Curcumin inhibits fibrosis-related effects in IPF fibroblasts and in mice following bleomycin-induced lung injury

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Current research suggests that IPF may begin with damage to lung alveoli and failure of alveolar reepithelialization after injury. Failure of reepithelialization allows lung fibroblasts to proliferate in the interstitium and then differentiate into myofibroblasts in response to normal wound healing signals such as transforming growth factor-β (TGF-β). The fibrotic changes seen in IPF largely reflect inappropriate deposition of collagen and extracellular matrix by these myofibroblasts (9, 19, 39, 40). With the failure of anti-inflammatory treatments and increased understanding of the underlying mechanisms of IPF, recent investigation of potential therapeutic strategies has focused on proliferation and differentiation mechanisms in lung fibroblasts.

Fibroblast to myofibroblast differentiation is characterized by de novo expression of α-smooth muscle actin (α-SMA) in response to TGF-β (10, 11, 41). Thus blockade of TGF-β activity and the signaling pathways through which it acts might significantly inhibit development of pulmonary fibrosis. Curcumin, the yellow pigment from the rhizomes of the Curcuma longa plant commonly known as turmeric, has long been used as a medicinal agent in many Asian countries (24, 35). This compound has been shown to exhibit a variety of potentially beneficial effects, including antioxidant and anti-inflammatory activities and promotion of wound healing (24). In particular, curcumin has been shown to inhibit processes essential to development of liver and pancreatic fibrosis. These processes include proliferation and differentiation of hepatic and pancreatic stellate cells as well as profibrotic expression of extracellular matrix genes and collagen deposition (17, 25, 48). These data suggest that curcumin may be an effective treatment for pulmonary fibrosis.

To better define the potential use of curcumin as a therapeutic option for pulmonary fibrosis, we investigated the effects of curcumin in IPF fibroblasts, including effects on TGF-β signaling pathways. Furthermore, we examined the antifibrotic effects of curcumin administration in a bleomycin-induced murine model of pulmonary fibrosis. Both oral and intraperitoneal routes of administration were employed, since oral bioavailability of curcumin is known to be limited in humans. We also examined the effects of delaying curcumin administration in the bleomycin model until after the acute inflammation had subsided.
MATERIALS AND METHODS

Reagents. Curcumin (Sigma-Aldrich, St. Louis, MO) for in vitro studies was prepared at a concentration of 100 mM in DMSO (Sigma-Aldrich) and stored in aliquots at −30°C. Cell culture reagents were purchased from Invitrogen (Carlsbad, CA). HBSS, RPMI 1640, and DMEM were each purchased from Gibco (Grand Island, NY). Human TGF-β and PDGF were purchased from R&D Systems (Minneapolis, MN).

Human lung fibroblast cell culture. All experiments were performed on normal human fetal lung fibroblasts (IMR-90; Institute for Medical Research, Camden, NJ) or fibroblasts grown from mechanically dissociated surgical lung biopsy of histologically normal or usual interstitial pneumonia (UIP) lung. All subjects provided written informed consent in accordance with the University of Michigan Institutional Review Board. Cells were used at passages 7–10. The fibroblasts were maintained in medium consisting of DMEM and supplemented with 10% FBS, 1% penicillin-streptomycin, and 1% Fungizone (each from Invitrogen).

Human lung fibroblast cell counts. At indicated times, media was removed, and cultures were washed and incubated in 500 μl of trypsin-EDTA. A 100-μl aliquot of the resulting suspension was diluted, and cells were counted using a Beckman Z2 Coulter Particle Count and Size Analyzer (Beckman Coulter).

Flow cytometric analysis. Cells were trypsinized, washed, and fixed with 70% ethanol for 30 min at room temperature. After incubation, cells were washed with PBS and resuspended in staining buffer [propidium iodide (50 μg/ml) and RNase (0.01%)] in PBS. The cells were analyzed by FACSVantage flow cytometer using a CellQuest acquisition and analysis program (Becton Dickinson, San Jose, CA). Gating was set to exclude cell debris, cell doublets, and cell clumps.

