Green tea catechins inhibit neointimal hyperplasia in a rat carotid arterial injury model by TIMP-2 overexpression

Xian Wu Chenga,b, Masafumi Kuzuyaa,*, Takeshi Sasaki,a, Shigeru Kanda,a, Norika Tamaya-Moría, Teruhiko Koikea, Keiko Maeda,a, Eisei Nishitanic, Akihisa Iguchia

aDepartment of Geriatrics, Nagoya University Graduate School of Medicine, 65 Tsuruma-Cho, Showa, Nagoya 466-8550, Japan
bCardiovascular Department, College of Medical, Yanbian University, 119 Juzijie, Yanjishi, Jilin Province, China
cCentral Research Institute, Itoen, Ltd., Shizuoka, Japan

Received 23 November 2003; received in revised form 17 January 2004; accepted 20 January 2004

Time for primary review 32 days
Available online on 17 March 2004

Abstract

Objective: Although it has been demonstrated that the antioxidant properties of tea catechins reduce atherosclerotic lesions in various animal models of hyperlipidemia, it is not yet clear whether these catechins prevent hyperlipidemia-independent arterial remodeling induced by balloon angioplasty. We evaluated the influence of the administration of the tea extract on vascular remodeling in a rat carotid artery balloon-injury model.

Methods and results: Male Wistar rats were supplied drinking water with or without green tea extract (1 mg/ml) supplement. Administration of the tea extract reduced the area of the intima (30%) and the ratio of the intimal area to the medial area (36.2%) in injured arteries compared with those of control rats at 14 days after the injury. Real-time RT-PCR, Western blot, and gelatin zymography revealed a significant increase in tissue inhibitor of matrix metalloproteinase (MMP)-2 (TIMP-2) expression as well as a significant reduction of gelatinolytic net activity and activated MMP-2 levels in the injured arteries as a result of the administration of the tea extract compared with those of control group. Similarly, epigallocatechin-3-gallate, a major constituent of green tea catechins, significantly upregulated TIMP-2 expression in cultured smooth muscle cells. Immunohistochemical analysis showed that the increase of TIMP-2 protein occurred preferentially in the developing neointima.

Conclusion: These results indicate that catechins inhibit intimal hyperplasia in a rat balloon-injury model through the upregulation of TIMP-2 expression to modulate MMP activity.

Keywords: Smooth muscle; Matrix metalloproteinase; Restenosis

1. Introduction

Green tea contains a large amount of polyphenols, especially flavan-3-ols, also known as catechins. Recent experiments suggest that green tea catechins reduce atherosclerotic lesions in various animal models of hyperlipidemia [1-3]. Although the precise mechanisms are not yet clear, it has been hypothesized that the anti-atherosclerotic activity of catechins is associated with their antioxidative activity [2-4], since some kinds of catechins inhibited in vitro low density lipoprotein (LDL) oxidation [5,6], and the intake of green tea polyphenols decreased the susceptibility of LDL oxidation [7]. Furthermore, recent studies in vitro have demonstrated that epigallocatechin-3-gallate (EGCG) suppresses vascular smooth muscle cells (SMCs) proliferation [8,9], suggesting another possible mechanism of the anti-atherogenic effect of catechins. However, the effect of green tea catechins on arterial remodeling such as endothelium injury-induced intimal hyperplasia remains unknown as of yet.

Proteolytic enzymes derived from SMCs are thought to facilitate cell migration, neointimal lesion formation, and degradation of the extracellular matrix (ECM) associated with vascular remodeling. Vascular injury has been shown to cause early upregulation of both matrix metalloproteinase-2 (MMP-2; gelatinase A) and MMP-9 (gelatinase B) after injury [10,11]. It is ultimately the balance between
the MMPs and their inhibitors, TIMPs, that determines the focal proteolysis around the SMCs of the arterial media. We have recently revealed that the primary MMP secreted from an SMC invasion assay was MMP-2 [12], and MMP-2 plays an important role in the arterial remodeling in a mouse ligation model [13]. Recently, we and other groups have demonstrated that some kinds of catechins possess the properties of anti-gelatinolytic activity, anti-pro-MMP-2 activation, and MMP-2 binding to TIMP-2 enhancement [14–16].

