumors but tumor growth. Using the same dietary regimens, the high retinyl palmitate diets significantly increased phagocytic ability and tumoricidal activity of peritoneal macrophages and mitogenesis of splenocytes and thymocytes in mice (Moriguchi et al. 1985). This evidence suggests that high retinyl palmitate diets may cause activation of both peritoneal macrophages and lymphocytes. Furthermore, in nude mice, defecting thymus gland development and lacking functional mature T lymphocytes, retinyl palmitate diets significantly stimulated phagocytosis of peritoneal macrophages only at the highest level. T-cell-dependent mitogens did not also cause significant mitogenesis in any dietary group, while lipopolysaccharide (LPS), a B-cell mitogen, did (Watson and Moriguchi 1989). These results suggest that mature T cells may be needed for retinyl palmitate to produce normal activation of macrophages, except at very high retinyl palmitate levels. As the in vitro

study showed that both retinoids and carotenoids at higher concentrations have inhibitory effects on human lymphocyte functions, the use of vitamin A or its derivatives for chemoprevention and therapeutic trials for cancer patients should be carefully considered in its design.

Beta-carotene is one of the carotenoids, which are pigments contributing to the yellow, orange, and/or red coloration in vegetables and fruits. Epidemiological studies have demonstrated that a high intake of food rich in beta-carotene is associated with reduced risk of certain types of cancers, especially lung cancer (Le Marchand et al. 1989). Since other carotenoids lacking provitamin A activity had the similar anticancer effect as that of beta-carotene, it has been suggested that the anticancer effects of beta-carotene is not due to its provitamin A activity. Thus, the anticancer and antibacterial effects of beta-carotene are considered to be due to not provitamin A functions but antioxidant and immunomodulatory functions (Bendich and Shapiro 1986). Proliferation of peripheral blood lymphocytes with PHA or ConA was 1.4- to 1.9-fold higher in the beta-carotene supplemented group compared to the control group, whereas there was no significant difference in NK cell activity between both groups (Fig. 5.6) (Moriguchi et al. 1996). In addition, the study on in vitro effect of beta-carotene (beta) and beta-carotene encapsulated in liposomes (L + beta) on tumoricidal activity of human monocytes has found that the use of liposomes with beta-carotene could induce higher tumoricidal activity of human monocytes following short-term incubation and incubation with lower concentration compared to those of beta-carotene (Fig. 5.7) (Moriguchi and Kishino 1990). Since many other reports support the action of beta-carotene against inhibition of tumorigenesis and tumor cell growth (Kune et al. 1989), and the enhancement of immune responses (Bendich 1989), it is believed that beta-carotene is a nutrient for improving cancer patients and aged people showing decreased cellular immunity. Other fat-soluble vitamins, D and E, are also known to have both inhibitory effects on tumor incidence and growth (Mehta and Mehta 2002, Yu et al. 2002) and enhancing effects on host immune response (Lemire 2000, Moriguchi and Muraga 2000).

Water-soluble vitamins B_6 and C are also known to have the immunoenhancing effects. In the experiment using athymic nude mice, vitamin B_6 supplementation caused increased response of B lymphocytes with lipopolysaccharide (LPS), but did not inhibit the development of human malignant melanoma (M21-HPB) xenografts (Gebhard et al. 1990). This evidence suggests that tumor inhibition by high dietary vitamin B_6 may be mediated by T-lymphocyte-dependent mechanisms. Vitamin C is also an essential nutrient playing a role in protecting against carcinogenesis. As one of the inhibitory actions of vitamin C against carcinogenesis, the enhancement of cellular immunity is involved (Glatthaar et al. 1986). However, when desiring stable immunoenhancement, a daily high-level intake of vitamin C (> 1000 mg/day) is needed (Anderson et al. 1980).

Role of Minerals in Cancer Prevention and Immunity

Selenium (Se) is an essential nutritional factor with a chemopreventive potential. An inverse correlation between cancer incidence and dietary intake of Se has been well estab-

