Gum Mastic Inhibits the Expression and Function of the Androgen Receptor in Prostate Cancer Cells

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Supported by the National Natural Science Foundation of the Peoples Republic of China (Projects 30470820 and 30371564).

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Received September 6, 2005; revision received December 16, 2005; accepted January 26, 2006.

Accumulating evidence suggests that the androgen receptor (AR) may play an important role in the development and progression of prostate cancer. To find new, useful compounds that effectively may attenuate the function of AR in prostate cancer cells, the authors investigated the effect of gum mastic, a natural resin, on AR activity. An androgen-responsive prostate cancer cell line LNCaP was used as a model for this study. Gene transfer, reverse transcriptase-polymerase chain reaction analysis, electrophoretic mobility shift assay, and Western blot analysis were used to test the effect of gum mastic on the expression and function of the AR. To demonstrate the inhibitory effect of gum mastic on the function of the AR, the expression of androgen-regulated genes, including prostate-specific antigen (PSA), human kallikrein 2 (hK2), and NKX3.1 were measured. In addition, transient transfection assays with the PSA promoter and the AR promoter also were used to test the effects of mastic. The results showed that gum mastic inhibited the expression of the AR at the transcriptional level, resulting in the down-regulation of both AR messenger RNA and protein levels. Therefore, the function of the AR was inhibited, as reflected by the reduced expression of NKX3.1 and PSA and by androgen-stimulated growth. Because gum mastic exhibited a strong in vitro potency to attenuate the expression and function of the AR, further investigation will be required to determine whether this naturally occurring substance has in vivo potency to inhibit prostate cancer development. Cancer 2006;106:2547–55. © 2006 American Cancer Society.

KEYWORDS: gum mastic, androgen receptor, androgen-regulated gene, prostate cancer cell line.

Androgens play a critical role in regulating the growth, differentiation, and survival of epithelial cells in the normal prostate. Accumulating evidence shows that androgens also may be involved in the development and progression of prostate cancer. The biologic effects of androgens in the prostate are mediated by the androgen receptor (AR), which is a ligand-activated transcription factor of the nuclear receptor superfamily.1 The objectives of endocrine therapy for prostate cancer are to reduce the levels of circulating androgens, to block agonist activation with antagonist, or both. However, endocrine therapy is only palliative. Prostate cancer recurrences generally occur within 1 or 2 years and become hormone refractory with a potentially fatal outcome after endocrine therapy.2 Many molecular mechanisms have been postulated as responsible for the development of recurrent, hormone-refractory tumors. Most of these mechanisms involve alterations in the function of the AR and its complex signaling pathways.3 Studies of patient tissue samples have demonstrated that nearly all cancer tissues retain AR expression regardless of clinical stage or hormone status.4–6 Indeed, the finding that the
majority of hormone-refractory cancers still expresses the androgen-regulated prostate-specific antigen (PSA) gene indicates that the AR signaling pathway is functional. It is interesting to note that amplification of the AR gene was detected in a subgroup of patients with prostate cancer who showed tumor progression. In addition, mutations in the AR that enable the receptor to respond to residual androgens, non-androgen steroids, or even antagonists have been suggested as potential causative factors for tumor recurrence and progression. Moreover, it was possible for the AR to remain active by growth factor-mediated activation in the absence or at very low levels of androgens. Therefore, minimizing or eliminating the function of the AR may be an effective strategy in the fight against prostate cancer.

Gum mastic is a resinous exudation that is obtained from the stem and leaves of Pistacia lentiscus trees. It has been used extensively for centuries in Mediterranean and Middle Eastern countries both as a dietary supplement and as an herbal remedy. Medical trials have shown that gum mastic may have cytoprotective or antiacid effects for the gastrointestinal system, such as relief of ulcers and reducing the intensity of gastric mucosal damage caused by antiulcer drugs and aspirin, with little or no side effects. Recent studies seemed to suggest that gum mastic may exhibit antibacterial properties. In the current work, we examined the effect of gum mastic on the AR in an androgen-responsive human prostate cancer cell line, LNCaP.

