Cinnamon and Immune Actions: Potential Role in Tristetraprolin-Mediated Inflammatory Diseases

Heping Cao

Key Points

- Inflammatory diseases place a heavy burden on the American health care system.
- Tristetraprolin, a zinc-dependent mRNA binding protein decreases the stability of mRNAs coding for some proinflammatory cytokines.
- Tristetraprolin-deficient mice develop a profound inflammatory syndrome.
- Tristetraprolin is a potential cancer therapy due to its control of vascular endothelial growth factor mRNA stability.
- Cinnamon extract stimulates the expression of antiinflammatory tristetraprolin.
- Bioactive compound(s) in cinnamon extract define its molecular mechanisms.
- Cinnamon is potentially important in tristetraprolin-mediated inflammatory diseases.

Key Words: Cancer, cinnamon, immunity, inflammation, insulin, macrophage, obesity, tristetraprolin.

30.1 INTRODUCTION

Inflammation and associated diseases have placed a heavy burden on the American health care system. Drug treatment for reducing inflammation and related diseases has not been satisfactory. Complementary and alternative approaches need to be evaluated. Bioactive plant extracts have historically been used as alternative medicines for the prevention, alleviation, and cure of various diseases. The mechanisms of how bioactive plant extracts work are poorly understood due in part to the lack of knowledge in the structures of bioactive components in most of the extracts.

Anti-inflammatory activities are proposed to play an important role in the mediation of various health conditions by these alternative therapies; however, the anti-inflammatory mechanisms are not completely understood. Recent results indicate
that tristetraprolin (TTP) is an anti-inflammatory protein that binds to the unstable elements of mRNAs coding for inflammation-related factors such as tumor necrosis factor-alpha (TNF-\(\alpha\)), granulocyte-macrophage colony-stimulating factor (GM-CSF), cyclooxygenase-2 (COX2), and some interleukins (ILs) mRNAs, and decreases their stability. The mRNA binding and destabilizing activities of TTP are zinc-dependent and regulated by phosphorylation. TTP-deficient mice develop a severe inflammatory syndrome with arthritis, autoimmunity, cachexia, dermatitis, and myeloid hyperplasia. The expression of TTP is reduced in fats of obese people with the metabolic syndrome and the brains of suicide victims. TTP is also proposed as a molecular target for cancer therapy due to its control in vascular endothelial growth factor (VEGF) mRNA stability.

Cinnamon extract (CE), like insulin, stimulates TTP gene expression in mouse adipocytes. Unlike insulin, CE also stimulates TTP expression in mouse macrophages. Given the importance of TTP in biology and diseases, and the benefits of cinnamon, it is important to identify the bioactive compound(s) in this botanical extract. This chapter reviews the biological, medical, and nutritional significance of TTP, and the potentials of cinnamon in TTP-mediated inflammatory diseases.

30.2 TRISTETRAPROLIN IS AN ANTI-INFLAMMATORY PROTEIN

TTP, or zinc-finger protein 36 (ZFP36), is an anti-inflammatory protein. TTP deficiency in knockout mice causes a complex inflammatory syndrome with arthritis, autoimmunity, cachexia, dermatitis, and myeloid hyperplasia (1, 2). This is largely due to excessive production of TNF-\(\alpha\) and GM-CSF from the corresponding mRNAs that are normally degraded after binding TTP, but stabilized and persistent in cells from TTP knockout mice (3, 4). Transforming growth factor-beta (TGF-\(\beta\)) is a pleiotropic cytokine that plays a critical role in modulating immune response and inflammation. TTP expression is upregulated by TGF-\(\beta\), suggesting a potential role of TTP in mediating the immune suppressive action of TGF-\(\beta\) in vivo (5).