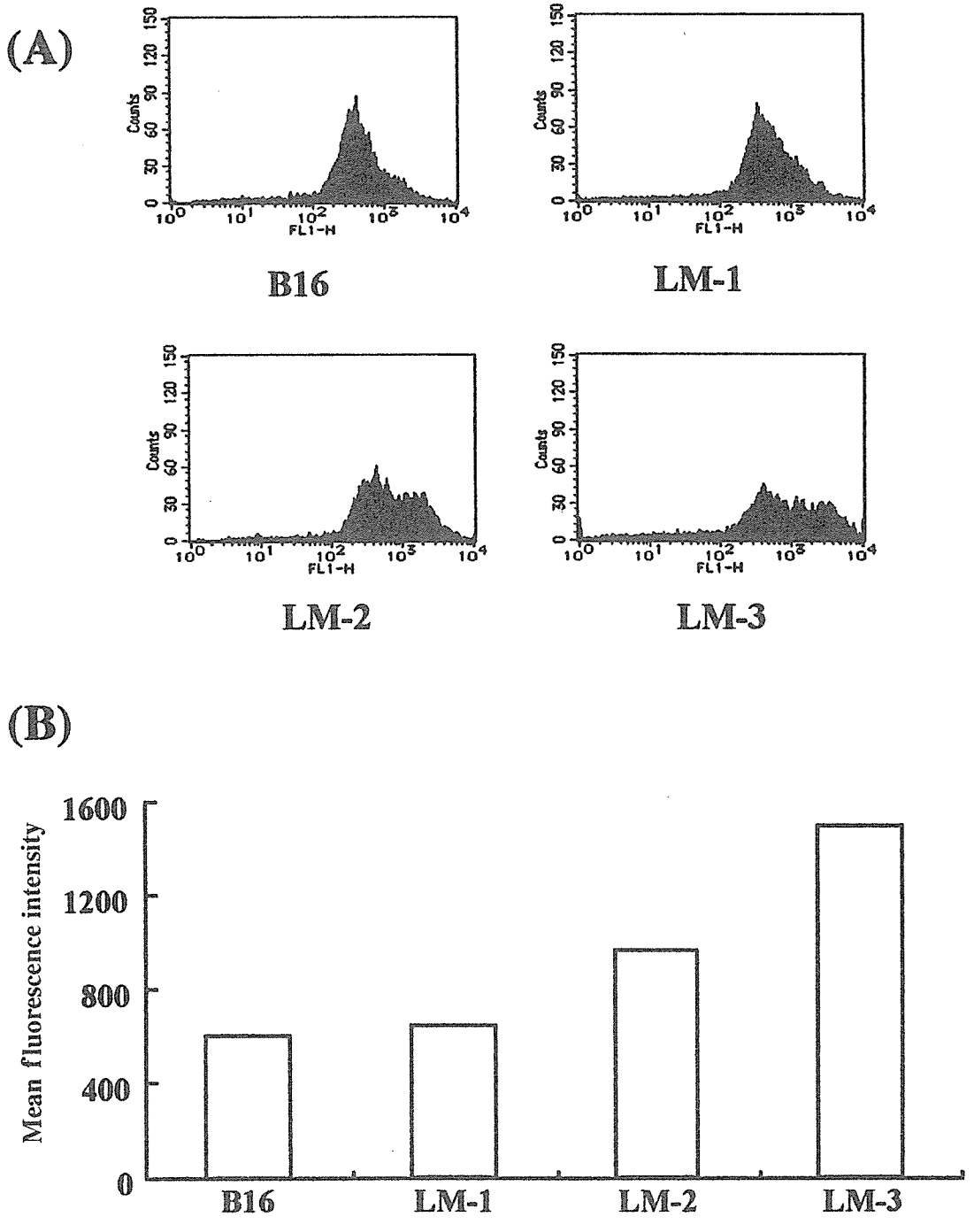

Figure 5.6. Expression of adhesion molecule, CD44 in B16 melanoma with various degrees of lung metastatic ability in male C57B1/6 mice. B16 melanoma cells with various degrees of lung metastatic ability were isolated from the lungs of mice. B16 melanoma cell lines in order of frequency of lung metastasis are LM-3, LM-2, LM-1, and B16. Distribution of melanoma cells with different fluorescence intensity (A) and mean fluorescence intensity in each melanoma cell line (B) are indicated. As shown in both figures, LM-3 cells having the high ability of lung metastasis showed the highest expression of CD44.