In the present study, we investigated whether the administration of green tea catechins could suppress the neointima formation using a rat balloon-injury model. In addition, we also examined the effects of administration of catechins on carotid arterial gelatinolytic activity and MMP-2 activation after injury as well as the expression of TIMP-1 and -2 in vivo and in vitro.

2. Materials and methods

2.1. Animal model

Male Wistar rats (3–4 months old; Japan SLC, Shizuoka, Japan) were used in the present study. All procedures conformed to the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-27, revised 1996). The animals were anesthetized by an intraperitoneal injection of ketamine (Sankyo Pharmaceutical, Tokyo, Japan, 70 mg/kg) and xylazine (Bayer, Pharmaceutical, Tokyo, Japan, 4.6 mg/kg), and a balloon catheter injury to the left common carotid artery was performed as previously described [10]. The administration of green tea extract (THEA-LAN 90s, lot. 000607; Itoen, Shizuoka, Japan), which was given to the tea group rats (1 mg/ml) via drinking water (42.3 ± 9.4 ml/day), was started 7 days before the injury, and continued the experimental period. Control group rats drank water alone (43.3 ± 10.4 ml/day). At various time points after the injury, the carotid arteries were flushed clear of blood using normal saline at physiological pressure. For quantitative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis, the vessels were fixed for 16 h with 4% phosphate-buffered formalin. The levels of catechin and lipids in Figure 2A were determined as previously described [10]. The administration of green tea extract (THEA-LAN 90s, lot. 000607; Itoen, Shizuoka, Japan), which was given to the tea group rats (1 mg/ml) via drinking water (42.3 ± 9.4 ml/day), was started 7 days before the injury, and continued the experimental period. Control group rats drank water alone (43.3 ± 10.4 ml/day). At various time points after the injury, the carotid arteries were flushed clear of blood using normal saline at physiological pressure. For quantitative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis, the vessels were fixed for 16 h with 4% phosphate-buffered formalin. The levels of catechin and lipids in rat plasma were determined as previously described [10].

2.1. Animal model

Male Wistar rats (3–4 months old; Japan SLC, Shizuoka, Japan) were used in the present study. All procedures conformed to the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-27, revised 1996). The animals were anesthetized by an intraperitoneal injection of ketamine (Sankyo Pharmaceutical, Tokyo, Japan, 70 mg/kg) and xylazine (Bayer, Pharmaceutical, Tokyo, Japan, 4.6 mg/kg), and a balloon catheter injury to the left common carotid artery was performed as previously described [10]. The administration of green tea extract (THEA-LAN 90s, lot. 000607; Itoen, Shizuoka, Japan), which was given to the tea group rats (1 mg/ml) via drinking water (42.3 ± 9.4 ml/day), was started 7 days before the injury, and continued the experimental period. Control group rats drank water alone (43.3 ± 10.4 ml/day). At various time points after the injury, the carotid arteries were flushed clear of blood using normal saline at physiological pressure. For quantitative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis, the vessels were fixed for 16 h with 4% phosphate-buffered formalin. The levels of catechin and lipids in rat plasma were determined as previously described [10].

2.2. Morphometry and immunohistochemistry

The sections (7 μm) at different parts (proximal, middle, and distal) from the carotid arterial segments (n = 9 for control group; n = 12 for tea group) were stained with hematoxylin and eosin, and were then analyzed using a computer-assisted morphometric analysis system (NIH image 1.62) with particular attention to the intimal and the medial areas, and to the medial area ratio. For staining of TIMP-1 and -2, the sections were respectively incubated with polyclonal TIMP-1 or -2 (both from Sigma-Aldrich, Louis, MO, each rate of dilution 1:100) antibodies or non-immune rabbit serum as a negative control for overnight at 4 °C.

2.3. Western blotting

Each individual artery was minced using a tissue homogenizer. The protein concentration for each sample of the catechin-conditioned media from cultured RSMCs (n = 6) and of the tissue extracts from vessels (n = 25 for each group) was determined using a protein assay system according to the manufacturer (Bio-Rad Dc; Bio-Rad Laboratories, Hercules, CA). Equal amounts of total protein were separated on 15% SDS-polyacrylamide gel and blotted onto PVDF membrane. After reaction with rabbit anti-TIMP-1 or -2 polyclonal antibodies, respectively, the membranes were treated with peroxidase-linked protein A (Amersham Biosciences, Buckinghamshire, England). Each time we do Western blot analysis, one for the Western blot analysis, another for the Coomassie brilliant blue staining to check the loading of protein as the same amounts. All assays were performed in duplicate. Band intensity was quantified an image analyzer system (NIH image 1.62).