Real-time quantitative RT-PCR amplification. Real-time quantitative PCR was performed using the TaqMan SYBR Green PCR master mix protocol. The following gene-specific primers were used: cyclin D1 (forward, 5′-ACCTGGATGCTGAGGCTTG-3′; reverse, 5′-GAACCTCAGACCTGGCACA-3′) and β-actin (forward, 5′-GGTGGGGGCCCCAGGCACA-3′; reverse, 5′-GCTCCGCGGCTG-GTGGTGAAGC-3′). Each set was designed using Primer Express software. Each averaged experimental gene expression sample was compared with the averaged control sample, which was set to 1.

Western blot analysis. Cells were lysed in ice-cold lysis buffer containing 0.5 mM sodium fluoride, 2 mM sodium orthovanadate, and 1:100 dilution of protease inhibitor. Samples were then clarified by centrifugation at 10,000 × g for 10 min, mixed with a commercial sample buffer (Invitrogen), and heated at 95°C for 5 min. Samples were then electrophoresed on 4–20% Novex Tris-Glycine SDS-polyacrylamide gels (Invitrogen), after which the gels were transferred to polyvinylidene difluoride (PVDF) membranes (0.45 μm). Blots were incubated overnight at 4°C with the primary antibody followed by appropriate secondary antibody. The blots were then washed and signal-detected using a SuperSignal chemiluminescent substrate Western blotting reagent (Pierce Biotechnology) with chemiluminescence-sensitive film. Densitometric analysis was performed using National Institutes of Health (NIH) ImageJ software. Primary antibodies employed in the various studies were: monoclonal mouse anti-α-SMA (Dako, Carpinteria, CA), monoclonal mouse anti-GAPDH (Santa Cruz Biotechnology, Santa Cruz, CA), and polyclonal rabbit anti-phospho-Smad2 and anti-phospho-Smad3 (Cell Signaling Technology, Danvers, MA).

α-SMA immunocytochemistry. Fibroblasts were cultured overnight on sterile glass coverslips. Cells were washed, fixed with chilled methanol (−20°C) for 15 min on ice, then washed again, air dried, and kept at −20°C for 1 h. After equilibration in a humidified chamber, the cells were blocked in 1% BSA in PBS for 30 min. The cells were then incubated overnight at 4°C with monoclonal anti-α-SMA antibody (1:100 dilution; Dako). Following incubation, the cells were washed three times with PBS and then incubated with FITC-conjugated sheep anti-rabbit IgG (1:200 dilution; Sigma-Aldrich) for 1 h at room temperature. The cells were washed as before, and the coverslips were mounted on glass slides and visualized under a fluorescent microscope.

Measurement of ERK. At each time point, cells were collected, and protein lysates were prepared using the Bio-Plex cell lysis kit (Bio-Rad, Hercules, CA). Briefly, 50 μl of cell lysate (adjusted to a concentration of 0.9 mg protein/ml) was plated in a 96-well filter plate coated with beads coupled to anti-total extracellular signal-regulated kinase (ERK) or anti-phospho-ERK1/2 antibody. The plate was incubated overnight at room temperature on a platform shaker at 300 rpm. After a series of washes to remove unbound proteins, biotinylated detection antibodies, each specific for a different epitope, were added to the reaction. Streptavidin-phycocerythrin was then added to bind to the biotinylated detection antibodies on the bead surface. Data were acquired with the Bio-Plex 200 system and analyzed with the Bio-Plex Manager software from Bio-Rad.

Measurement of lung morphometry. Two slices were randomly selected for morphometric analysis. The lung was fixed to glass slides and stained with hematoxylin and eosin. Morphometry was performed using C.A.S.T. (Computer Assisted Stereology Toolbox) software (Olympus). Using a ×2 low magnification, the lung sections were scanned at 2.5× magnification. The total lung area was then calculated as the product of the total area of the slide and the magnification factor.

Lung inflammatory cell analysis. Mice were euthanized by CO2 asphyxia, the lung vascular bed was perfused with PBS, and the lungs were excised, minced, and digested enzymatically with digestion solution (RPMI 1640, 1 mg/ml collagenase, and 30 U/ml DNase) at 37°C for 30 min. The suspension was dispersed by repeated aspiration through a 10-ml syringe fitted with an 18-gauge blunt-tip needle. The cells were then washed twice with HBSS, resuspended in RPMI 1640, and filtered through a 100-μm nylon mesh. Lung leukocytes were purified by spinning through a 20% discontinuous Percoll gradient. Cells were spun onto glass slides using a cytocentrifuge (Shandon, Pittsburgh, PA) and stained with Diff-Quik (Fisher Scientific, Pittsburgh, PA). Aliquots of cells from lung tissue digests were stained with trypan blue, and the cells were counted using a hemocytometer.

