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Matrix Metalloproteinase-1 Is Regulated in Tuberculosis by a p38 MAPK-Dependent, p-Aminosalicylic Acid-Sensitive Signaling Cascade

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Mycobacterium tuberculosis (M. tb) must cause lung disease to spread. Matrix metalloproteinases (MMPs) degrade the extracellular matrix and are implicated in tuberculosis-driven tissue destruction. We investigated signaling pathways regulating macrophage MMP-1 and -7 in human pulmonary tuberculosis and examine the hypothesis that the antimycobacterial drug p-aminosalicylic acid acts by inhibiting such pathways. In primary human macrophages, M. tb up-regulates gene expression and secretion of MMP-1 (interstitial collagenase) and MMP-7 (matrilysin). In tuberculosis patients, immunohistochemical analysis of lung biopsies demonstrates that p38 MAPK is phosphorylated in macrophages surrounding granulomas. In vitro, M. tb drives p38 phosphorylation. p38 inhibition suppresses M. tb-dependent MMP-1 secretion by 57.8% and concurrently increases secretion of its specific inhibitor TIMP-1 by 243.7%, demonstrating that p38 activity regulates matrix degradation by macrophages. p38 signals downstream to the cyclooxygenase 2/PGE2 pathway. p-Aminosalicylic acid, an agent used to treat drug-resistant tuberculosis, inhibits M. tb-driven MMP-1 but not MMP-7 gene expression and secretion. PAS acts by blocking PGE2 production without affecting M. tb growth. In summary, p-aminosalicylic acid decreases MMP-1 activity by inhibiting a p38 MAPK-PG signaling cascade, suggesting that this pathway is a therapeutic target to reduce inflammatory tissue destruction in tuberculosis. The Journal of Immunology, 2009, 182: 5865–5872.
effect in part by modulating the host immune response to limit tissue destruction.

Materials and Methods

M. tb culture

M. tb H37Rv Pasteur was cultured in Middlebrook 7H9 medium (BD Biosciences) with 10% ADC enrichment medium (BD Biosciences), 0.2% glycerol, and 0.02% Tween 80 with agitation. M. tb at mid-log growth phase at OD 0.60 (Biowave Cell Density Meter; WPA) was used in all infection experiments. For determination of CFU, macrophages were lysed with 0.1% Triton X-100 at 72 h and 50 μl of lysate was serially diluted in 7H9 medium and plated onto 7H11 plates. Plates were incubated at 37°C and colonies were counted after 11–15 days.

Macrophage purification and differentiation

Human monocyte-derived macrophages were isolated from single donor buffy coats (National Blood Transfusion Service) by density centrifugation (Ficoll-Paque; Amersham Biosciences) and monocytes were adhesion purified. Monocytes were differentiated into macrophages in RPMI 1640 with 10% FCS, 2 mM glutamine, 10 μg/ml amphotericin, and 100 ng/ml M-CSF (R&D Systems) for 4 days at 37°C/5% CO2. Macrophages were then cultured in RPMI 1640 with 10% FCS, 2 mM glutamine, and 10 μg/ml amphotericin for 24 h. The medium was then changed to macrophage serum-free medium (Invitrogen) at the start of the experiment (experimental day 0).

M. tb infection of human macrophages

In all experiments, macrophages were infected with M. tb after 5 days of maturation. In inhibition experiments, macrophages were preincubated for 2 h with the p38 MAPK inhibitor SB203580, ERK inhibitor PD98059 (Calbiochem), cyclooxygenase (COX) inhibitors indomethacin and NS-398 (Sigma-Aldrich), PAS (Sigma-Aldrich), or anti-TLR2 Ab (clone 2.1; eBioscience). For TLR2 inhibition experiments, specificity was confirmed with the isotype control Ab. Two hours after infection with M. tb, cells were washed with warmed HBSS to remove nonadherent bacilli and replaced with fresh macrophage serum-free medium inhibitors when stated. Cell culture supernatants were harvested after 72 h and sterilized by filtration through a 0.2-μm Durapore filter (Millipore), which does not remove MMPs from tissue culture fluid (27).