30.3 TRISTETRAPROLIN IS A ZINC-DEPENDENT mRNA BINDING AND DESTABILIZING PROTEIN

TTP is a zinc-binding protein with two zinc-finger binding motifs (6, 7). The biochemical function of TTP is binding to AU-rich elements (AREs) with high binding specificity for class II AREs within the 3′-untranslated regions of mRNA molecules (3, 4, 8–15). The binding of TTP to AREs results in the subsequent removal of the poly(A) tails and degradation of the RNA bodies (3, 13). Most of the TTP-targeted mRNAs identified so far code for proinflammatory factors such as TNF-\(\alpha\) (3, 10, 11, 13), GM-CSF (4), COX2 (16, 17), IL2 (18), IL3 (14), IL8 (19), IL10 (20), cytokine signaling 3 (21), E47 (22), and plasminogen activator inhibitor type 2 (23).

The mRNA binding activity of TTP is dependent on zinc. The removal of zinc from binding reaction mixtures destroys TTP’s ability to bind to TNF-\(\alpha\) mRNA ARE (10, 11). TTP mRNA and protein are detected in a number of tissues including
spleen, thymus, lymph node, lung, liver, and intestine (24, 25). The expression levels of TTP mRNA and protein in mammalian cells are increased in response to several kinds of stimuli, including insulin and other growth factors, and in response to stimulators of innate immunity, such as the bacterial endotoxin lipopolysaccharide (LPS) (24, 25).

30.4 TTP IS A LOW-ABUNDANCE, INDUCIBLE, CYTOSOLIC, AND HYPER-PHOSPHORYLATED PROTEIN

TTP is a hyper-phosphorylated protein in extraordinarily low abundance and is inducible, stable, and cytosolic (10–12, 24, 26). We have produced high-titer antibodies and used them successfully in characterizing the patterns of TTP expression in mouse tissues and cells. TTP is a very low-abundance protein in normal mouse tissues (24); however, it is induced several hundredfold by LPS in mouse RAW264.7 cells (Fig. 30.1) and in the rat spleen (24).

TTP is phosphorylated extensively in vivo (11, 24, 26) and is a substrate for multiple protein kinases (10, 11, 27). We have identified multiple phosphorylation sites in mammalian TTP by mass spectrometry and site-directed mutagenesis; some of which are predicted by motif scanning to be phosphorylated by several protein kinases (7, 26, 28).

30.5 TRISTETRAPROLIN IS ASSOCIATED WITH CANCER

TTP is widely present in human cancer cell lines (11, 29). TTP binds to the 3'-untranslated region of COX2 mRNA in human colorectal adenocarcinoma cell lines (16). Recent studies provide evidence that VEGF, an angiogenic cytokine, is a target of TTP (19, 30). These studies suggest that TTP is a new target for antiangiogenic therapies. VEGF has been proposed as the most important regulator of physiological and pathological angiogenesis (31). VEGF mRNA level is regulated by hypoxia, growth factors and hormones through both transcriptional and posttranscriptional mechanisms. VEGF mRNA has a short half-life and its abundance is regulated by stabilizing proteins HuR (32) and hRNP-L (33) and destabilizing proteins such as TTP and its family members (34), which bind to the 3'-untranslated region of VEGF mRNA. TTP binds to VEGF mRNA 3'-untranslated region and plays a key role by inducing VEGF mRNA degradation (30). TTP decreases RasVal12-dependent VEGF expression and the development of vascularized tumors in nude mice (30). TTP is ubiquitously expressed in the tissues and cell lines of primary malignant glioma (a highly aggressive tumor of the central nervous system) (19). Conditional over expression of TTP as a transgene in malignant glioma cells leads to RNA destabilization of IL8 and VEGF and down-regulation of IL8 and VEGF protein production. In vivo RNA binding indicates a shift of mRNA toward ectopic TTP and away from endogenous HuR. The biochemical phenotype is associated with a decrease in cell proliferation, loss of cell viability, and apoptosis (19). Taking together, these results suggest that TTP represents a novel antiangiogenic and antitumor agent acting through its destabilizing activity on VEGF mRNA.
Fig. 30.1. TTP is an extraordinary low-abundance protein that is inducible and cytosolic in mammalian cells. (a) Induction of TTP in RAW macrophage cells. Cells were treated with LPS (0.1 μg/ml) or PBS for 3 h, then fixed and stained with either the anti-MBP-mTTP serum (I) or preimmune serum (PI). (b) Cytosolic localization of TTP in RAW cells. Cells were stimulated with LPS (0.1 μg/ml) for 2 h and stained with anti-MBP-mTTP serum. Serial optical sections of the same cell were collected at 0.5 μm intervals. (c) Time-course of TTP induction in RAW cells. Cells were stimulated with LPS (0.1 μg/ml) for 0, 2, 3, and 5 h as indicated and stained with anti-MBP-mTTP serum. (d) TTP immunostaining during cell division in RAW cells. Unstimulated cells were stained with the anti-MBP-mTTP serum. Immunoreactive TTP was visible in the cytoplasm of the dividing cell indicated by the arrowheads in (d1), whereas no cytoplasmic staining was visible in the other cells in the field. A light microscopic image of the same field of cells is also shown (d2).