Collagen assays. Hydroxyproline levels were determined as described by Huaux et al. (15). Briefly, levels were determined by homogenizing the lung in glacial acetic acid (0.5 M). Samples were then vacuum dried for 24 h and hydrolyzed in 6 N HCl overnight at 110°C. Hydroxyproline concentration was determined by colorimetric analysis at 550 nm. Data were expressed as micrograms of hydroxyproline per lung as determined by standard curve. Soluble collagen levels were performed using a Sircol assay kit according to manufacturer’s protocol (Accurate Chemical and Scientific, Westbury, NY). Briefly, fibroblasts were plated onto a six-well plate. Fibroblasts were treated, supernatants were collected, and collagen levels were quantified at an absorbance of 540 nm.

Measurement of lung morphometry. Quantitative lung morphometry was analyzed as previously described with modifications (38). Briefly, lungs were inflated by an intratracheal instillation of 10% formalin in PBS and then stored in 10% formalin in PBS for 24 h. Lung tissue was then removed and cut into 3-mm slices along the long axis. Two slices were randomly selected for morphometric analysis. The slices were embedded in paraffin, after which 6-μm histological sections were fixed to glass slides and stained with hematoxylin and eosin. Morphometry was performed using C.A.S.T. (Computer Assisted Stereology Toolbox) software (Olympus). Using a ×2 low magnification, the lung sections were scanned at 2.5× magnification. The total lung area was then calculated as the product of the total area of the slide and the magnification factor.
power objective, the entire area of lung from each tissue section was outlined and included in the assessment area. The microscope objective was then changed to ×20, and a meander sampling protocol was initiated in which the software chose a random starting field from the selected lung area and subsequent fields were determined by a computer-controlled fixed step in the x- and y-position of the microscope stage. To assess the extent of open air spaces following bleomycin injury, a nine-point grid was imposed on each ×20 field. Individual points were then counted at 24, 48, and 72 h. Points falling within large airways, were excluded from the analysis. An air space score was then calculated by dividing the number of points that resided in the air spaces of the lung by the sum of the air space and tissue points.

HPLC analysis of plasma. Isolation of plasma and isocratic HPLC analysis was performed according to the method of Pak et al. (28) with minor modifications. Briefly, blood samples were collected from the right ventricle of euthanized mice at specific time points. Red blood cells were separated from plasma by centrifugation at 2,000 g for 10 min. Plasma was then subsequently transferred to fresh 2-ml polypropylene tubes. Two hundred microliters of control plasma was spiked with varying concentrations of curcumin (to create standard curve) or β-estradiol (internal standard) followed by two volumes of ethyl acetate. Samples were mixed for 5 min on a rocker and centrifuged at 5,000 rpm for 10 min at room temperature. The supernatant was transferred to a clean glass tube and dried under nitrogen at 40°C. Samples were reconstituted in 100 μl of mobile phase, and 50 μl was injected onto the HPLC system, a Waters 717, UV detector, and a Waters 515 pump (Milford, MA). A visible wavelength of 430 nm was used to detect curcumin and 280 nm to detect β-estradiol. Curcumin separation was accomplished by using the isocratic HPLC method. Samples were injected onto an Apollo reversed-phase C18 column, 150-mm × 3.9-mm × 5-μm particle size (Alltech Associates, Deerfield, IL). The column was operated at a flow rate of 1 ml/min at room temperature. The mobile phase consisted of 1% (wt/vol) citric acid solution, adjusted to pH 3.0 using a 45% potassium hydroxide solution, in HPLC grade water, which was mixed with tetrahydrofuran in a 50:50 (vol/vol) ratio. The solution was filtered through a 0.2-μm filter.

Statistical analysis. Data are represented as means ± SE and were analyzed with the Prism 4.0 statistical program (GraphPad Software, San Diego, CA). Comparisons among experimental groups were performed with one-way ANOVA followed by Dunnett adjustment for multiple comparisons or one-sided Student’s t-test as applicable. All data shown are averages from at least 3 independent experiments. Differences were considered significant if P was <0.05.