Analysis of MMP-1 and MMP-7 concentrations by Luminex

MMP-1 and MMP-7 concentrations in samples were analyzed using the Fluorokine MAP profiling kit according to the manufacturer’s protocol (R&D Systems). Sample concentrations were detected using the Luminex platform (Bio-Rad). The minimum level of detection for MMP-1 and MMP-7 is <10 and <20 pg/ml, respectively.

Phospho-MAPK array

The Proteome Profiler phospho-array (R&D Systems) was performed according to the manufacturer’s protocol and developed with the ECL system (Amersham Biosciences). Thirty minutes after macrophages were infected with M. tb, cells were washed with ice-cold PBS, solubilized in lysis buffer (R&D Systems), and filtered through an Anopore 0.2-μm filter (Whatman). Total protein concentration was measured by Bradford assay (Bio-Rad) and equal total protein was loaded onto each array. Densitometric analysis of each array was performed using NIH Image version 1.61.

Western blotting

Macrophages were infected with M. tb and lysed with 200 μl of SDS sample buffer (62.5 mM Tris (pH 6.8), 2% SDS, 10% glycerol, 50 mM DTT, and 0.01% bromphenol blue) at defined time points. Samples were filtered through a 0.2-μm Anopore filter and frozen at −80°C. Forty-microliter aliquots were heat denatured and run on a 10% acrylamide gel at 200 V (running buffer 25 mM Tris base, 192 mM glycine, and 0.1% SDS) for 3 h. Gels were electrotransferred to a nitrocellulose membrane (Amersham Biosciences) and blocked for 1 h with 5% milk protein/0.1% Tween 20. The membrane was incubated with primary Ab (total p38 or phospho-p38; Cell Signaling Technology) in 5% BSA/0.1% Tween 20 at 4°C overnight. Blots were then washed three times and incubated with HRP-linked anti-rabbit secondary Ab (1/2000 dilution in 5% milk protein/0.1% Tween 20; Cell Signaling Technology) for 1 h. Luminescence was detected with the ECL system (Amersham) according to the manufacturer’s protocol. Immunoblotting for total p38 confirmed equal loading between samples.

Immunohistochemistry

Paraffin-embedded lung biopsies from five nonimmunosuppressed patients with culture-proven M. tb infection were immunostained for p38. Sections of 4-μm thickness were dewaxed and endogenous peroxidase activity was blocked with 0.6% hydrogen peroxide for 15 min. Sections were microwaved for 20 min in citrate buffer (0.01M citrate, pH 6.0) and blocked with 5% normal goat serum for 10 min. The primary Ab (p38; Sigma-Aldrich clone M8177 at 1/200 dilution) was applied in 0.01M PBS/azide/BSA for 1 h at room temperature. Ab was detected with the Menarini nonbiotinylated kit according to manufacturer’s instructions. Peroxidase activity was developed with the diaminobenzidine system (Menarini). Slides were counterstained with Coles’ hematoxylin, dehydrated, and mounted. Ethical consent was obtained from the Hammersmith Hospitals Research Ethics Committee for the use of archived lung biopsies. Tissue samples were provided by the Human Biomaterials Resource Centre at the Hammersmith Hospitals. Other investigators may have received samples from these same tissues.

RNA extraction, cDNA synthesis, and quantitative RT-PCR

Macrophages were lysed with TRIzol reagent (Sigma-Aldrich) and total RNA was extracted and then reverse transcribed with Superscript III (Invitrogen) as previously described (8). Quantitative real-time RT-PCR was performed using Brilliant QPCR master mix (Stratagene) according to
TIMP-1 was 30 pg/ml. To the manufacturer’s instructions. The lower level of sensitivity for cell culture medium were measured by ELISA (R&D Systems) according instructions. The lower level of sensitivity was 15.9 pg/ml. TIMP-1 levels in binding immunoassay (R&D Systems) according to the manufacturer’s in—

the manufacturer’s instruction on a Stratagene Mx3000P platform as described elsewhere (28). VIC-labeled 18S Ribosomal control reagent (Applied Biosystems) was analyzed in parallel. MMP primers and probes have been described previously (28). MMP mRNA accumulation was normal—