30.6 TRISTETRAPROLIN EXPRESSION IS REDUCED IN FATS OF OBESE PEOPLE WITH THE METABOLIC SYNDROME

Several lines of evidence suggest that TTP is involved in obesity. First, TTP mRNA levels are four to fivefold lower in visceral fat of obese people with the metabolic syndrome compared to those without the metabolic syndrome (35). Second, TTP gene is located in regions of linkage for the metabolic syndrome (35). Third, TTP mRNA levels in visceral adipose tissue in women are negatively correlated with fasting insulin levels, the insulin resistance index, and 2-h postglucose insulinenia, and positively correlated with adiponectinemia, suggesting that TTP gene expression in omental adipose tissue may contribute to partial protection against the development of insulin resistance and diabetes (36). Finally, TTP is abundantly expressed and increased by insulin in mouse
3T3 fibroblasts over expressing normal human insulin receptors (25) and 3T3-L1 adipocytes (37, 38), and induced by fetal bovine serum and differentiation mixtures during the differentiation of preadipocytes (39). These studies suggest that TTP may be an important factor for the physiological control of obesity-associated metabolic disorders.

30.7 TRISTETRAPROLIN EXPRESSION IS REDUCED IN BRAINS OF SUICIDE VICTIMS

TTP is potentially involved in normal brain activity because TTP gene expression is reduced in the brains of suicide victims. The cause of suicidal behavior is multifactorial, involving multiple genes, environmental factors, and gene-environment interactions. Thalmeier et al. studied the transcriptomic expression profile of postmortem brain tissue of suicide victims to identify new candidate genes and biological patterns for suicidal behavior (40). The authors analyzed the expression of over 23,000 mRNAs in postmortem orbitofrontal cortex tissue derived from 11 suicide victims and 10 nonpsychiatric controls. 124 transcripts are significantly changed with 59 underexpressed and 65 overexpressed in the suicide group (40). Both microarray and quantitative RT-PCR assays show that TTP gene expression is reduced by approximately twofold in postmortem orbitofrontal cortex of violent suicide victims (40). These results suggest that reduced TTP expression is involved in the pathophysiology of suicide.

30.8 TRISTETRAPROLIN IS ASSOCIATED WITH BLOOD PRESSURE

Microarray and function studies show that immediate-early response gene 3 mRNA turnover is decreased in cells derived from TTP-knockout mice (41). Since immediate-early response 3 protein is related to the regulation of blood pressure, TTP is therefore potentially involved in this important process.

30.9 TRISTETRAPROLIN EXPRESSION IS INCREASED BY MICRONUTRIENTS

The micronutrient, zinc (Zn), is the first metal shown to regulate TTP gene expression in mammalian cells. TTP gene expression is markedly increased by 50–100 μM ZnSO₄ in intact TK-L cells within 1 h, reached peak levels in 4 h, and remained constant to 12 h (42). Similar Zn effects are reported in Swiss 3T3 fibroblasts, primary mouse embryonic fibroblasts, H4 cells, normal human skin fibroblasts, and 1321-N1 human astrocytoma cells (42). TTP gene expression is also increased in liver, lung, kidney, and brain of mice 3 h after injection of ZnSO₄ (50 mg/kg) but not in mice after the consumption of 50 mM ZnSO₄ in water for 14 days (42). TTP gene expression is also increased by 50–100 μM CdCl₂ and AgNO₃ in TK-L1 cells (42).

