Effects of Lycopene Supplementation on Plasma and Tissue Lycopene Levels in Various Rodent Strains

Chin-Shiu Huang, Cheng-Hung Chuang and Miao-Lin Hu

Department of Food Science, National Chung-Hsing University, 250 Kuo-Kuang Road, Taichung, 402 Taiwan, ROC

Received for publication: March 20, 2006; Accepted for publication: June 27, 2006

Abstract: Lycopene has been shown to have various biologic effects, and rats and mice are often used for elucidating its *in vivo* effects and mechanisms. Here, we compared plasma and tissue lycopene levels in F344 rats, BALB/c mice, nude mice, and gerbils by oral supplementation with lycopene (20 mg/kg BW· 2d) every other morning for 10 days. We found that livers accumulated substantially more lycopene than kidneys and that the hepatic lycopene contents varied greatly in these animals, with gerbils being most efficient (1432 ± 235 nmol/g), followed by nude mice (524 ± 133 nmol/g), F344 rats (28 ± 11 nmol/g), and BALB/c mice (5 ± 2 nmol/g). Plasma lycopene concentrations also varied greatly, of which the highest was found in gerbils (667 ± 160 nmol/L), followed by nude mice (224 ± 51 nmol/L), then by BALB/c mice and F344 rats (198 ± 52 and 139 ± 41 nmol/L, respectively). Interestingly, plasma and tissue β-carotene concentrations in these animals were markedly decreased by lycopene supplementation. To determine the steady-state levels of plasma lycopene, we fed 10 gerbils with lycopene (20 mg/kg BW· 2d) for 20 days, and we found a steady-state level of plasma lycopene between 597 to 722 nmol/L. Our results demonstrate that gerbils and nude mice are better accumulators than F344 rats and BALB/c mice, and that the former species may be more useful for studying the *in vivo* effects of lycopene.

Key words: Lycopene, β-carotene, metabolism, animal model, gerbils

Introduction

Lycopene is an important carotenoid because epidemiologic studies have shown that high lycopene intakes are associated with lowered risk of heart disease, stroke, and several types of cancer including lung, breast, prostate, and those affecting the gastrointestinal tract [1–5]. Similar to β-carotene, lycopene has 11 *trans* conjugated double bonds [6], which play an important role in quenching singlet oxygen ($^1O_2$) [7] and in trapping peroxyl radicals [8]. Although lycopene has no vitamin A activity because of the lack of β-ionone ring, it exhibits other biological properties such as suppression of cell proliferation of human cancer cells [9] and induction of gap-junction communication [10].

Rats and mice are used in many areas of scientific research, including the study of carotenoid nutrition. Specific applications for these strains include cancer studies

DOI 10.1024/0300-9831.76.6.377

[11, 12] and studies evaluating immune function [13, 14]. These rodents have various strains, including knock-outs and transgenic animals. Athymic nude mice have been used to study the growth and metastatic behavior of various human neoplasms [15–19], including the effect of carotenoids on cancer prevention [20]. However, it is known in nutrition that most rodents do not accumulate carotenoid because they absorb carotenoid poorly and can convert β-carotene to vitamin A. Although lycopene is not a pro-vitamin A, several studies using rats for lycopene studies have shown little accumulation in tissues and plasma [21, 22]. Thus, rats and mice may not be appropriate for studying carotenoid absorption and bioavailability.

The Mongolian gerbil has lipoprotein profiles that are more similar to those of humans than to those of other rodents [23], and this strain has been found to be an acceptable model for studying lipid metabolism and atherosclerosis [24–26]. Recently, the Mongolian gerbil has been suggested as a possible model for studies of carotenoid metabolism [27–29]. Mongolian gerbils can both cleave β-carotene and absorb it intact [30]. House *et al* [27] demonstrated that male gerbils grow normally when fed the AIN-93G rodent diet and absorb large amounts of intact β-carotene. Lee *et al* [31] indicated that gerbils convert β-carotene to vitamin A at a ratio similar to that of humans. Conversely, Molldrem and Tanumihardjo [32] reported that lutein, as a daily supplement in oil, is not bioavailable to Mongolian gerbils. However, the accumulation of lycopene in gerbils has not been reported.

In this study we compared plasma and tissue distribution of lycopene in male F344 rats, BALB/c mice, nude mice, and Mongolian gerbils, after supplementation with lycopene for 10 days. We hypothesized that Mongolian gerbils and nude mice are more suitable animal models for lycopene research than are F344 rats and BALB/c mice. To our knowledge, this is the first report on direct comparison of lycopene accumulation in various rodents.

Materials and Methods

Animals

Adult (6-to 8-week-old) male F344 rats (185–200 g, n = 12), male BALB/c mice (20–25 g, n = 24), and male athymic nude mice (17–22 g, n = 24) were purchased from the animal Center of the National Science Council. Male Mongolian gerbils (49–56 g, n = 30) were purchased from the Animal Center of the National Taiwan University. The study protocol was approved by the Animal Research Committee of National Chung Hsing University.