RESULTS

Curcumin inhibits proliferation of lung fibroblasts from normal and IPF patients. Fibroblast proliferation is thought to play a key role in the development of IPF; as such, blockade of this step would be important in inhibiting disease progression. We accordingly assessed potential antiproliferative effects of curcumin. Human lung fibroblasts were treated with curcumin at varying concentrations (0–20 μM) and for varying times (24, 48, and 72 h). Curcumin inhibited proliferation of all lung fibroblast types in a dose- and time-dependent manner. This inhibition was seen both in the absence (Fig. 1A, left) and the presence (Fig. 1A, right) of the fibroblast mitogen PDGF (5 ng/ml). It is significant that similar antiproliferative effects were seen in fibroblasts not only isolated from normal lungs (n = 4), but also from those of IPF patients (n = 4; Fig. 1B, left and right, respectively). To further examine these antiproliferative effects, we performed cell cycle analysis of human lung fibroblasts treated with curcumin. Cells initially synchronized by 48-h serum deprivation were treated with curcumin (0–20 μM)
for an additional 48 h, after which the number of cells in each stage of the cell cycle was analyzed by flow cytometry. Results demonstrated a dose-dependent decrease in the number of cells in S phase with a proportional increase in G0/G1 phase cells (Fig. 2A). These results suggest blockage of cell cycle progression at G1 phase. We confirmed this effect of curcumin on the cell cycle by analyzing mRNA levels of cyclin D1, which increases during G1 to facilitate the onset of S phase (37). Addition of curcumin to cells caused a significant decrease in cyclin D1 mRNA levels, as would be expected when the cell cycle is blocked at G0/G1 (Fig. 2B).

Curcumin inhibits myofibroblast differentiation. TGF-β-dependent differentiation of fibroblasts to myofibroblasts, which express α-SMA, is an essential step in development of fibrosis. To determine whether curcumin could inhibit this process, serum-starved fibroblasts from histologically normal patient lungs (n = 4) were treated with curcumin (0–20 μM) for 2 h and then incubated in the presence of TGF-β (2 ng/ml) for 24 h.Extent of differentiation was assessed by measurement of α-SMA using Western blotting and immunocytochemical analysis. TGF-β treatment resulted in enhanced expression of α-SMA that was inhibited by curcumin in a dose-dependent manner (Fig. 3, A–C).

Curcumin inhibits TGF-β-induced phosphorylation of Smad2/3 and ERK1/2. Activation of the TGF-β receptor results in phosphorylation of Smad2 and Smad3 as well as ERK1/2. To determine whether the ability of curcumin to inhibit TGF-β-induced myofibroblast differentiation reflected inhibition of these signaling pathways, we measured changes following different periods of TGF-β exposure in levels of phosphorylated Smad2, Smad3, and ERK1/2 in the presence of curcumin. Human fibroblasts obtained from histologically normal lungs were pretreated with curcumin at 20 μM for 2 h before TGF-β addition. At 30, 60, and 120 min following addition of TGF-β (2 ng/ml), cells were lysed, and amounts of phosphorylated signaling molecules were determined. Curcumin significantly reduced the amount of both phospho-Smad2 (Fig. 4A) and phospho-Smad3 (Fig. 4B) at all time points. Phosphorylation of ERK1/2 was maximal 10 min after TGF-β addition, declining to near control levels by 1 h (Fig. 4C). Curcumin again
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myofibroblasts in the lung interstitium (33). To examine possible effects of curcumin on collagen production, fibroblasts isolated from IPF patients (n = 3) were treated with curcumin (5 or 10 μM) for 2 h and then incubated in the absence (Fig. 5A) and presence (Fig. 5B) of TGF-β (6 ng/ml) for 24 h in serum-free medium. TGF-β treatment led to increased collagen production (data not shown), whereas curcumin treatment significantly inhibited both baseline and TGF-β-induced collagen secretion in a dose-dependent manner.


Intraperitoneal, but not oral, administration of curcumin shows beneficial effects in bleomycin-induced lung injury. Our results with curcumin treatment of lung fibroblasts from normal and IPF patients suggested that curcumin could be effective in vivo. We tested this hypothesis using a murine bleomycin-induced model of pulmonary fibrosis. Since oral bioavailability of curcumin may be limited, we conducted parallel experiments using either oral or intraperitoneal administration of curcumin.