2.4. Real-time quantitative RT-PCR analysis of TIMP-1 and -2 mRNA expression

After extraction of total RNA from cultured rat SMCs (n = 6, RSMCs) and each individual vessels (n = 25 for each group) using Rneasy Protect Mini Kit according to the manufacturer’s instruction, 20 ng of cellular RNA was analyzed by measuring the specific fluorescent signal from the TaqMan probe during RT-PCR according to the manufacturer’s protocol. The primers used here were a forward primer for TIMP-1 (5’-CCTTCGCAACTGGAAGTGACA-3’), a reverse primer for TIMP-1 (5’-ATGGTCTCGCTAGTGAAACGG-3’), a forward primer for TIMP-2 (5’-AGAACCTAAACCAAGGTACCAGAT-3’), and a reverse primer for TIMP-2 (5’-CTACTCACGGAAGACCTACCTGA-3’). Each mRNA quantity was normalized in regard to its respective GAPDH mRNA quantity. All assays were performed in duplicate.

2.5. Assay for gelatinolytic net activity

Gelatinolytic net activity was assayed as previously described with some modifications [18]. Equal amounts of total protein (50 μg) from the individual artery (n = 25


for each group) were added to a 96-well plate which was precoated with 500 μg/ml denatured FITC-labeled type I collagen (Collagen Research Center, Tokyo, Japan) and incubated overnight at 37 °C using a shaker. The solubilized gelatin fragments were then measured using Fluoroskan Ascent CF (Labsystems, excitation/emission maxima at 480 nm/520 nm). To identify the specific inhibitors for the gelatinolytic net activity present in the tissue extracts from the injured control arteries (n = 5 for each subgroup) at day 7 after the injury, the samples were incubated at room temperature with 10 μmol/l GM6001 (a MMP inhibitor; Calbiochem, San Diego, CA), 20 μmol/l E64 (a cysteine protease inhibitor; Molecular Probes, Eugene, OR), or 2 mmol/l phenylmethylsulfonylfluoride (a serine protease inhibitors; Sigma-Aldrich) for 30 min before being added to the substrate. Blank values were determined by the incubation in the absence of the tissue extract, and these were subtracted from counts determined in the presence of the tissue extracts. Five vessels for each time point were analyzed and each vessel was analyzed in duplicate.

2.6. Gelatin zymography

Gelatin zymography was performed as previously described [15]. After electrophoresis, the gels were washed twice for 30 min in 2.5% Triton X-100 (v/v) to remove the SDS, and then incubated overnight at 37 °C. Quantitative results of assays were obtained by densitometry. Six vessels for each group were analyzed.

2.7. Cell culture

RSMCs were obtained from rat aortic media using a tissue explant method and were cultured in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 10% fetal bovine serum and antibiotics [14]. The catechins used experiments in vitro were EGCG, epicatechin-gallate (ECG), catechins (C), epicatechin (EC), and epigallocatechin (EGC) (Sigma-Aldrich).

To examine the effect of catechins on the TIMPs expression in cultured RSMC, RSMCs in 80% confluent state were cultured in serum-free DMEM for 24 h in 24-
well plate and then treated with or without catechins at indicated concentrations for indicated time periods. At the end of the incubation, the conditioned media were collected and concentrated for Western blot analysis, and total cellular RNA was extracted for real-time RT-PCR analysis. All experiments used RSMCs between the 7th and 12th passages.

2.8. Statistical analysis

Values are expressed as mean ± S.D. Significant differences were analyzed by using a Student’s t-test or ANOVA followed by a Scheffe’s multiple-comparison post hoc test. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Treatment with catechins inhibits neointimal hyperplasia

The effect of catechins on the neointimal hyperplasia was quantified by histomorphometric analysis of the carotid arterial cross-sections at day 14 after the injury. A 30% reduction in neointimal area in the tea group arteries was seen compared with the control group arteries (0.091 ± 0.023 and 0.064 ± 0.026 mm² in the control and tea groups, respectively) (Fig. 1A–E). Similarly, the ratio of the intimal area to the medial area was 36.2% less in the tea group arteries than in the control group arteries (Fig. 1G). There were no significant differences in the medial area between two groups at day 14 after the injury (Fig. 1F).