Diets and experimental design

The animals were housed individually in hanging wire mesh cages with controlled temperature (25 ± 2° C), humidity (65 ± 5%), and alternating 12-hour light:dark cycle. Upon arrival, animals were acclimated for 2 weeks, during which they were fed a standard rodent diet (Lab 5001, Purina Mills, St. Louis, MO) and water *ad libitum.* The standard diet contains 4.5% crude fat and 4.5 mg β-carotene/kg but had no detectable amount of lycopene, as indicated by the supplier.

F344 rats, BALB/c mice, nude mice, and gerbils received either corn oil alone (10 mL/kg BW·2d; Wako, Japan) as controls or were supplemented orally with lycopene (20 mg/kg BW·2d) in corn oil every other morning (10 AM) for 10 days. Body weights and plasma lycopene were measured every 2 days. Blood samples of animals were obtained from the retro-orbital plexus every other day, as it has been shown that lycopene absorption and distribution are ongoing processes during the first 24 hours after dosing (plasma lycopene concentrations peak at ~15 hours) [33]. After blood drawing, the animals were sacrificed by CO_2 asphyxiation, and the liver, kidneys, lung, brain, and testes were collected. Blood samples were collected from both the retro-orbital plexus and heart in a 10-mL vacutainer tube containing K_3EDTA, and were centrifuged (400 × g, 10 minutes) to separate plasma. Tissues and plasma were collected and stored at –80° C until analysis.

In order to determine the steady-state concentration of plasma lycopene in gerbils for a longer period, we conducted an additional experiment by supplementing 10 extra gerbils with lycopene (20 mg/kg BW· 2d) for 20 days. Plasma lycopene concentrations were measured every 2 days during the 20-day supplementation period.

Measurement of plasma carotenoid contents

Carotenoids were extracted from plasma by a modification of a method described previously [34]. Briefly, aliquots (200 μL) of pooled plasma, kept on ice, were placed in 100 × 13 mm borosilicate glass tubes and extracted with 200 μL of 95% ethanol containing α-tocopherol acetate (200 μL/mL) and retinol acetate (570 ng/mL). After being vortexed for 45 seconds, they were extracted with hexane (1.0 mL, containing 0.01% BHT) and vortexed for 1 minute. The phases were separated by centrifugation (1400 × g, 10 minutes, 4° C). The upper organic phase was removed and evaporated in a glass test tube (as above) under a stream of nitrogen at room temperature. The residue was reconstituted in 15 μL of chloroform and vortexed for 40 seconds. Initial dissolution in chloroform was necessary for efficient recovery of

carotenoids. A 35-µL volume of acetonitrile-methanol (1:1) was added and vortexed for a further 40 seconds.

Measurement of tissue carotenoid contents

β-carotene and lycopene were extracted and analyzed using reverse-phase high-performance liquid chromatography (HPLC) as described elsewhere [35]. The tissues were extracted without saponification using 6.0 mL of $CHCl_3$: CH_3OH (2:1, v/v). Retinyl acetate and α-tocopherol acetate were added as internal standards. The tissue mixtures were centrifuged for 10 minutes at 320 × g at 4° C, and the chloroform layer was evaporated to dryness under nitrogen. The residue was redissolved in 15 µL chloroform and 35 µL acetonitrile-methanol mixtures (1:1, v/v). A 20-µL aliquot of final extract was injected onto the HPLC system.

Lycopene and β-carotene were then analyzed using HPLC, as we described previously [36], which was modified from Su *et al* [34]. Absorption maxima of β-carotene and lycopene were 450 nm and 470 nm, respectively. This method determines only lycopene and does not allow the differentiation of isomers. The efficiency of extraction of internal standards ranged from 76 to 85% in plasma samples and 81 to 87% in tissue samples. In this study, lycopene was stable in the plasma stored at –80° C for 1 month in the dark (data not shown).

Statistical analysis

Values are expressed as means ± SD and analyzed using one-way ANOVA, followed by Duncan's multiple range test for comparisons of group means. When only two groups are compared, we used unpaired Student's *t*-test for statistical analysis. The statistical analysis was performed using SPSS for Windows, version 10 (SPSS, Inc.); a p value < 0.05 was considered statistically significant.

Results

Effect of lycopene supplementation on body weights and appearance

Neither oral corn oil nor lycopene-containing corn oil affected body weight gain ($p > 0.05$, data not shown). Lycopene supplementation for 10 days produced no overt toxic side effects except for a brownish discoloration of the tail in the four strains of rodents studied (data not shown).