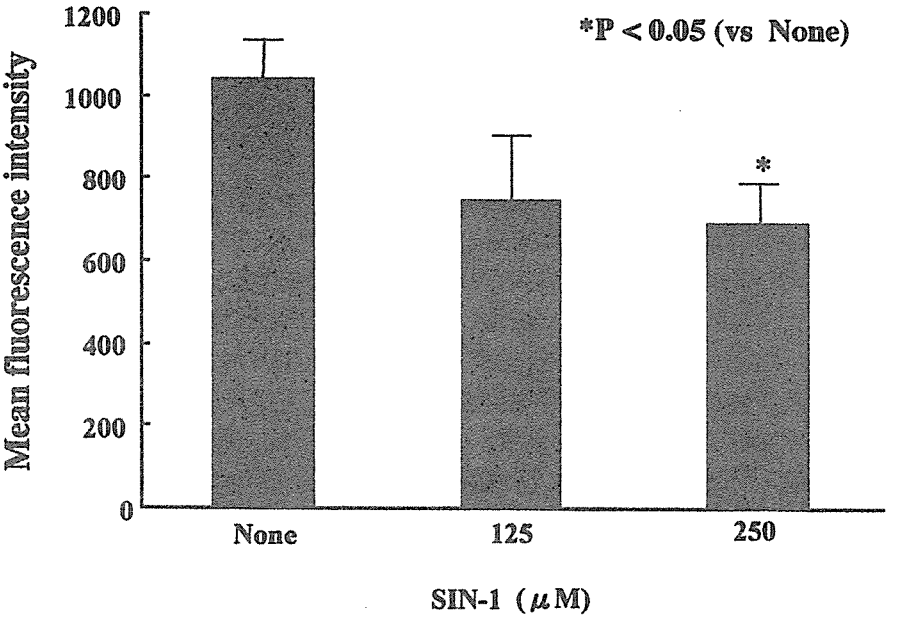

Figure 5.7. In vitro effect of nitric oxide (NO) generated from SIN-1 on expression of adhesion molecule, CD44, in LM-2 melanoma cell line. After LM-2 melanoma cells were incubated with various concentrations of SIN-1, NO generator for 4 hours, they were washed and stained with anti-CD44 antibody conjugated with FITC. Then their fluorescence intensity was measured by using Flow cytometer. Values are means ± SD; significantly different from the culture with medium only (*P < 0.05).

lished in epidemiological and experimental studies. It is known that patients either with newly diagnosed cancers or with metastases or who are undergoing therapy have statistically significant less blood, urine, and hair Se than age- and sex-matched healthy controls. It seems that Se supplementation is important for cancer patients because Se has an ability to enhance various humoral and cellular immune responses.

The ability of C57BL/6J mice, maintained for 8 weeks on a Se-deficient (0.02 ppm Se), normal (0.20 ppm Se), or Se-supplemented (2.00 ppm Se) diet, to generate cytotoxic lymphocytes (CTL) and to destroy tumor cells was examined. Lymphocytes from mice fed the Se-supplemented diet had a greater ability to destroy tumor cells than those from mice fed the normal diet, whereas Se deficiency reduced the cytotoxicity (Roy et al. 1990). In addition, it is proposed that the enhancement of in vivo cytotoxicity of NK or CTL following Se supplementation is likely to act synergistically with tumor growth inhibition in the reduction of tumor incidence (Fig. 5.8) (Petrie et al. 1989). It seems that Se's direct effects on host defense cells to suppress or enhance their actions as well as effects on tumor cells occur in the promotion phase (Talcott et al. 1984).

Zinc is also an important nutrient for maintaining cellular immune functions. Zinc status was determined in patients with newly diagnosed squamous cell carcinoma of the oral cavity, oropharynx, larynx, and hypopharynx. In this case, patients with metastatic disease and with severe comorbidity were excluded. Results showed that approximately 50% of the subjects were zinc-deficient based on cellular zinc criteria and had decreased production of Th1 cytokines but not Th2 cytokines, decreased NK cell activity, and decreased