Microarray and quantitative PCR technologies were used to investigate Zn responsiveness of known genes that influence Zn homeostasis and to identify genes that may relate to phenotypic outcomes of altered dietary Zn intake (43). Human monocytic/macrophage THP-1 cells were either acutely Zn depleted, using a cell-permeable Zn-specific chelator or were supplemented with Zn to alter intracellular Zn concentrations. Microarrays composed of approximately 22,000 elements were used to identify
those genes responsive to either Zn depletion, Zn supplementation, or both conditions. Approximately 5% or 1,045 genes are Zn responsive. Among them, 104 genes respond to Zn linearly in a positive mode (i.e., increased expression as cellular Zn increases). Of the 104 genes in this group, TTP is the most Zn-responsive gene and its expression exhibits a 14-fold reduction in Zn-depleted cells and approximately twofold increase in Zn-supplemented cells (43).

30.10 INSULIN INCREASES TTP AND DECREASES VEGF GENE EXPRESSION IN ADIPOCYTES

Insulin was shown to increase TTP mRNA levels in HIR3.5 preadipocytes (25) and during the differentiation of preadipocytes (39). TTP mRNA is also rapidly induced in adipocytes by 10 and 100 nM insulin treatment, with a 30-min induction resulting in an approximately five- and sevenfold increase over the control, respectively (38). TTP protein is barely detected in untreated cells, but is significantly induced by 10 and 100 nM of insulin treatment for 3 h (38). In contrast, ZFP36L1 (a TTP homologue) protein levels are not significantly affected by insulin treatment using ZFP36L1 antibodies produced with the method similar to that for TTP antibodies (24, 38, 44).

To test the functional consequences of elevated TTP protein levels in mouse adipocytes, RT-PCR was used to screen the expression of 42 other genes in insulin-treated adipocytes (38). VEGFA mRNA levels are decreased approximately 30–50% by 10 and 100 nM insulin treatments for 30–120 min (38), and that VEGF mRNA levels are also significantly decreased by the same treatments (38). VEGF mRNAs code for VEGF, a proangiogenic factor important for the development of obesity (45, 46) and cancers (47), whose stabilities are known to be destabilized by TTP family proteins in cancer cells (19, 30, 34).

30.11 CINNAMON EXTRACT, LIKE INSULIN, INCREASES TTP AND DECREASES VEGF GENE EXPRESSION IN ADIPOCYTES

Cinnamon and other spices including cloves, turmeric, and bay leaves have insulin-like activity in vitro (48), and are proposed to be effective in the treatment of diabetes (49). However, not all studies have reported positive effects of cinnamon in patients with diabetes (50, 51). This discrepancy may be due to the selection of patients, level of glucose control, oral hypoglycemic agents, and/or diet or type of cinnamon used.

We prepared a water-soluble CE and HPLC-purified cinnamon polyphenols (CP) from CE (52). The structure of a trimer is shown in Fig. 30.2a. These polyphenols have been shown to be absorbed (53) and to increase the activity and sensitivity of insulin (37, 52, 54, 55). Microscopic observation indicated that approximately 80–90% of the differentiated mouse 3T3-L1 fibroblasts cells accumulated lipid drops (an indication of differentiation from preadipocytes to adipocytes) (Fig. 30.2b). The cells were serum-starved for 3–4 h before treatments.

TTP mRNA levels in 10 and 100 μg/ml CE-treated adipocytes are up to two- and sixfold, respectively, those of the controls (37). TTP protein is barely detected in untreated cells but is significantly induced by 10 and 100 μg/ml of CE in 3T3-L1 adipocytes after 3 h treatment (37). The purified CP at 10 and 100 μg/ml also increases the
Fig. 30.2. Cinnamon polyphenol and differentiated adipocytes. (a) The structure of a CP purified from CE. The CP structure was determined as a doubly linked procyanidin type-A polymer by nuclear magnetic resonance, mass spectroscopy, and infrared spectroscopy as described (52). (b) Differentiated mouse 3T3-L1 adipocytes (37).