Effect of lycopene supplementation on total lycopene levels in plasma

There was no detectable lycopene in the plasma or tissues of the control animals (data not shown). After supplementation with lycopene (20 mg/kg BW· 2d) for 10 days, the plasma lycopene concentrations were significantly increased in all the strains studied; the highest level (667 ± 160 nM) was found in gerbils, followed by nude mice (224 ± 51 nM), then by the BALB/c mice (198 ± 52 nM) and F344 rats (139 ± 41 nM) (Figure 1), although only that of

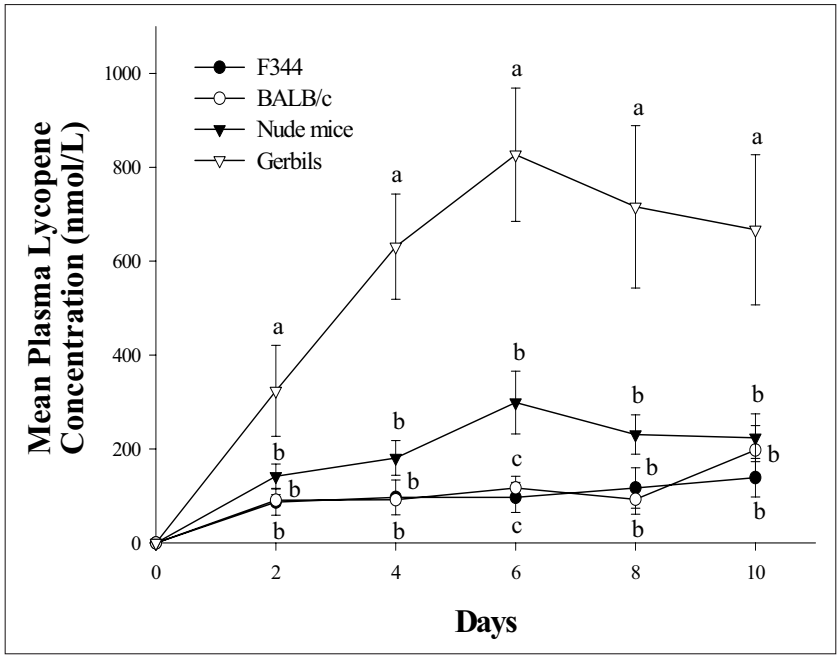

Figure 1: Lycopene concentrations in plasma of F344 rats, BALB/c mice, nude mice and gerbils after supplementation with lycopene at 20 mg/kg BW· 2d for 10 days. Values (means ± SD, $n > 6$) at the same time point with different superscripts are significantly different ($p < 0.05$).

gerbils was significantly different from that of other rodents ($p < 0.05$).

Effect of lycopene supplementation on total lycopene levels in tissues

Lycopene was not detected in the liver, kidney, lung, brain, and testes from the four strains of animals without lycopene supplementation. In all four strains of animals supplemented with lycopene, the lycopene levels were highest in the liver, followed by the kidney, while little or no detectable amounts of lycopene were detected in the lung, brain, and testes (data not shown). Liver levels of lycopene in the four strains of rodents were in the order: gerbils (1432 ± 235 nmol/g), nude mice (524 ± 133 nmol/g), F344 rats (28 ± 11 nmol/g), and BALB/c mice (5 ± 2 nmol/g). Similarly, kidney lycopene concentrations were in the order of gerbils (76.7 ± 31.9 µg/g), nude mice (60.0 ± 21.6 nmol/g), F344 rats (4.8 ± 1.3 nmol/g), and BALB/c mice (0.6 ± 0.2 nmol/g).

Plasma and tissue levels of β-carotene

As revealed in Figure 2, plasma β-carotene levels in gerbils and nude mice were about 10 times higher than those in F344 rats and BALB/c mice. Interestingly, the plasma β-carotene levels were generally higher in the control animals than in lycopene-supplemented animals during the 10-day feeding period, and these differences were particularly striking in nude mice and gerbils.

The livers and kidneys of gerbils and nude mice also accumulated more β-carotene than those of F344 rats and BALB/c mice, with about 330–550 % difference between the liver β-carotene levels of gerbils and those of F344 rats and BALB/c mice (Table I). Similarly, the control animals contained more tissue β-carotene than lycopene-supplemented animals, although the differences were not significant in the livers of nude mice and in the kidneys of BALB/c mice.

Steady-state plasma lycopene concentration in gerbils during the 20-day supplementation period

During the 20-day dosing of gerbils with lycopene (20 mg/kg BW·2d), the plasma lycopene concentrations increased in the first 6 day (i.e. the first three oral feedings) reaching the highest lycopene concentration (827 nM) on day 6. Thereafter and until day 20, the plasma lycopene concentrations decreased and fluctuated between approximately 537 nM (day 14) and 731 nM (day 18), with no significant differences between day 6 and day 20 (Figure 3).