**MATERIALS AND METHODS**

**Cell Culture and Treatments**

The human prostate cancer cell line LNCaP and PC-3 was obtained from the American Type Culture Collection (Rockville, MD). The LNCaP cell line was established from a lymph node metastasis from a patient with prostate cancer and expresses AR. LNCaP and PC-3 cells were seeded in 35-mm culture dishes in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS) and 5% carbon dioxide at 37°C until they reached approximately 50% to 70% confluence. Cells were maintained in serum-free RPMI-1640 medium for an additional 24 hours before experiments to deprive them of steroid hormones. Cells were then treated with gum mastic at indicated concentrations in RPMI-1640 medium that contained 5% charcoal-stripped FBS (GIBCO BRL, Grand Island, NY) with or without 1 nM synthetic androgen (mibolerone [Mib]). Gum mastic (no. G0878; Sigma Chemical Company, St. Louis, MO) was dissolved in dimethyl sulfoxide (DMSO), which also was used as a control vehicle in the cell proliferation assay and in other analyses for this study. In these assays, every group received same amount of DMSO.

**Cell Proliferation Assay**

For the methyl-thiazoldiphenyl tetrazolium (MTT) assay (Sigma Chemical Company), cells were cultured in 96-well culture plates at a density of 1000 cells per well with 200 μL of culture medium with or without androgen. After a 2-day incubation, gum mastic was added for 48 hours. At the time cell growth was evaluated, 20 μL MTT (final concentration, 0.5 mg/mL) were added to each well. After another 4-hour incubation, formazan crystals that were produced by living, cultured cells were dissolved with 100 μL DMSO to measure the absorbance at 570 nanometers (nm).

**Reverse Transcriptase-Polymerase Chain Reaction Analysis**

Total RNA was isolated from treated cells by using TRizol reagent (Invitrogen, Carlsbad, CA). Two micrograms of total RNA were used to reverse transcribe using M-Mulv reverse transcriptase in the presence of random hexamer primer. The resulting combinational DNA preparation was subjected to polymerase chain reaction (PCR) amplification by using a PCR kit from TaKaRa Biotech (Dalian, China). The following primers were used: For the AR, the sense primer was 5′-TCTCAAGAGTTTGTAGATTGCTCC-3′, and the antisense primer was 5′-TCAGGCTGGATGACCTCC-3′; for the housekeeping gene β-actin, the sense primer was 5′-GTGGCGGCCTCAACG-3′, and the antisense primer was 5′-CCTCTGATTGACCACCG-3′. PCR conditions consisted initial denaturation at 94°C for 3 minutes and 28 cycles of amplification with denaturation at 94°C for 40 seconds, primer-annealing at 60°C for 40 seconds, and primer extension at 72°C for 40 seconds. The final primer extension was performed at 72°C for 10 minutes. The PCR products were analyzed by electrophoresis on a 1.5% agarose gel containing ethylene bromide, and the gels were photographed under ultraviolet light.

**Nuclear Extracts**

LNCaP cells were grown in the same conditions as described above and were treated with gum mastic for 24 hours. Then, 2 × 10⁶ cells were pelleted and resuspended in 1 mL cold hypotonic buffer (10 mmol/L 4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid [HEPES] [pH 7.9], 1.5 mmol/L MgCl₂, 10 mmol/L KCl, 0.5 mmol/L dithiothrietol [DTT], and 0.5 mmol/L phenyl methyl sulfonil fluoride [PMSF]). After a 15-minute incubation on ice, the cells were lysed by adding 50 μL of 10% NP-40 and centrifuged at 7000
revolutions per minute for 5 minutes at 4°C. The pellets were resuspended in 70 μL cold hypertonic buffer (20 mmol/L HEPES [pH 7.9], 1.5 mmol/L MgCl₂, 420 mmol/L NaCl, 0.2 mmol/L ethylenediamine tetraacetic acid [EDTA], 25% glycerol, 10 μg/mL aprotinin, and 0.5 mmol/L PMSF), stirred gently at 4°C for 30 minutes, and centrifuged at 12,000 revolutions per minute for 5 minutes at 4°C. The supernatant fluid was dialyzed against the dialysis buffer (20 mmol/L HEPES [pH 7.9], 50 mmol/L KCl, 25% glycerol, 0.5 mmol/L DTT, and 0.5 mmol/L PMSF) for 2 hours at 4°C. The protein concentration of the dialyzed nuclear extracts was determined by using the bicinchoninic acid method, and the extracts were stored at −80°C in small aliquots.