COX-2 FACS

Macrophages were infected with M. tb in the presence or absence of inhibitors as above. Cells were fixed in 4% paraformaldehyde for 30 min at room temperature, then lifted mechanically. Anti-COX II FITC-labeled intracellular staining was performed according to the manufacturer’s instructions (Cayman Chemicals). Briefly, cells were washed and permeabilized with 0.5% BSA, 0.1% sodium azide, and 0.1% saponin solution (Sigma-Aldrich). After a further wash step, cells were incubated with primary Ab (1/10 dilution) or IgG control (1/200 dilution, mouse IgG1 FITC; Serotec) for 30 min at room temperature, then lifted mechanically. Anti-TLR2 Ab was pre—

PGE2 and TIMP-1 ELISAs

PGE2 levels in cell culture medium were determined by a competitive binding immunoassay (R&D Systems) according to the manufacturer’s instructions. The lower level of sensitivity was 15.9 pg/ml. TIMP-1 levels in cell culture medium were measured by ELISA (R&D Systems) according to the manufacturer’s instructions. The lower level of sensitivity for TIMP-1 was 30 pg/ml.

Statistical analysis

Multiple intervention experiments were compared with a one-way ANOVA followed by Tukey’s correction for multiple comparisons. A $p < 0.05$ was taken as statistically significant. For secretion analysis, experiments were all performed in triplicate on at least two occasions, while RNA analysis was performed on individual samples on a minimum of three separate experiments.

Results

M.tb-infected human macrophages secrete MMP-1 and MMP-7

First, we examined the kinetics of MMP-1 and -7 secretion from M. tb-infected primary human macrophages and then investigated the dose dependency with different M. tb multiplicities of infection (MOI). Infected macrophages secreted greater MMP-1 and MMP-7 concentrations than uninfected control cells (Fig. 1, A and B). MMP-1 secretion was maximal 72 h after stimulation, with

![FIGURE 2.](image)

**FIGURE 2.** M. tb infection drives phosphorylation of signaling kinases in macrophages. A, Proteome profiler array of uninfected macrophages (control) and M. tb-infected macrophages at 30 min. M. tb drives phosphorylation of multiple signaling pathways compared with uninfected cells. B, Densitometric analysis of phospho-array. Baseline ERK 1/2 phosphorylation is increased by infection and p38α and p38δ phosphorylation is markedly increased. Bars represent mean ± SD from three independent experiments. *$p < 0.05$ and **$p < 0.01$. Ctrl, Control; HSP, heat shock protein.

![FIGURE 3.](image)

**FIGURE 3.** p38 MAPK is phosphorylated in the lungs of tuberculosis patients and is TLR2 dependent. A, p38 phosphorylation kinetics. M. tb drives phosphorylation in macrophages from 30 min that peaks at 60 min and persists at 4 h. Representative data from three independent experiments are shown. B, p38 phosphorylation immunohistochemistry. Lung biopsies from patients with culture-proven tuberculosis infection and is TLR2 dependent.
A blot analysis was performed over a 4-h period (Fig. 3). To investigate M. tb-driven p38 phosphorylation, kinetic Western blots were performed. In macrophages within tuberculosis granulomas, p38 is phosphorylated (Fig. 3B). No immunoreactivity was demonstrated with isotype control Ab or secondary Ab alone, confirming specificity of staining. We have previously shown that such macrophages surrounding the caseous center of tuberculosis granulomas are immunoreactive for MMP-1 and MMP-7 (8). Since mycobacteria may activate monocytic cells via TLR2 (29, 30), we investigated TLR2 regulation of p38 phosphorylation in human macrophages. Inhibition of TLR2 signaling by preincubation with anti-TLR2 Ab prevented M. tb-dependent p38 phosphorylation (Fig. 3C).