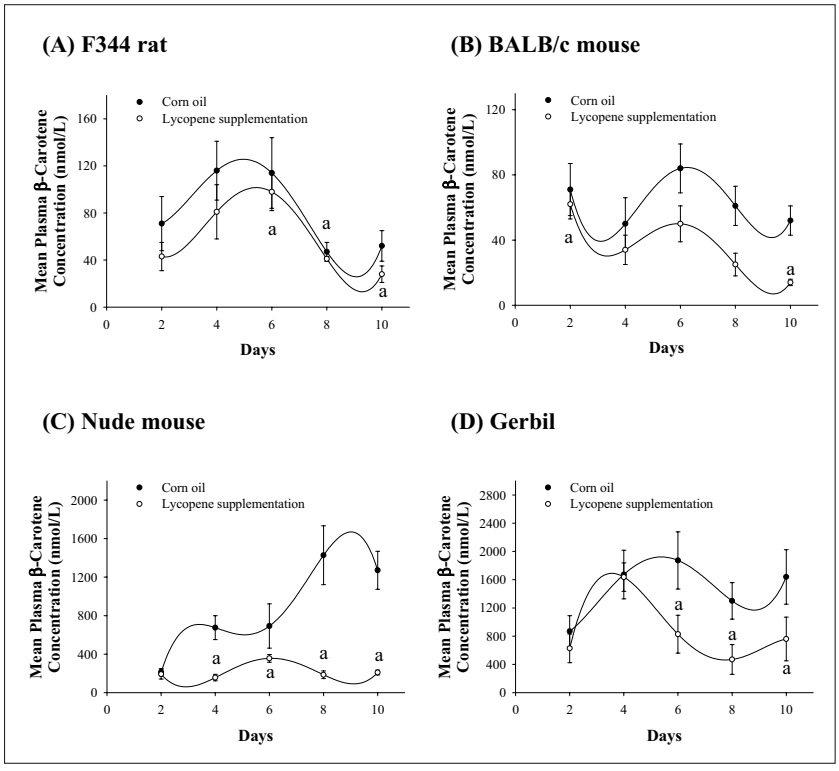

Figure 2: β-Carotene concentrations in plasma of **(A)** F344 rats, **(B)** BALB/c mice, **(C)** nude mice, and **(D)** gerbils after supplementation with lycopene at 20 mg/kg BW·2d for 10 days. Values (means ± SD, $n \geq 6$) were curve-fitted with regressions in a quaternary order manner ($r^2 = 1$). [a] Significantly different ($p < 0.01$) from the control group (supplemented orally with corn oil) at the same time point in the same species of animals (analyzed by Student's *t*-test).

Table I: Concentrations of β-carotene in tissue of F344 rats, BALB/c mice, nude mice, and gerbils after supplementation at 20 mg/kg BW·2d for 10 days.

Animal	n	Lycopene supplementation	β-carotene content in tissues	
			Liver	Kidney
		mg/(kg BW·2d)	*nmol/g*	
F344 rat	6	0	38 ± 9	10.2 ± 3.0
	6	20	22 ± 6[a]	0.7 ± 0.2[a]
BALB/c mouse	12	0	49 ± 11	4.1 ± 1.0
	12	20	35 ± 3[a]	3.4 ± 0.7
Nude mouse	12	0	60 ± 13	28.9 ± 6.1
	12	20	62 ± 18	15.6 ± 1.6[a]
Gerbil	10	0	160 ± 22	43.2 ± 11.3
	10	20	121 ± 9[a]	24.8 ± 1.7[a]

Values are means + SD, n > 6

[a] Significantly different ($p < 0.01$) from the control group (supplemented orally with corn oil) in the same strains of animals