Our preliminary experiments showed that after administration of the tea extract with free drinking for 7 days, plasma levels of total EGCG and ECG were in the range of ~ 0.27 and ~ 0.17 μmol/l (before the administration, they were not detected). It should be noted that there were no significant differences between the tea group and control group rats in plasma lipid levels before and after injury at day 14.

3.2. Gelatinolytic net activity

Balloon-injury resulted in a marked increase in gelatinolytic net activity in the tissue extracts of the injured arteries (Fig. 2A). Changes in the gelatinolytic net activity of the injured control arteries appeared as early as day 1 and reached a sevenfold peak at day 7 after the injury. The gelatinolytic net activity was reduced in the injured tea group’s arteries compared with the injured control arteries between days 3 and 14 after the injury (Fig. 2A). The gelatinolytic net activity of the injured control vessels was significantly (77%) inhibited by the addition of EGCG (1 μmol/l) as well as GM6001, an inhibitor of MMPs (80%).

---

Fig. 2. Gelatinolytic net activities of injured carotid artery. (A) Gelatinolytic net activity of tissue extracts from each individual vessel at various time points ($n = 5$ for each time point) after injury. (B) Effects of protease inhibitors on gelatinolytic net activity of the injured control vessels ($n = 5$) at day 7 after injury. Active recombinant MMP-2 (100 ng) was used as a positive control. (C) Gelatin zymographic analysis of the tissue extracts of the injured vessels ($n = 6$ for each group) at 7 days after injury. Lower panel shows the ratio of the activated form to the total MMP-2 at day 7 after injury. (D) The total MMP-2 in the injured vessels from both groups ($n = 6$ for each group) at day 7 after injury. Data were expressed as mean ± S.D. *$p < 0.05$, **$p < 0.01$ vs. uninjured control arteries. *$p < 0.05$, **$p < 0.01$ vs. control group at days 3, 7, and 14.
No significant inhibition was observed in samples incubated with PMSF or E64. Gelatin zymographic analysis of the tissue extracts from the injured vessels at day 7 after the injury revealed that major gelatinolytic activity was observed at a molecular mass of 72 kDa, which was most likely to correspond to the inactive form of MMP-2 (Fig. 2C). A 62-kDa band was also detected in the tissue extracts, and was assigned as activated form of MMP-2 (Fig. 2C). Quantitative analysis of these gelatinolytic bands showed no significant difference in total gelatinases (inactive plus activated form of MMP-2) in the injured vessels between the control and tea groups (Fig. 2D). However, the ratio of the activated form to the total MMP-2 of the extracts of the injured vessels from the tea group was less (62%) than that from the control group (Fig. 2C).

3.3. Effects of catechins on the expression of TIMP-1 and -2 in vivo

As shown in Fig. 3A, the levels of TIMP-2 mRNA did not change in the injured control vessels until 3 days after the injury. The relative mRNA level of TIMP-2 increased 2.9-fold over that of the uninjured control vessels at day 7 after the injury, and then decreased at day 14. In the tea group, the levels of TIMP-2 mRNA in the injured vessels were significantly higher than those of the control group between days 1 and 14 after the injury (Fig. 3A). There were no significant differences in the TIMP-1 mRNA profile in their group’s carotid arteries during the follow-up periods (Fig. 3B). No significant change of TIMP-2 mRNA was observed in either group’s uninjured right carotid arteries at any of the time points (data not shown).

Western blot analysis showed that the TIMP-2 protein levels in the tea group increased significantly from day 1 up to day 14 after injury, reaching their highest levels at day 7 (2.9-fold over the injured control artery), and levels of TIMP-2 protein were observed that were significantly higher than those of the control group (Fig. 4). The TIMP-2 protein was not detected in uninjured right carotid arteries at any of the time points (data not shown). In contrast with TIMP-2, no significant differences were observed in the TIMP-1 protein expression in the carotid arteries between the tea and control groups (data not shown).