**FIGURE 4.** p38 MAPK pathway regulates the divergence between MMPs and TIMP-1. A–C, Macrophages were preincubated with the p38 inhibitor SB203580 (SB) or the ERK inhibitor PD98059 (PD) for 120 min, then infected with M. tb at MOI 1. MMP-1, MMP-7, and TIMP-1 secretion was measured at 72 h. SB203580 and PD98059 suppress MMP-1 and MMP-7 secretion in a dose-dependent manner. In contrast, inhibition of p38 signaling by SB203580 increased TIMP-1 secretion. Mean ± SD from a single experiment performed in triplicate is shown and is representative of three independent experiments. *, p < 0.05 and **, p < 0.001. D–F, Macrophages were pretreated with MAPK inhibitors for 2 h, then infected with M. tb for 24 h. Gene expression was measured by RT-PCR after 24 h relative to ribosomal 18S. MMP-1 and MMP-7 mRNA accumulation was inhibited by both SB203580 and PD98059. TIMP-1 mRNA accumulation increased in infected cells pretreated by SB203580. Mean ± SEM of relative mRNA levels from three separate donors is shown.

Minimal secretion by uninfected cells over the time course (p < 0.001 at 48 and 72 h after infection). MMP-7 secretion peaked 48 h after stimulation and reached a plateau thereafter (p > 0.001 compared with baseline). Uninfected macrophages constitutively expressed MMP-7. In dose-response experiments, MMP-1 and MMP-7 secretion increased from MOI 0.1 to MOI 1 (Fig. 1A–C, and D; p < 0.001 and p < 0.05, respectively). There was no further increase in MMP secretion after infection between MOI 1 and MOI 10; therefore, in subsequent experiments an MOI of 1 was used. In contrast to MMP secretion, TIMP-1 secretion was not altered by macrophage infection by M. tb (Fig. 1E).

**M. tb drives p38 MAPK phosphorylation in macrophages and in patients**

To dissect the intracellular pathways regulating the divergent MMP/TIMP secretion, an analysis of MAPK and serine/threonine kinase phosphorylation was performed. At 30 min, M. tb stimulated phosphorylation of multiple signaling pathways, including ERK, JNK, p38, MSK, heat shock protein, and AKT (Fig. 2A). Densitometric analysis demonstrated that ERK1/2 phosphorylation is detectable in control cells and increased by M. tb infection (Fig. 2B). However, the greatest fold increase was in p38 phosphorylation after stimulation by M. tb. Of the p38 isoforms, p38α phosphorylation was up-regulated 32.6-fold after infection (p < 0.05) and p386 149.6-fold (p < 0.01) after infection (Fig. 2B). To further investigate M. tb-driven p38 phosphorylation, kinetic Western blot analysis was performed over a 4-h period (Fig. 3A). No basal phosphorylation was observed. M. tb stimulated p38 phosphorylation at 30 min, which increased at 60 min and remained up-regulated compared with control cells at 4 h.

To investigate the relevance of cellular data to clinical disease, lung biopsies from nonimmunosuppressed patients with active, culture-proven M. tb infection were immunostained for phosphorylated p38. In macrophages within tuberculosis granulomas, p38 is suppressed by inhibition of both p38 and ERK MAPK pathways (Fig. 4D). Changes in mRNA levels reflected secretion but did not achieve statistical significance due to donor-to-donor variability in

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**PAS REGULATION OF MMP-1 IN TUBERCULOSIS**

To further dissect kinase regulation of MMP-1, MMP-7 and TIMP-1 in M. tb-infected macrophages, the p38 and ERK pathways were blocked using specific chemical inhibitors (31). p38 inhibition suppressed MMP-1 secretion in a dose-dependent manner, with a significant decrease in secretion at 10 μM SB203580 (Fig. 4A; p < 0.05). MMP-1 secretion was also significantly suppressed by 1 μM SB203580 when multiple donors were concurrently analyzed (p < 0.01). Similarly, ERK inhibition significantly decreased MMP-1 secretion at 10 μM PD98059 (p < 0.05). Neither inhibitor reduced cell viability at these concentrations (data not shown). MMP-7 secretion was also significantly suppressed by p38 and ERK pathway inhibition (Fig. 4B; p < 0.05). In contrast, p38 inhibition increased TIMP-1 secretion in infected macrophages in a dose-dependent manner (Fig. 4C; 1 μM, p < 0.05 and 10 μM, p < 0.001). Inhibition of ERK did not alter TIMP-1 secretion.