**Western Blot Analysis**

For Western blot analysis, 40 μg of nuclear extracts were separated on 10% sodium dodecyl sulfate/polyacrylamide gel electrophoresis gels, and the gels were transferred onto a nitrocellulose membrane, which was blocked immediately with 5% nonfat milk in phosphate-buffered saline for 1 hour at room temperature. After blocking, the membrane was incubated with specific anti-AR, anti-NKX3.1 (BD Biosciences, San Diego, CA), anti-p21WAF-1/CIP1 (Cell Signaling, Beverly, MA), or anticyclin D1 (Sigma Chemical Company) antibody at 4°C for 12 hours. This was followed by incubation with peroxidase-labeled secondary antibody for 1 hour; then, immunoreactive bands were visualized by enhanced chemiluminescence (ECL) (Santa Cruz Biotechnology, Inc., Santa Cruz, CA). β-Tubulin (BD Biosciences) or Ponceau S-protein staining was used to normalize the quantity of the protein on the blot.

**Electrophoretic Mobility Shift Assay**

Equal amounts of sense and antisense oligonucleotides that contained an androgen-response element (ARE)16,17 of the PSA gene were mixed and annealed in 10 mmol/L Tris-HCl (pH 8.0), 200 mmol/L NaCl, and 1 mmol/L EDTA by heating to 95°C for 5 minutes and cooling to room temperature over 3 hours. The corresponding oligonucleotides were labeled with digoxigenin (DIG). The following oligonucleotides were used for electrophoretic mobility shift assay (EMSA) experiments: for ARE, the sense oligonucleotide was 5’-TGCGAGACAGAAGTGCTAGC-3’, and the antisense oligonucleotide was 3’-ACGTCTTGTGCTACGATCG-5’. Binding reactions were performed at room temperature for 30 minutes in a mixture that contained 4% glycerol, 1 mmol/L MgCl₂, 0.2 mmol/L EDTA, 0.5 mmol/L DTT, 50 mmol/L NaCl, 10 mmol/L Tris-HCl, 2 μg poly(dI-dC), 10 μg nuclear extracts, and DIG-labeled oligonucleotide probe. The reaction mixtures were subjected to electrophoresis on 5% nondeaturing polyacrylamide gels in 0.25 × Tris/borate/EDTA buffer. Based on the instructions for the DIG Gel Shift Kit (Roche; Indianapolis, IN), electroblotting and chemiluminescent detection were performed. The specificity of ARE binding was confirmed by adding a 125-fold excess of unlabeled DNA probe to the assay or 2 μg of anti-AR antibody.

**Transient Transfection Assay**

Transient cotransfections were performed with a plasmid of the 6-kilobase (kb) PSA promoter luciferase (2 μg), human kallikrein 2 (hK2) 3-ARE luciferase (1 μg), 2 kb AR promoter luciferase (1 μg), and cytomegalovirus (CMV)-driven human AR expression (0.5 μg) or a corresponding parental empty plasmid (1 or 2 μg) using Lipofectin™ 2000 reagent (Invitrogen) as described previously.18 A CMV promoter-driven β-galactosidase (β-gal)-expressing plasmid (0.3 μg) also was included in the transfections for monitoring transfection efficiency. After transfection, cells were incubated with designated concentrations of gum mastic ± 1 nM Mib for an additional 20 hours in RPMI-1640 medium that contained 5% charcoal-stripped serum. Cell extracts were prepared for luciferase and β-gal assays according to the manufacturer’s instructions. Luciferase activity was normalized with β-gal activity. At least 3 independent transfections were performed, and standard deviations were calculated.

**RESULTS**

**Gum Mastic Inhibits the Proliferation of LNCaP Cells by Androgens**

First, we examined the effect of gum mastic at various doses on prostate cancer cell proliferation stimulated by androgens. Cell proliferation, as measured by the MTT assay, was inhibited by gum mastic in a dose-dependent manner. The data illustrated in Figure 1 show that, consistent with previous reports, LNCaP cell proliferation was increased moderately with androgen treatment at physiologic concentrations (i.e., approximately 1 nM). However, it was possible to reduce this stimulatory effect with gum mastic treatment.