In one set of experiments, mice were pretreated with curcumin (300 mg/kg) or vehicle by oral gavage 72 h before a BLM (0.05 units) intratracheal injection. This was followed by daily administration of curcumin until the mice were killed. Inflammatory cells from digested lungs were quantified on day 4. There was no significant difference between the vehicle- and curcumin-treated mice in number of inflammatory cells following bleomycin injury (Fig. 6A). Collagen deposition in these animals was assessed by measuring concentrations of the collagen-specific amino acid hydroxyproline in lungs from animals on day 10. There was no significant difference between curcumin-treated and control mice (Fig. 6B). Morphometric analysis of the lung likewise demonstrated no significant difference between curcumin and vehicle treatment (Fig. 6C). Lastly, we did not observe a difference in mortality rate between vehicle- and curcumin-treated mice following a higher dose (0.075 units) of bleomycin (Fig. 6D).

In the second set of experiments, curcumin or vehicle was administered intraperitoneally. The protocol was otherwise as described for oral administration. In contrast to oral administration, intraperitoneal administration resulted in marked differences between curcumin-treated mice and untreated controls. Total cells, mononuclear cells, and polymorphonuclear cells in lung tissue were reduced in curcumin-treated mice at day 4 (Fig. 7A), indicating reduced inflammation. In addition, lung hydroxyproline content at day 21 was significantly diminished, almost to baseline levels, in curcumin-treated mice (Fig. 7B). Morphometric analysis likewise demonstrated significant improvement in the extent of open air spaces in curcumin-treated mice (Fig. 7C). These observed improvements in inflammation and collagen deposition were also reflected by a trend in improved survival (Fig. 7D; P > 0.05).

To extend our findings further, we sought to determine whether curcumin treatment could be effective after bleomycin injury but delayed intraperitoneal curcumin treatment until day 10. Figure 7, E and F, shows that even with delayed administration, curcumin significantly reduced lung hydroxyproline content and improved morphometric air space score in treated mice.
Plasma levels of curcumin are significantly greater via intraperitoneal compared with oral administration. Because we found a great discrepancy between oral and intraperitoneal curcumin delivery in the effectiveness with which they reduced bleomycin-induced injury, we hypothesized that bioavailability of curcumin differed significantly according to the method of delivery. To test this hypothesis, we used HPLC to measure plasma curcumin levels in mice following oral or intraperitoneal administration of curcumin (each 300 mg/kg). No curcumin was found in control mice (Fig. 8A), whereas murine plasma obtained 2 h after an oral dose (Fig. 8B) had a concentration of 15.7 ± 3.8 ng/ml (~43 nM). In contrast, intraperitoneal administration of curcumin (Fig. 8C) resulted in a much higher curcumin plasma level, 181 ± 23.1 ng/ml (~506 nM). Thus intraperitoneal administration of curcumin provided increased plasma levels and a higher effective systemic dose than did oral administration. These results provide a rationale for the more profound biological effects we saw with intraperitoneal administration of curcumin following bleomycin lung injury.

DISCUSSION

In this study, we show that curcumin effectively inhibits fibroblast proliferation, differentiation to myofibroblasts, and secretion of collagen, important processes in the progression of pulmonary fibrosis. We also show that intraperitoneal but not oral curcumin inhibits fibrotic changes following bleomycin administration in mice and that this remains true even when curcumin administration is delayed until after acute inflammation has subsided. This delayed administration is potentially relevant to human disease, since patients do not typically seek treatment until some degree of fibrosis has already occurred. Furthermore, we explain the differing results seen with the two routes of curcumin administration by measuring the respective plasma levels. We find that oral bioavailability of curcumin is highly limited and that plasma levels are much lower following oral administration than following intraperitoneal administration of the same dose. This limited oral bioavailability of curcumin parallels previous findings in humans (8, 34, 35).