MMP-1, MMP-7, and TIMP-1 gene expression were investigated using quantitative RT-PCR. MMP-1 gene expression was suppressed by inhibition of both p38 and ERK MAPK pathways (Fig. 4D). Changes in mRNA levels reflected secretion but did not achieve statistical significance due to donor-to-donor variability in
PAS inhibits MMP-1 secretion by M. tb-infected macrophages via a PG-dependent mechanism

We hypothesized that PAS, which is derived from aminosalicylic acid and is structurally very similar (Fig. 6A), may have an immunomodulatory effect by altering PG signaling and MMP secretion in infected macrophages. First, we demonstrated that macrophage MMP-1 secretion was suppressed by indomethacin, a nonselective COX inhibitor, in a dose-dependent manner. Indomethacin significantly decreased MMP-1 secretion compared with M. tb alone at 1 and 10 µM (p < 0.05 and p < 0.01, respectively; data not shown). Indomethacin had no effect on MMP-7 secretion. Next, we used a COX-2 selective inhibitor, NS-398, to determine whether inhibition was specific. NS-398 caused a dose-dependent suppression of MMP-1 secretion (Fig. 6B) but did not suppress MMP-7 secretion (Fig. 6C). Similarly, preincubation of macrophages with PAS for 2 h before infection similarly inhibited MMP-1 secretion in a dose-dependent manner (Fig. 6D). In contrast, MMP-7 secretion was unaffected (Fig. 6E), demonstrating the same pattern of inhibition as indomethacin and NS-398. Analysis of mRNA accumulation demonstrated that the effect of PAS on secretion was secondary to inhibition of MMP-1 gene expression (Fig. 6F).

To determine whether the effect of PAS was secondary to inhibition of the COX-PG pathway, we investigated PG secretion by M. tb-infected macrophages. One-tenth millimolar PAS significantly suppressed PGE2 secretion (Fig. 7A, p < 0.05) and 1 mM PAS completely suppressed PG secretion (p < 0.001). Because this inhibition might be secondary to PAS reducing bacterial replication, we analyzed growth of viable intracellular M. tb in control and PAS-treated macrophages. At 72 h, no decrease in CFU recovered from infected macrophages was observed in PAS-treated cells (Fig. 7B). In parallel, PAS was cocultured with M. tb over a period of 3 days and bacterial growth was measured by OD. PAS
COX inhibition by indomethacin (Fig. 8). The PG pathway is a key downstream effector of p38 activity, since we showed that M. tb drives COX-2 accumulation, COX-2 inhibition suppresses MMP-1 secretion, and p38 inhibition prevents COX-2 accumulation and MMP-1 secretion. The PG pathway plays an important role in control of inflammation in response to infection (37) and regulates MMP expression (8, 20, 23, 38). Up-regulation of MMP-9 expression in murine macrophages by *Mycobacterium avium* is PGE2-dependent (39). During the chronic phase of experimental murine tuberculosis, administration of a PG synthesis inhibitor with a TGF-β antagonist reduced pulmonary inflammation, fibrosis, and bacillary load (40), consistent with our hypothesis that excess COX-2 activity is associated with immunopathology. Similarly, inhibition of PG accumulation with either aspirin or ibuprofen increased the efficacy of pyrazinamide in a murine model (41).

PAS, which has been used since the 1940s, is again becoming important in treatment of tuberculosis due to emergence of multi- and extensively drug-resistant strains (1). Since it is derived from salicylic acid, we hypothesized that it may modulate the PG pathway and consequently MMP secretion. PAS suppressed MMP secretion without demonstrating mycobactericidal activity over (0.1 and 1 mM) had no significant effect on bacterial replication (Fig. 7C). Costimulation of infected cells with dibutyryl cAMP (B2cAMP), a synthetic analog of cAMP, increased MMP-1 secretion in PAS-treated cells in a dose-dependent manner (Fig. 7D), demonstrating that supplementing the PG pathway downstream of COX-2 reverses the inhibition of MMP-1 secretion by PAS. No effect of the PG pathway inhibition or supplementation on MMP-7 secretion was demonstrated. Finally, to confirm that the suppression of PGE2 secretion was due to inhibition of host cell signaling pathways as opposed to inhibition of mycobacterial growth, LPS-stimulated monocytes were preincubated with PAS for 2 h and then stimulated with LPS. Up-regulation of PGE2 secretion by LPS was suppressed by 1 mM PAS, demonstrating a similar efficacy to COX inhibition by indomethacin (Fig. 8).