**Gum Mastic Inhibits Expression of the AR Gene**

The results described above suggested that gum mastic may affect androgen-stimulatory effects. Therefore, we began to assess whether the inhibitory effect was because of an alteration in AR expression, and reverse transcriptase-PCR was used to measure the steady levels of AR messenger RNA (mRNA). Figures 2A and
show that AR mRNA expression was down-regulated by gum mastic treatment in a dose-dependent fashion. The reduced expression can be observed, especially at gum mastic levels \(6\) and \(8\) g/mL. To demonstrate further the inhibitory effect of gum mastic on AR protein expression, Western blot analysis was used to evaluate AR protein levels. The results illustrated in Figures 2C and 2D demonstrate that the expression of AR protein was decreased significantly by gum mastic, consistent with the effect of gum mastic on AR mRNA expression. To understand the potential mechanism by which the expression of AR can be affected by gum mastic, transient transfections with an AR promoter-luciferase construct were performed to determine whether transcriptional activity of the AR gene was changed by gum mastic. Figure 2E shows that the activity of the AR promoter was inhibited significantly by gum mastic, consistent with the results illustrated in Figure 2A through 2D. Therefore, we concluded that the inhibitory effects of gum mastic on AR expression most likely occur mainly at the transcriptional level, which subsequently affects the levels of AR mRNA and protein.

Gum Mastic Decreases in Vitro the AR Binding Activity to ARE Sequence

Next, we wanted to investigate whether the function of the AR is affected by gum mastic. We used the EMSA as an in vitro AR functional assay to determine ARE DNA-binding activity. The results in Figure 3 show that AR binding activity to ARE largely was decreased by \(6\) \(\mu\)g/mL and \(8\) \(\mu\)g/mL of gum mastic after 24 hours of treatment compared with the control. The results confirmed that the bands were a result of specific binding for ARE, because the DNA-protein complex can be competed out by a 125-fold molar excess of unlabeled ARE oligonucleotide. Furthermore, the intensity of the band could be reduced by a specific anti-AR antibody.

FIGURE 1. The effects of gum mastic on the proliferation of LNCaP cells are illustrated. LNCaP cells were treated with various amounts of gum mastic for 48 hours with or without androgen. A methyl-thiazoldiphenyl tetrazolium (MTT) assay was used as described in the text. The average MTT measurements for the group that received only mibolerone (Mib) were presented as 100\% (\(n=4-6\) experiments). Double asterisks indicate \(P<.05\) compared with the group (solvent control) that did not receive gum mastic or Mib treatment; a single asterisk indicates \(P<.05\) compared with the group that received Mib treatment only.

Gum Mastic Inhibits the AR Transcriptional Activity Function on the Androgen-Regulated Genes

PSA and \(hK2\) are 2 typical androgen-inducible genes with promoters that contain positive AREs for AR to bind and, therefore, to activate their expression. Transient transfection assays were performed in LNCaP cells to investigate whether the activities of these 2 AR-regulated genes could be affected by gum mastic. The reporter gene expression vector, pGL3-SV40-\(hK2\) 3-ARE and pGL3-basic-6-kb PSA promoter, were used in this experiment. In addition, PC-3 cells were used in a cotransfection with pGL3-basic-6-kb PSA promoter and AR expression vector to determine the effect of gum mastic. The results (Fig. 4) show that gum mastic largely inhibited luciferase activity of the PSA promoter and/or \(hK2\) 3-ARE constructs. It is noteworthy that the effective concentrations were somewhat higher in PC-3 cells than in LNCaP cells.

Gum Mastic Inhibits PSA Protein Expression

We demonstrated that the expression of PSA and \(hK2\) is inhibited by gum mastic at the transcriptional level, as demonstrated by the transient transfection experiment described above. We wanted to test whether endogenous PSA protein expression also would be reduced consistently by gum mastic. LNCaP cells were treated with different concentrations of gum mastic for 24 hours. Spent media were harvested for assaying total PSA proteins. The normalized data in Figure 5 show that PSA protein levels in LNCaP cells were decreased by treatment with gum mastic in a dose-dependent manner.