Immunohistochemical analysis revealed a staining for TIMP-2 in the endothelial cell layer in uninjured vessels and only a weak staining in the medial region (Fig. 5A1 and B1). TIMP-2 staining of the carotid arterial cross-sections of the control and tea groups at days 7 and 14 after injury produced a strong positive-stained region in the intima of the carotid arteries (Fig. 5A2, A3, B2, and B3). There appeared to be no grossly visible differences in the intensity of TIMP-2 staining in the media region between day 0 and day 7 or 14 after the injury. Control preparation with non-immune serum used in place of the primary antibody showed virtually no background or nonspecific staining (Fig. 5A4).

3.4. Effects of catechins on TIMP-1 and -2 expression in vitro

As shown in Fig. 6A, EGCG stimulated TIMP-2 protein production from RSMCs in a concentration-dependent man-

![Fig. 3. Effects of administration of the tea extract on TIMP-2 (A) and TIMP-1 (B) mRNA expression. Total cellular RNA (20 ng) from an individual artery at each time point (n = 5 for each time point) was analyzed by real-time RT-PCR. Data were expressed as mean ± S.D. *p < 0.05, **p < 0.01 vs. uninjured control arteries. †p < 0.05 vs. control group at days 1, 3, 7, and 14.](https://academic.oup.com/cardiovascres/article-abstract/62/3/594/320053/)

![Fig. 4. Effects of administration of the tea extract on TIMP-2 protein production. 150 μg of total extracted from a single vessel at each time point (n = 5 for each time point) was loaded in each line. Upper panels show representative Western blots of TIMP-1 and -2. Values are taken from densitometric evaluation of Western blot bands. Data were expressed as mean ± S.D. †p < 0.05 vs. those of the controls at days 1, 3, 7, and 14.](https://academic.oup.com/cardiovascres/article-abstract/62/3/594/320053/)
ner, but had no effect on TIMP-1 production (Fig. 6A). When RSMCs were incubated with other catechin derivatives, C, EC, and EGC did not influence the level of TIMP-2 protein, but ECG as well as EGCG significantly increased the TIMP-2 protein level in the conditioned media (Fig. 6B). There was no change in the expression of TIMP-1 protein using various components of catechins as above (data not shown). The time course of both TIMP-1 and -2 mRNA after stimulation with EGCG (1 μmol/l) showed that EGCG significantly upregulated the expression of TIMP-2 mRNA level between 4 and 12 h of incubation, with the highest TIMP-2 mRNA expression at 8 h. (Fig. 6C). In contrast, EGCG did not affect the expression of TIMP-1 mRNA levels after incubation at any time point (Fig. 6C).

The effects of EGCG on the expression of TIMP-2 mRNA level at sequential concentrations were assessed

![Fig. 5. Immunohistochemistry of balloon-injured vessels from the control (A1–A3) and tea groups (B1–B3) with antibody to TIMP-2. Non-immune serum as a primary antibody was used for negative control (A4). L indicates lumen; solid arrow indicates internal elastic lamina; M indicates media.](image-url)
following 8 h of incubation. As shown in Fig. 6D, EGCG significantly increased TIMP-2 mRNA expression in a concentration-dependent manner.

4. Discussion

In the present study, we found that the free drinking of water with green tea extract in rats significantly inhibits balloon-induced intimal hyperplasia compared with control rats. Our result of the inhibitory effect of catechins on hyperlipidemia-independent intimal lesion formation is compatible with the previous report by Sachinidis et al. [19], although they did not perform the morphometric analysis.

The proliferation and migration of SMC play a major role in the lesion formation of intimal hyperplasia. In previous works, relatively high concentrations of catechins have been found to inhibit SMC proliferation in vitro [8,9]. We observed that freely available drinking water with tea extract produced plasma concentrations of EGCG in rats in the range of ~0.27 μmol/l, very similar to the concentration levels found in the plasma of human moderate tea drinkers (0.1–0.3 μmol/l) [20]. These concentrations of EGCG seem to be about 10- to 100-fold lower than those at which EGCG were found to inhibit SMC proliferation in previous reports [8,9], suggesting that the anti-proliferative effect of catechins on SMC may not be involved in the present study.