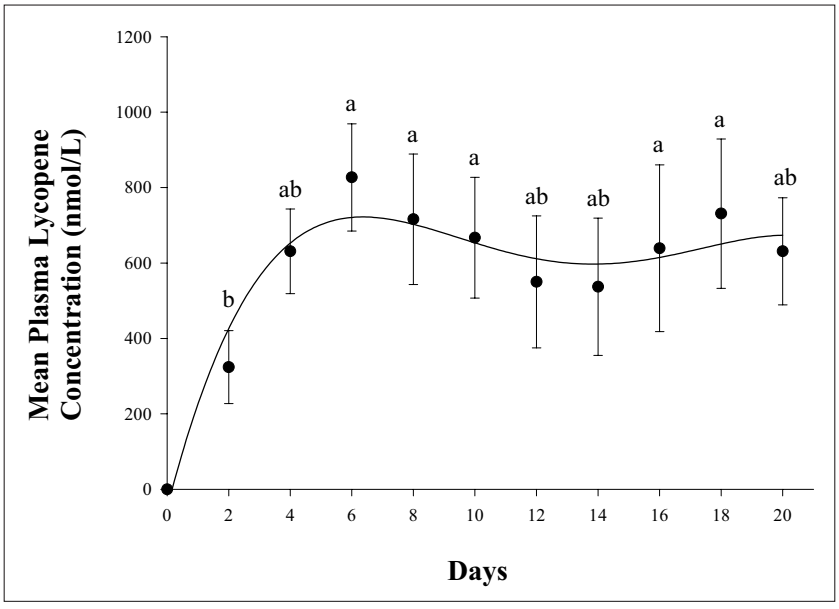

Figure 3: Lycopene concentrations in plasma of gerbils after supplementation with lycopene at 20 mg/kg BW·2d for 20 days. Values (mean ± SD, n ≥ 3) were curve-fitted with regressions in a quaternary order manner ($r^2 = 0.92$). Values not sharing a common superscript are significantly different ($p < 0.05$).

The 20-day supplementation of lycopene resulted in an accumulation of lycopene of 2045 nmol/g in the liver of gerbils, which was somewhat, but not significantly, higher than that (1432 nmol/g) in the liver of gerbils from the 10-day dosing experiment ($p = 0.069$). The lycopene concentrations in the kidney were essentially the same (approximately 80 nmol/g) between the 10-d and 20-d dosing experiments ($p = 0.856$).

Discussion

Animal studies for elucidating the biological effect of lycopene are limited in part due to a lack of knowledge concerning the absorption, metabolism, and tissue distribution of lycopene. Although rats and mice have often been used for lycopene studies, it is questionable as to whether these animals are suitable for such studies because of their poor absorption of carotenoids relative to humans [37, 38]. In this study, we found no detectable plasma lycopene in the four strains of rodents before lycopene supplementation, which may simply reflect the lack of lycopene in the standard diet (Purina Laboratory chow, 5001). Oral treatment with lycopene (20 mg/kg BW·2d) for 10 days (5 dosing days) resulted in the appearance of lycopene in plasma and accumulation of lycopene in livers, but accumulation of lycopene occurred to a much lower extent in kidneys in the four strains of rodents. Previous studies in rats and monkeys have also shown a much greater accumula-

tion of lycopene in the liver than in the kidney after lycopene supplementation [39]. It has been suggested that the lycopene concentration in the liver is of two orders of magnitude higher than that in other organs [40]. Therefore, liver is an important target for evaluating accumulation of lycopene.

Mongolian gerbils have been advocated as an appropriate animal model for studying carotenoid absorption and metabolism and the availability of vitamin A from carotenoid precursors [28, 29, 37]. However, the evidence for such an advocacy is largely based on the fact that Mongolian gerbils readily absorb β-carotene intact [30], with little evidence from other carotenoids such as lycopene. Although others have reported the effective accumulation of lycopene in tissues by Mongolian gerbils [37, 41, 42], no comparisons have been made among different strains of rodents. Here, we clearly demonstrate that gerbils accumulate large amounts of lycopene in the liver, kidney, and plasma and that the gerbils are by far the best accumulator of lycopene among the four strains of rodents studied.

Not surprisingly, F344 rats and BALB/c mice are poor accumulators of lycopene, and the evidence indicates that they are not appropriate surrogate animals for human studies on lycopene absorption and metabolism. However, it is noteworthy that the nude mice are much better accumulators of lycopene than are F344 rats and BALB/c mice, although the nude mice accumulated significantly less lycopene in plasma, livers, and kidneys than did Mongolian gerbils. Although ferrets absorb lycopene efficiently and have been used as an animal model for lycopene research [43, 44], they are more expensive than rats and mice, and gerbils and are not readily available to many investigators. Our present findings that the gerbils accumulate lycopene efficiently suggest that this smaller, less expensive, and commercially available animal species is an appropriate model for carotenoid research.

The differences in plasma level and tissue storage of lycopene between these rodent species may depend on the fractions of lipoprotein. Carotenoids in mammalian blood are located in the circulating lipoproteins and accumulated within fat store in the tissues. The gerbil model is more similar to humans than other rodent species in terms of plasma lipoprotein distribution and responses to dietary changes [45].

In order to elucidate the steady-state concentrations of plasma lycopene in gerbils, we conducted a 20-day dosing experiment. We found that the steady state of plasma lycopene levels, which were determined using curve fitting from Figure 3, were between 597 and 722 nM (r^2 = 0.92), with the highest level achieved only after 3 dosings of lycopene (i.e. on day 6 of supplementation). Our results agree well with those reported by Korytko *et al* in gerbils [33], in which a steady-state plasma lycopene concentration between 785 and 997 nM was found after oral treatment with 30 mg/(kg BW·d) for 28 days. These steady-state plasma concentrations in gerbils are comparable to those in humans (664–1300 nM) who were supplemented with dietary lycopene at 30 mg/day for 28 days [47].