The amount of TTP in the adipocytes after 3 h treatment. Higher concentrations of CE and CP treatments result in more TTP in the adipocytes (37).

30.12 CINNAMON EXTRACT, UNLIKE INSULIN, INCREASES TTP GENE EXPRESSION IN MACROPHAGES

Mouse RAW264.7 macrophages are widely used as a cell model for inflammation research. TTP gene expression has been investigated extensively using this cell line (24, 56). TTP protein is rapidly induced by LPS and accumulated in the cytosol of these cells (24, 57). We utilized this model to evaluate the effect of CE on TTP gene expression in RAW macrophages (58). CE rapidly increases TTP mRNA levels in mouse RAW cells. TTP mRNA levels in cells treated with 100 μg/ml CE for 30–240 min are 150–200% of those in the corresponding controls (Fig. 30.3a). Insulin does not exhibit any significant effect on TTP mRNA levels in RAW cells (Fig. 30.3a). LPS possesses a much more potent effect on TTP gene expression in RAW cells. TTP mRNA levels in cells treated with 0.1 μg/ml LPS for 30–240 min are 9–39-fold of the controls, respectively (Fig. 30.3b).

TTP protein is increased in cells treated with 100 μg/ml CE for 90–180 min (Fig. 30.3c, lanes 6–8). LPS increases TTP protein levels in RAW cells much earlier and with a greater magnitude than CE induction (Fig. 30.3c, lanes 9–14). However, TTP protein levels are below detection in cells treated with insulin for the same length of time (58).
Further analyses showed that: (1) CE induces TTP gene expression more rapidly than those of proinflammatory cytokine mRNAs encoding TNFα, COX2, and IL6 in mouse macrophages; (2) the net increases of TTP mRNA levels are larger than those of proinflammatory cytokines; (3) CE increases more GLUT1 gene expression than LPS; and (4) CE effects on the expression pattern of these genes are different from those of LPS in RAW macrophages during the initial treatment (58). These results indicate that CE is capable of affecting inflammatory responses by regulating anti- and proinflammatory as well as the major GLUT gene expression in macrophages.
30.13 CONCLUSIONS AND PERSPECTIVES

Diet and lifestyle play major roles in disease prevention. The consumption of a nutritious diet is important for maintaining long-term health and decreasing the risk of chronic diseases. Research is urgently needed to determine dietary means, including consumption of bioactive food components that may alleviate or prevent diseases; however, there is a lack of sound evidence at the molecular level to support this practice.

Cinnamon extract (CE) exhibits insulin-like activity in cells, animals, and people with type 2 diabetes (49, 54, 55, 59–62). This is supported by several lines of evidence including (1) CE increases glucose metabolism in a fat cell assay (52); (2) CE increases insulin receptor β auto-phosphorylation and decreases tyrosine phosphatase activity in vitro (54); (3) CE increases glucose uptake and glycogen biosynthesis, activates glycogen synthase, and inhibits glycogen synthase kinase-3β (55); (4) CE potentiates in vivo insulin-regulated glucose utilization in rats fed a high-fructose diet (60); (5) CE decreases serum glucose levels and increases insulin in rats (62) and decreases blood pressure (59); (6) cinnamon powder decreases the levels of glucose, triglycerides, and LDL cholesterol in people with type 2 diabetes (49, 63); and (7) CE, like insulin (38), increases TTP

Fig. 30.4. A model that links cinnamon extract, insulin, TTP, and cytokines to inflammation and associated diseases. Like insulin, CE increases TTP gene expression in mouse adipocytes. However, unlike insulin, CE also increases TTP gene expression in mouse macrophages. The detailed evidence is described in the text (“+” represents positive effect and “−” represents negative effect). The model is modified from Cao et al. (37, 64, 65).
expression in mouse adipocytes (37, 38). However, unlike insulin, CE also increases TTP expression in mouse macrophages (58). Based on these results, we have proposed a model to link cinnamon polyphenols, insulin, TTP, and cytokines to inflammatory diseases and inflammation in a wide variety of related diseases (Fig. 30.4). More detailed studies are required to fully understand the health benefits of CE.

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Dietary Components and Immune Function

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