Since SMCs in large vessels are usually surrounded by and embedded in ECM, the migration of SMCs and the remodeling of tissues during intimal thickening require the controlled degradation of the ECM. During the processes of SMC migration from the tunica media to intima, SMCs must degrade and breach the ECM proteins surrounding each cell [10,13]. The balance of MMPs:TIMPs plays an important role in vascular remodeling by degrading the ECM and thereby allowing SMC migration [21]. In fact, the inhibition of MMPs by synthetic inhibitors results in impaired SMC migration in several in vitro [12] and in vivo models [22]. A number of studies have shown that the expression of MMP-2 and -9 are upregulated after vascular injury [10,11]. The present results extend these observations by providing quantitative analyses of the temporal changes in the gelatinolytic net activity of the injured vessels. This assay system demonstrated that balloon-injury led to a shift in the gelatinolytic balance toward a proteolytic state in vessel and suggested that most of gelatinolytic net activity was via MMPs based on observation using specific inhib-
mediated gene transfer of the human TIMP-2 gene inhibited of SMCs agrees with the previous finding that adenovirus-form. Our hypothesis that the administration of tea extracts due to the administration of the tea extract may be involved Therefore, the upregulation of the TIMP-2 in the vessels high affinity for MMP-9 and TIMP-2 for MMP-2[23,24]. involved in the inhibition of MMP activity. TIMP-1 shows a activity in the injured arteries of the tea group. MMP-2 may be involved in the decrease of gelatinolytic net activity in the injured arteries of the tea group.

TIMPs are multifunctional proteins that are principally involved in the inhibition of MMP activity. TIMP-1 shows a high affinity for MMP-9 and TIMP-2 for MMP-2 [23,24]. The administration of the tea extract significantly upregulated the expression of TIMP-2 mRNA and protein in the injured carotid arteries from day 1 to 14 after the injury, reaching the highest level at day 7, but had no effect on TIMP-1. Furthermore, it was reconfirmed by in vitro experiments that EGCG stimulated the expression of TIMP-2 in cultured RSMCs in a concentration-dependent manner, but no effect on TIMP-1. Immunohistochemical analysis showed that the increased TIMP-2 occurred preferentially in the developing neointima. These observations may suggest that the decreased gelatinolytic net activity in the arteries after the injury in the tea group compared with that of the control group is due to the upregulation of TIMP-2 expression in the injured arteries caused by the administration of the tea extract in combination with the reduced levels of the active form of MMP-2 as described above. Because TIMP-2 forms a unique complex with MMP-2 [23], TIMP-2 is more effective than TIMP-1 in inhibiting MMP-2 activity [24], and inhibits not only MMP-2 activity but also the conversion of its latent form to its active form [25]. Therefore, the upregulation of the TIMP-2 in the vessels due to the administration of the tea extract may be involved in the reduction of latent MMP-2 conversion to the active form. Our hypothesis that the administration of tea extracts inhibits intimal hyperplasia through TIMP-2 overexpression of SMCs agrees with the previous finding that adenovirus-mediated gene transfer of the human TIMP-2 gene inhibited neointimal formation in a balloon-injury model [26].

However, it should be noted that catechins, especially EGCG, may directly contribute to the reduction of the levels of the active form of MMP-2 in the injured arteries, since we and others have demonstrated that EGCG blocks the conversion of the latent form of MMP-2 to the active form [14,16]. In addition, in the present study we observed that EGCG, a major component of green tea catechins, suppressed the gelatinolytic net activity of the injured vessels, consistent with the previous findings that EGCG directly blocks MMPs activity [15]. This observation provided another possible mechanism for the effect of administration of the catechins on intimal hyperplasia. This hypothesis is supported by our previous finding that EGCG inhibited the SMC invasion through the basement membrane barrier without any influence of SMC migration across the basement membrane protein thin-coated filter, suggesting that the inhibitory effect of EGCG on SMCs invasion is not due to cell motility impairment, but rather to the inhibition of their proteolytic activities by blocking MMPs derived from SMCs [14]. Therefore, it is possible that the ingestion of catechins inhibits the neointimal formation through shifting the proteolytic balance towards the anti-proteolytic state in the injured vascular wall via two different mechanisms: Catechin may upregulate TIMP-2, and it may directly block MMP activity.

In summary, this study demonstrated that administration of the tea catechins inhibits intimal hyperplasia in balloon-injured rat carotid arteries. The upregulation of TIMP-2 of SMCs by catechins as well as the direct effect of catechins on MMP activity may be involved in this inhibition. The present findings may represent a novel therapeutic strategy to prevent angioplasty-induced restenosis.

References