An interesting observation of the present study is that short-term supplementation with lycopene resulted in significant decreases in plasma β-carotene concentrations in all four strains of rodents studied. The results suggest a competitive absorption between lycopene and β-carotene. Indeed, lycopene supplementation (5 mg/day for 42 days) in humans significantly decreases the β-cryptoxanthin contents in plasma [48]. High-dose β-carotene supplementation (300 mg/day for 21 days) in humans has been shown to strongly decrease serum lycopene levels [49]. In addition, supplementation of β-carotene at 100 mg/day for 6 days in humans decreases the lycopene content in low-density lipoprotein (LDL) [50]. Van den Berg *et al* [51] have suggested that carotenoids appear to compete each other for incorporation into micelles, carotenoid exchange between lipoproteins in the postprandial state, and inhibition of pro-vitamin A (β-carotene) cleavage.

In summary, this study demonstrates that gerbils and nude mice are better accumulators of lycopene than F344 rats and BALB/c mice. Because humans are known to accumulate carotenoids, as opposed to rodents [52], our results suggest that gerbils and nude mice are more useful than F344 rats and BALB/c mice for studying the *in vivo* effects of lycopene for humans. However, further studies are needed to determine whether the absorption and metabolism of lycopene are similar between these two species and humans.

Acknowledgment

This research was supported by a grant (NSC-92-2320-B005-003) from the National Science Council, ROC.

References

1. Bub, A., Barth, S., Watzl, B., Briviba, K., Herbert, B.M., Luhrmann, P.M., Neuhauser-Berthold, M. and Rechkemmer, G. (2002) Paraoxonase 1 Q192R (PON1–192) polymorphism is associated with reduced lipid peroxidation in R-allele-carrier but not in QQ homozygous elderly subjects on a tomato-rich diet. Eur. J. Nutr. 41, 237–243.
2. Mayne, S.T. (1996) Beta-carotene, carotenoids, and disease prevention in humans. FASEB J. 10, 690–701.
3. Steinmetz, K.A. and Potter, J.D. (1996) Vegetables, fruit, and cancer prevention: a review. J. Am. Diet Assoc. 96, 1027–1039.