Our studies demonstrate that curcumin blocks proliferation not only in human lung fibroblast cell lines and primary fibroblast cultures from normal human lungs, but also in primary cultures from IPF patients. This is the first time that the antiproliferative effects of curcumin have been shown in fibroblasts from lungs of IPF patients or healthy adults. These antiproliferative effects appear to reflect blockade of cell cycle progression, as we show that curcumin causes accumulation of proliferating lung fibroblast cells in the G2/G1 phase of the cell cycle and causes a decrease in expression of cyclin D1, which is important for progression to G2. Previous reports have
Curcumin was first demonstrated in Jurkat T cells (4) and has since been observed in a wide variety of cell types. In hepatic stellate cells, the major effector cells of liver fibrosis, curcumin inhibition of proliferation and activation is accompanied by a reduction in ERK phosphorylation but not in total ERK protein levels (5), whereas its ability to reduce connective tissue growth factor and collagen production is mimicked by inhibitors of ERK phosphorylation (3). Inhibitors of ERK phosphorylation also mimic the ability of curcumin to block TGF-β-induced differentiation of fetal lung fibroblasts into myofibroblasts (13). ERK is not unique in this respect, however, as these authors and others have obtained similar results with blockage of other MAPK signaling pathways. Curcumin inhibition of Smad2/3 phosphorylation has similarly been observed in connection with inhibition of TGF-β-induced collagen expression by renal fibroblasts (7). Curcumin has also been shown to counteract the ability of TGF-β to downregulate expression of the nuclear transcription factor peroxisome proliferator-activated receptor-γ (PPARγ) in hepatic stellate cells (49). Antifibrotic effects of PPARγ activation have been demonstrated (2, 11, 26, 47), although this current study did not examine a possible role for PPARγ in the effects we observed.

Our in vivo studies in the bleomycin-induced murine model of pulmonary fibrosis show that intraperitoneal but not oral administration of curcumin significantly inhibits development of fibrotic changes, with improvements in inflammation, collagen deposition, and survival. Importantly, collagen deposition was inhibited even when administration was delayed until acute inflammation had subsided. We note that inflammation is typically minimal or absent at the time IPF patients present for treatment, raising the possibility that such delayed administration may be relevant to treatment of human disease. Not only is our study the first to demonstrate that curcumin is effective during what has been referred to as “the therapeutic period,” but also very few agents of any type have proven effective at this time (27).

HPLC measurement of curcumin levels in mouse plasma after oral and intraperitoneal administration provide an explanation for the lack of effect seen with oral curcumin, as we found a plasma concentration of curcumin >10 times as great following intraperitoneal injection as following oral dosing. This is in accord with results in humans, where use of oral curcumin treatment is hampered by poor bioavailability (8, 34, 35). A recent dose escalation study of oral curcumin toxicity and bioavailability in human volunteers reported very low concentrations (30–60 ng/ml) or unmeasurable curcumin in plasma even at the highest doses (22). In addition, two clinical studies detected only low nanomolar or no curcumin in plasma during what has been referred to as “the therapeutic period,” but also very few agents of any type have proven effective at this time (27).

Interestingly, previous studies in rats have shown beneficial effects of early oral curcumin administration in bleomycin- or amiodarone-induced pulmonary fibrosis (30, 31, 42, 45). There is no obvious explanation for the difference from our negative results, even with early administration. Although intestinal
metabolism of curcumin is lower in the rat than in the human (16), bioavailability remains very low even following high doses of 500 mg/kg (46). It is possible to suppose that the vehicle in which curcumin is administered affects oral bioavailability to some extent or that curcumin from different sources may not be fully equivalent. Neither possibility seems particularly likely, however, in view of the consistency in human data from several different groups.

Given the antifibrotic effects of curcumin demonstrated by this study, our results suggest that curcumin could potentially be an effective treatment for IPF. Attractiveness of this option is increased by the other beneficial therapeutic effects of curcumin such as antioxidant activity and promotion of wound healing. In addition, curcumin has demonstrated low toxicity (22, 34, 36), whereas the drugs currently being used for IPF often result in significant adverse effects. However, oral curcumin is not likely to be effective, and other therapeutic strategies should be considered. Delivery of nebulized curcumin directly to the lungs might be one such strategy, since use of nebulized pharmaceutical preparations is common and effective for treatment of other lung conditions such as asthma. A liposome-encapsulated curcumin formulation suitable for intravenous use has also been developed and shown to be effective in an animal model (23). We suggest that curcumin administered in either manner could potentially provide a safe and effective treatment for IPF.

REFERENCES


GRANTS

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DISCLOSURES

No conflicts of interest are declared by the author(s).

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