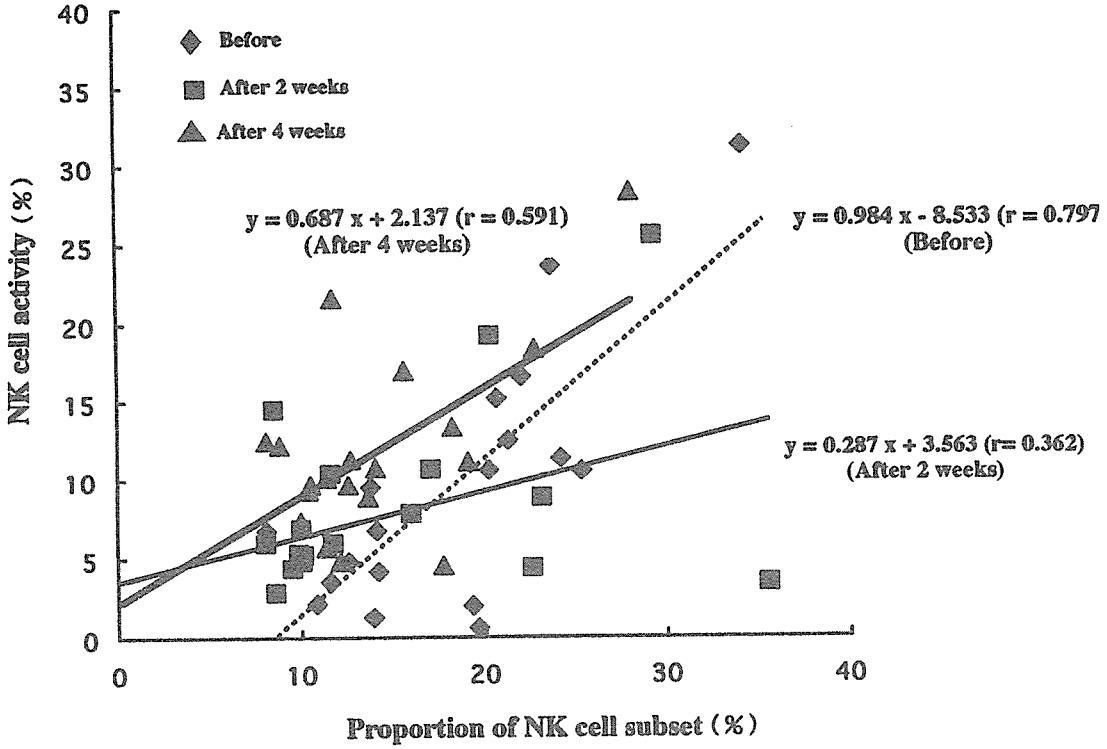

Figure 5.8. Changes in the activity and the proportion of natural killer (NK) cells in peripheral blood lymphocytes (PBL) of subjects with Aojiru drinking for 4 weeks. Nineteen female university students were selected as subjects (aged 20 to 22) in this study. They daily drank 90 ml of Aojiru juice for 4 weeks. At 2 and 4 weeks, peripheral blood was taken and their PBL were isolated. NK activity in the vertical axis and proportion of NK cell subset in the horizontal axis were plotted. As shown in this figure, NK activity of subjects with lower proportion of NK cell subset was largely enhanced following Aojiru drinking.

proportion of $CD4^+CD45RA^+$ cells in the peripheral blood (Prasad et al. 1998). Zinc concentration in polymorphonuclear cells was also decreased in the hospitalized subjects (Goode et al. 1991).

Role of Some Foods in Cancer Prevention and Immunity

Both epidemiological and animal studies have found anticarcinogenic potential in garlic and its constituent compounds. A review on a historical perspective on garlic and cancer was recently published (Milner, 2001). This review shows that water- and lipid-soluble allyl sulfur compounds have an ability to block experimentally induced tumors in a variety of sites including skin, breast, and colon, which mechanism is related to changes in DNA repair and immunocompetence. In vitro effects of garlic derivative (alliin) on both peripheral blood mononuclear cell (PBMC) proliferation and cytokine production induced by the mitogen were examined and increases in pokeweed mitogen (PWM)-induced lymphocyte proliferation, and interleukin (IL)-1 beta and tumor necrosis factor (TNF)-a productions were found (Salman et al. 1999). Lamm and Riggs (2001) have also reviewed the antitumor effect of garlic and described that the immune stimulation of garlic is able to

reduce the incidence of cancer. In addition, it has been also reported that aged garlic extract (AGE) significantly inhibits the growth of Sarcoma-180 (allogenic) and LL/2 lung carcinoma (syngenic) cells transplanted into mice and increases natural killer (NK) and killer activities of spleen cells in Sarcoma-180-bearing mice (Kyo et al. 2001).

In Japan, 40,000 households periodically purchase and drink Aojiru. Aojiru is named from its color and is a juice prepared from kale, which is a plant related to cabbage. The beneficial effect of Aojiru was investigated by measuring the activity of natural killer (NK) cells, which play an important role in protecting the body from bacteria and viral infections, and in excluding transformed cells and suppressing carcinogenesis (Cooley et al. 1999, Hirose and Kuroda 1999, and Baraz et al. 1999). NK activity of splenocytes from rats fed the freeze-dried Aojiru supplemented diet was about three times higher than that of control rats (Moriguchi and Muraga 2000).