4. Heber, D. and Lu, Q. Y. (2002) Overview of mechanisms of action of lycopene. Exp. Biol. Med. 227, 920–923.
5. Giovannucci, E., Ascherio, A., Rimm, E. B., Stampfer, M. J., Colditz, G. A. and Willett, W. C. (1995) Intake of carotenoids and retinol in relation to risk of prostate cancer. J. Natl. Cancer Inst. 87, 1767–1776.
6. Stahl. W. and Sies, H. (1996) Lycopene: a biologically important carotenoid for humans? Arch. Biochem. Biophys. 336, 1–9.
7. Di Mascio, P., Kaiser, S. and Sies, H. (1989) Lycopene as the most efficient biological carotenoid singlet oxygen quencher. Arch. Biochem. Biophys. 274, 532–538.
8. Burton, D. W. and Ingoid, K. U. (1984) β-Carotene: an unusual type of lipid antioxidant. Science 224, 569–573.
9. Levy, J., Bosin, E., Feldman, B., Giat, Y., Miinster, A., Danilenko, M. and Sharoni, Y. (1995) Lycopene is a more potent inhibitor of human cancer cell proliferation than either alpha-carotene or beta-carotene. Nutr. Cancer 24, 257–266.
10. Zhang, L. X., Cooney, R. V. and Bertram, J. S. (1991) Carotenoids enhance gap junctional communication and inhibit lipid peroxidation in C3H/10T1/2 cells: relationship to their cancer chemopreventive action. Carcinogenesis 12, 2109–2114.
11. Sato, N., Gleave, M., Burchovsky, N., Rennie, P. S., Beralde, E. and Sullivan, L. D. (1997) A metastatic and androgen-sensitive human prostate cancer model using intraprostatic inoculation of LNCaP cells in SCID mice. Cancer Res. 57, 1584–1589.
12. Thompson, T. C., Truong, L. D., Timme, T. L., Kadmon, D., McCune, B. K., Flanders, K. C., Scardino, P. T. and Park, S. H. (1993) Transgenic models for the study of prostate cancer. Cancer 71, 1165–1171.
13. Turini, M. E., Boza, J. J., Gueissaz, N., Moennoz, D., Montigon, F., Vuichoud, J., Gremaud, G., Pouteau, E., Piguet, C., Perrin, I., Verguet, C., Finot, P.A. and German, B. (2003) Short-term dietary conjugated linoleic acid supplementation does not enhance the recovery of immunodepleted dexamethasone-treated rats. Eur. J. Nutr. 42, 171–179.
14. Jyonouchi, H., Zhang, L., Gros, M. and Tomita, Y. (1994) Immunomodulating actions of carotenoids: enhancement of *in vivo* and *in vitro* antibody production to T-dependent antigens. Nutr. Cancer 21, 47–58.
15. Rygaard, J. and Povlsen, C. O. (1969) Heterotransplantation of human malignant tumor to nude mice. Acta. Pathol. Microbiol. Scand. 77, 758–760.
16. Sharkey, F. E. and Fogh, J. (1984) Considerations in the use of nude mice for cancer research. Cancer Metastasis Rev. 3, 341–360.
17. Sharkey, F. E. and Fogh, J. (1979) Metastasis of human tumors in athymic nude mice. Int. J. Cancer 24, 733–738.
18. Fidler, I.J. (1986) Rationale and methods for the use of nude mice to study the biology and therapy of human cancer metastasis. Cancer Metastasis Rev. 5, 29–49.
19. Kryiazis, A. P., Kryiazis, A. A., McCombs, W. B. and Kereiakes, J. A. (1981) Biological behavior of human malignant tumors grown in the nude mouse. Cancer Res. 41, 3995–4000.
20. Tang, L., Jin, T., Zeng, X. and Wang, J. S. (2005) Lycopene inhibits the growth of human androgen-independent prostate cancer cells *in vitro* and in BALB/c nude mice. J. Nutr. 135, 287–290.
21. Ferreira, A. L., Yeum, K. J., Liu, C., Smith, D., Krinsky, N. I., Wang, X. D. and Russell, R. M. (2000) Tissue distribution of lycopene in ferrets and rats after lycopene supplementation. J. Nutr. 130, 1256–1260.
22. Johansson, M. B. and Karlsson, B. W. (1976) Lipoproteins in serum of rat, mouse, gerbil, rabbit, pig and man studied by electrophoretical and immunological methods. Comp. Biochem. Physiol. B 54, 495–500.
23. van Vliet, T. (1996) Absorption of β-carotene and other carotenoids in humans and animal models. Eur. J. Clin. Nutr. 50, 32–37.
24. DiFrancesco, L., Allen, O. B. and Mercer, N. H. (1990) Long-term feeding of casein or soy protein with or without cholesterol in Mongolian gerbils. II. Plasma lipid and liver cholesterol responses. Acta Cardiol. 45, 273–290.
25. Potter, S. M., Jimenez-Flores, R., Pollack, J., Lone, T. and Berber-Jimenez, M. D. (1993) Protein-saponin interaction and its influence on blood lipids. J. Agric. Food Chem. 41, 1287–1291.
26. Tasker, T. E. and Potter, S. M. (1993) Effects of dietary protein source on plasma lipids, HMG CoA reductase activity, and hepatic glutathione levels in gerbils. J. Nutr. Biochem. 4, 458–462.
27. House, W. A., Apgar, J. and Smith, J. C. (1997) The gerbil: a model for studying the metabolism of β-carotene and minerals. Nutr. Res. 17, 1293–1302.
28. Deming, D. M., Teixeira, S.R. and Erdman, J. W. Jr. (2002) All-trans beta-carotene appears to be more bioavailable than 9-cis or 13-cis beta-carotene in gerbils given single oral doses of each isomer. J. Nutr. 132, 2700–2708.
29. Tanumihardjo, S. A. and Howe, J. A. (2005) Twice the amount of alpha-carotene isolated from carrots is as effective as beta-carotene in maintaining the vitamin A status of Mongolian gerbils. J. Nutr. 135, 2622–2626.
30. Pollack, J., Campbell, J. M., Potter, S. M. and Erdman, J. W. Jr. (1994) Mongolian gerbils (Meriones unguiculatus) absorb β-carotene intact from a test meal. J. Nutr. 124, 869– 873.
31. Lee, C. M., Lederman, J. D., Hofmann, N. E. and Erdman, J. W. Jr. (1998) The Mongolian (Meriones unguiculatus) is an appropriate animal model for evaluation of the conversion of β-carotene to vitamin A. J. Nutr. 128, 280–286.
32. Molldrem, K. L. and Tanumihardjo, S. A. (2004) Lutein supplements are not bioavailable in the Mongolian gerbil while consuming a diet with or without cranberries. Int. J. Vitam. Nutr. Res. 74, 153–160.
33. Korytko, P. J., Rodvold, K. A., Crowell, J. A., Stacewicz-Sapuntzakis, M., Diwadkar-Navsariwala, V., Bowen, P. E., Schalch, W. and Levine, B. S. (2003) Pharmacokinetics and tissue distribution of orally administered lycopene in male dogs. J. Nutr. 133, 2788–2792.
34. Su, Q., Rowley, K. G. and O'Dea, K. (1999) Stability of individual carotenoids, retinol and tocopherols in human plasma during exposure to light and after extraction. J. Chromatogr. B: Biomed. Sci. Appl. 729, 191–198.