Gum Mastic Inhibits the Expression of \(\text{NKX3.1}, \text{Cyclin D1}, \text{and} \ p21^{\text{WAF-1/CIP1}}\)

In addition to the PSA and \(hK2\) genes, \(\text{NKX3.1}\) also is a prostate-specific, androgen-regulated homeodomain transcription factor gene that plays a critical role in the development of normal prostate gland and the progression of prostate cancer. We anticipated that the expression \(\text{NKX3.1}\) would be inhibited by gum mastic. Indeed, Western blot analysis showed that
Gum mastic was able to reduce the expression of NKX3.1 protein, as expected. Together, the results illustrated in Figures 4, 5, and 6 demonstrate that gum mastic may have a general inhibitory effect on androgen-regulated genes.

We also examined whether gum mastic would affect the expression of cyclin D1 and p21 WAF-1/CIP1, because those 2 proteins may be related to cell proliferation or survival. The Western blot analysis illustrated in Figure 7 shows that gum mastic largely reduced the levels of these 2 proteins.

**DISCUSSION**

The LNCaP cell line is a well established, androgen-responsive prostate cancer cell line that expresses the AR and a number of prostate-specific, androgen up-regulated genes, such as PSA, hK2 and NKX3.1.

In the current study, the results showed that gum mastic inhibited the androgen-stimulated growth of LNCaP cells and inhibited the expression of all 3 androgen up-regulated genes. Because the AR is essential for androgen-stimulated proliferation of prostate cancer cells, the effect of gum mastic presumably works through the suppression of AR-mediated action. The results of the current study clearly demonstrated that gum mastic inhibited both the expression and function of the AR in LNCaP cells. Moreover, we observed that gum mastic inhibited the protein level of cyclin D1 and p21 WAF-1/CIP1. Cyclin D1 is a positive factor for cell proliferation and can be enhanced in mitogenic androgen effects on LNCaP cells. It is believed that cyclin D1 is reduced in the treatment. However, p21 has been recognized as a cell proliferation inhibitor, although recent studies suggest that p21 may promote cell survival in prostate cancer cells. The inhibitory effect of gum mastic on p21
may be beneficial in the repression of prostate cancer cell growth.

It has been demonstrated that PSA is the most sensitive biochemical marker available for monitoring the presence of prostate cancer and response to therapy. The primary regulator of expression of PSA is the AR, which induces PSA expression through at least 3 androgen-responsive elements located in the proximal 6-kb promoters of the PSA gene. Gum mastic decreased PSA expression levels as a result of AR down-regulation and inhibited ARE DNA-binding activity in the EMSA assay. In addition, gum mastic influenced the expression of other androgen-regulated genes, such as hK2, NKX3.1. hK2, and PSA, which belong to the human kallikrein gene family, are highly up-regulated by androgens, and are potential biomarkers for prostate cancer. NKX3.1, which is a prostate-specific homeodomain transcription factor, is related closely to the development of normal prostate gland and the progression of prostate cancer. Its expression is highly up-regulated by androgens and recently has been associated with a more aggressive phenotype of prostate cancer. Therefore, the current study results strongly suggest that gum mastic may have a general effect on androgen-regulated gene expression, although it is possible that gum mastic may have effects on nonandrogen-related pathways.

Endocrine therapy for prostate cancer is directed toward the reduction of serum androgens and the inhibition of AR functions. However, androgen-ablation therapy ultimately fails, and prostate cancer often progresses to a hormone-refractory state and eventually becomes incurable. In fact, as discussed above, the AR still is expressed in many of apparently hormone-refractory cancers. Mutations and gene amplification of the AR gene, aberrant expression of AR coregulators, and growth factors can contribute to activation of the AR independent of androgens. It has been suggested that inhibition of the AR through mechanisms other than ligand manipulation or antag-
onists may provide additional therapeutic and/or preventative benefits.\textsuperscript{36} Inhibition of AR expression has been achieved by potential chemopreventive agents, such as resveratrol\textsuperscript{37} and quercetin,\textsuperscript{38} and by the application of AR antisense oligonucleotides.\textsuperscript{39,40} Data from the current study clearly demonstrated that gum mastic can inhibit the expression of the AR at the transcriptional level. The down-regulation of AR levels by gum mastic may be a major mechanism for the reduction of AR function, as reflected by in vitro ARE DNA-binding and androgen-regulated gene expression assays. Therefore, the current study provides evidence of a new potential agent against prostate cancer mainly through inhibition of the AR-mediated pathway.