To investigate its mechanism, the effect of Aojiru drinking on NK activity of peripheral blood lymphocytes of young female university students was examined. NK activity following Aojiru drinking for 4 weeks was significantly increased. As shown in Figure 5.8, the enhancement of NK activity is due not to increased proportion of NK cells but to increased activity of NK cell per se (Ogawa et al. 2001). Measuring cytokines in serum of these subjects, there was a significant increase of interleukin-2 (IL-2), inducing the activation of NK cells, after 4 weeks of Aojiru drinking (Fig. 5.9).

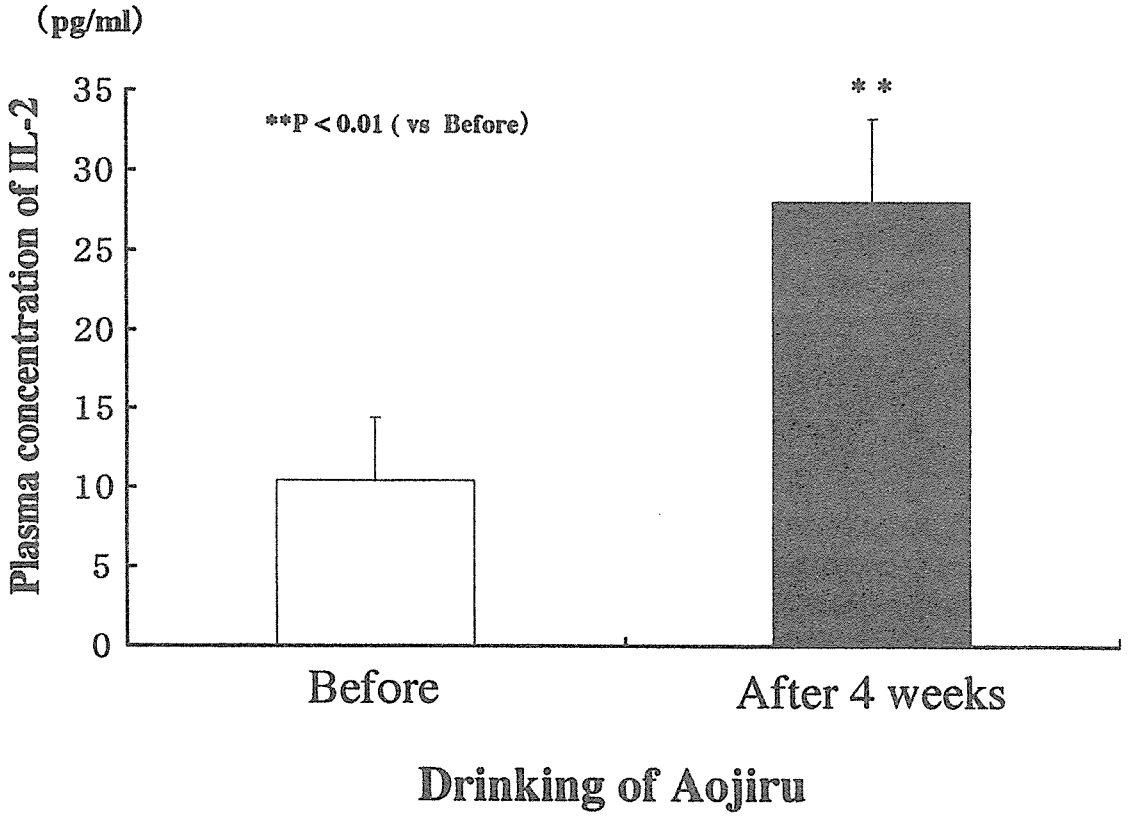

Figure 5.9. Plasma concentration of IL-2 in female university students following Aojiru drinking for 4 weeks. Values are means ± SD (n = 19); significantly different from plasma concentration of IL-2 of subjects before Aojiru drinking (**P <0.01).

These results suggest that the intake of some foods having immunoenhancing effect is beneficial for preventing carcinogenesis and maintaining health.

Conclusion

Nutritional supplementation is important for both maintenance of host immune function for perioperative cancer patients and the suppression of cancer incidence and promotion.

As described in this chapter, there are many nutrients having immunoenhancing effects. Some of them act directly to inhibit tumorigenesis and tumor growth. Even if cancer patients fall into the immunodeficient status following malnutrition, enteral or parenteral nutrition for supplying adequate nutrition can improve their nutritional status and immune functions and result in prolonging their survival time. In addition, to protect tumorigenesis in our body simply and with certainty, we have two options: one is not eating foods with possible carcinogens and the other is eating foods with immunoenhancing effects described in this chapter.

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