35. Lederman, J.D., Overton, K.M., Hofmann, N.E., Moore, B.J., Thornton, J. and Erdman, J.W. (1998) Ferrets (Mustela putoius furo) inefficiently convert beta-carotene to vitamin A. J. Nutr. 128, 271–279.
36. Yeh, S.L., Huang, C.S. and Hu, M.L. (2005) Lycopene enhances UVA-induced DNA damage and expression of heme oxygenase-1 in cultured mouse embryo embryo fibroblasts. Eur. J. Nutr. 44, 365–370.
37. Lee, C.M., Boileau, A.C., Boileau, T.W., Willams, A.W., Swanson, K.S., Heintz, K.A. and Erdman, J.W. Jr. (1999) Review of animal models in carotenoid research. J. Nutr. 129, 2271–2277.
38. Boileau, T.W., Clinton, S.K. and Erdman, J.W. Jr. (2000) Tissue lycopene concentrations and isomer patterns are affected by androgen status and dietary lycopene concentration in male F344 rats. J. Nutr. 130, 1613–1618.
39. Mathews-Roth, M.M., Welankiwar, S., Sehgal, P.K., Lausen, N.C., Russett, M. and Krinsky, N.I. (1990) Distribution of [^{14}C]canthaxanthin and [^{14}C]lycopene in rats and monkeys. J. Nutr. 120, 1205–1213.
40. Zhao, Z., Khachik, F., Richie, J.P. Jr. and Cohen, L.A. (1998) Lycopene uptake and tissue disposition in male and female rats. Proc. Soc. Exp. Biol. Med. 218, 109–114.
41. Sulaeman, A., Giraud, D.W., Naslund, M.M. and Driskell, J.A. (2002) Mongolian gerbils can utilize provitamin-A carotenoids in deep-fried carrot chips. J. Nutr. 132, 211–217.
42. Pollack, A., Oren, P., Stark, A.H., Eisner, Z., Nyska, A. and Madar, Z. (1999) Cataract development in sand and galactosemic rats fed a natural tomato extract. J. Agric. Food Chem. 47, 5122–5126.
43. Wang, X.D. (2005) Can smoke-exposed ferrets be utilized to unravel the mechanisms of action of lycopene? J. Nutr. 135, 2053S–2056S.
44. Liu, C., Lian, F., Smith, D.E., Russell, R.M. and Wang, X.D. (2003) Lycopene supplementation inhibits lung squamous metaplasia and induces apoptosis via up-regulating insulin-like growth factor-binding protein 3 in cigarette smoke-exposed ferrets. Cancer Res. 63, 3138–3144.
45. Hidiroglou, N., Gilani, G.S., Long, L., Zhao, X., Mader, R., Cockell, K., Belonge, B., Ratnayake, W.M. and Peace, R. (2004) The influence of dietary vitamin E, fat, and methionine on blood cholesterol profile, homocysteine levels, and oxidizability of low density lipoprotein in the gerbil. J. Nutr. Biochem. 15, 730–740.
46. Walder, K., Oakes, N., Fahey, R.P., Cooney, G., Zimmet, P.Z. and Collier, G.R. (2002) Profile of dyslipidemia in Psammomys obesus, an animal model of the metabolic syndrome. Endocr. Regul. 36, 1–8.
47. van Breemen, R.B., Xu, X., Viana, M.A., Chen, L., Stacewicz-Sapuntzakis, M., Duncan, C., Bowen, P.E. and Sharifi, R. (2002) Liquid chromatography-mass spectrometry of cis- and all-trans-lycopene in human serum and prostate tissue after dietary supplementation with tomato sauce. J. Agric. Food Chem. 50, 2214–2219.
48. Bohm, V. and Bitsch, R. (1999) Intestinal absorption of lycopene from different matrices and interactions to other carotenoids, the lipid status, and the antioxidant capacity of human plasma. Eur. J. Nutr. 38, 118–125.
49. Prince, M.R., Frisoli, J.K., Goetschkes, M.M., Stringham, J.M. and LaMuraglia, G.M. (1991) Rapid serum carotene loading with high-dose beta-carotene: clinical implications. J. Cardiovasc. Pharmacol. 17, 343–347.
50. Gaziano, J.M., Johnson, E.J., Russell, R.M., Manson, J.E., Stampfer, M.J., Ridker, P.M., Frei, B., Hennekens, C.H. and Krinsky, N.I. (1995) Discrimination in absorption or transport of beta-carotene isomers after oral supplementation with either all-trans- or 9-cis-beta-carotene. Am. J. Clin. Nutr. 61, 1248–1252.
51. van den Berg, H. (1999) Carotenoid interactions. Nutr. Rev. 57, 1–10.
52. Brody, T. (1999) Nutritional Biochemistry, 2nd ed., pp. 556, Academic Press, Singapore.

Ph.D. Professor Miao-Lin Hu

Phone (fax): +886-4-22812363
E-mail: mlhuhu@dragon.nchu.edu.tw