It has been shown that gum mastic has potential use for treating benign gastric ulcers and duodenal ulcers.\textsuperscript{10–13} In a double-blind clinical trial with 38 patients who had symptomatic and endoscopically proven duodenal ulcers, the results demonstrated that mastic gum at an oral dose of 1 g per day for 2 weeks exhibited a significant therapeutic response.\textsuperscript{11} It was suggested that mastic may have an ulcer-healing effect with very few side effects during the treatment period. Results from animal studies also appear to support the protective effect of gum mastic. More recently, in vitro studies also suggested that mastic may have the ability to protect human LDL from oxidation\textsuperscript{41} and to induce

**FIGURE 5.** The effects of gum mastic on the protein levels of prostate-specific antigen (PSA) are illustrated. LNCaP cells were treated with gum mastic and androgen at designated concentrations for 24 hours, and PSA protein levels were normalized to cell density by using the methyl-thiazoldi phenyl tetrazolium assay. Error bars indicate the standard error of 3 separate experiments. An asterisk indicates $P<.05$ compared with the group that did not receive gum mastic (dimethyl sulfoxide was used as a control vehicle in this group).

**FIGURE 6.** Gum mastic inhibited the expression of NKX3.1. (A) Western blot analysis for NKX3.1 protein levels. $\beta$-Tubulin was used as an internal control for protein loading and transfer efficiency. (B) A densitometric measurement for NKX3.1 protein levels normalized to $\beta$-tubulin was performed, and the results are expressed in relative units.

**FIGURE 7.** Gum mastic inhibits the expression of cyclin D1 and p21\textsuperscript{WAF-1/CIP1}. Western blot analysis for cyclin D1 and p21\textsuperscript{WAF-1/CIP1} protein levels is shown. A protein band stained by Poseau S was used as an internal control for protein loading and transfer efficiency. Densitometric measurements for p21 and cyclin D1 protein levels (shown under each blot) normalized to Poseau S protein staining were performed, and the results are expressed in relative units.
the apoptosis of human colon cancer HCT116 cells. It is noteworthy that mastic exhibited killing effects on Helicobacter pylori in vitro; however, the in vivo effects have not been substantiated. Conversely, double-blind, randomized studies on 20 dental students were performed to determine whether gum mastic has any antiplaque activity. The results showed that mastic chewing gum may be useful in reducing the bacterial growth in saliva and plaque formation on teeth. Finally, the results of the current study strongly suggest that gum mastic may have antiprostase cancer effect through its suppressive effect on the expression and function of the AR.

In addition to gum mastic, there are other herbal gum resins, including those from Boswellia serrata and oleo. The main active ingredients of these gum resins, including those from Boswellia serrata and function of the AR. In a gas chromatography-mass spectrometry (GC-MS) analysis, it was observed that gum mastic contains mainly α-pinene (40%), β-pinene (1.5%), β-myrcene (9%), limonene (1%), and β-caryophyllene (5%), most of which are monoterpenes. Many monoterpenes, including α-pinene, may exhibit anticancer activities. Based on the current results, we speculate that the major component of gum mastic, α-pinene, may be the active compound for repressing AR expression in LNCaP cells, although we cannot rule out the possible involvement of other components in gum. Because other gum resins can be administered systemically for disease treatments in animal models, we expect that gum mastic or its active components may be useful in vivo for prostate cancer prevention and treatment. Animal studies and clinical trials on the anti-prostate cancer effect of gum mastic should be performed to determine its clinical utility. In addition, further investigation is on going in our laboratory to gain a better understanding of the possible mechanisms of gum mastic on prostate cancer cells and their potential use in therapy.

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