Discussion
In this study, we investigated signaling pathways regulating MMP-1 and MMP-7 secretion in primary human macrophages infected with M. tb and whether the anti-tuberculous drug PAS modulates these. Analysis of signaling cascades demonstrates that M. tb primarily drives p38 and ERK phosphorylation and p38 is the key regulatory point increasing MMP expression while suppressing the inhibitor TIMP-1. In patients with pulmonary tuberculosis, p38 is phosphorylated in epithelioid macrophages that express MMP-1 and -7 surrounding caseating granulomas. Downstream, p38 signals to the COX-2/PGF2 pathway, which regulates MMP-1 but not MMP-7 secretion. PAS modulates this inflammatory immune response, suppressing MMP-1 up-regulation by M. tb-infected macrophages by a PGE2-dependent mechanism without affecting mycobacterial replication or MMP-7 secretion.

We first examined phosphorylation of multiple signaling pathways in macrophages. Although we demonstrated that the p38, ERK, JNK, AKT, and heat shock protein pathways were all activated by M. tb infection, the greatest up-regulation of phosphorylation was of p38 and ERK, occurring within 30 min of infection. These data are consistent with previous findings demonstrating mycobacteria and their cell wall components, including lipoolarabinomannan, activate p38 and ERK MAPK pathways in primary human monocytes (29, 33–35) and in murine macrophages (30). Isoform analysis of p38 MAPK demonstrated that p38α and p38β were phosphorylated in M. tb-infected macrophages. p38α is involved in inflammatory signaling pathways and specific p38α isoform inhibitors are in development and may soon enter the clinical arena (36). p38 activity was the critical switch up-regulating MMP-1 and MMP-7 gene expression and secretion and down-regulating TIMP-1. We found a similar central role for p38 in pulmonary epithelial cells (18). Upstream of p38 we identified that M. tb signals, at least in part, via TLR2 to phosphorylate p38. This result is consistent with TLR2-dependent p38 phosphorylation in human primary monocytes stimulated with mycobacteria or mycobacterial components (29).
PAS suppresses MMP-1 in a PGE2-dependent manner without inhibiting mycobacterial growth. A, Macrophages were preincubated with PAS for 120 min, then infected with M. tb. PGE2 secretion was measured at 72 h. PAS inhibited PGE2 secretion by infected macrophages in a dose-dependent manner. Mean ± SD from a single experiment performed in triplicate is shown and is representative of two experiments. *, p < 0.05 and **, p < 0.001. B, Intracellular mycobacterial growth is not suppressed by PAS. Macrophages were preincubated with PAS for 120 min, then infected with M. tb. Macrophages were lysed at 72 h and bacteria were plated out for CFU determination. PAS did not reduce mycobacterial growth. Mean ± SD from independent experiments. **, p < 0.01.

the experimental time course. Although Lehman (42) identified PAS by its ability to inhibit the growth of mycobacteria in culture, its precise mechanism of action remains uncertain (25, 26). We demonstrated that PAS inhibits MMP-1 secretion by M. tb-infected macrophages and that this was secondary to an inhibition of PGE2 synthesis. Although PAS completely suppressed PGE2 accumulation, some MMP-1 secretion persisted, demonstrating that the PGE2 pathway is not the sole regulator of MMP-1 secretion. Similarly, MMP-1 is regulated by multiple cellular signaling pathways in LPS-stimulated monocytes (20).

In summary, we define a p38 MAPK-PGE2 pathway that regulates MMP gene expression and secretion by primary human macrophages in tuberculosis. p38 is phosphorylated in patients with active pulmonary tuberculosis and p38 activity regulates a matrix-degrading phenotype. Targeting this pathway could limit tuberculosis-related immunopathology and inhibitors of p38 signaling cascade are now entering clinical use (36, 43). PAS, an established drug treatment of tuberculosis for over 60 years, suppresses MMP-1 secretion without inhibiting mycobacterial replication. Immunomodulation has been proposed as a novel therapeutic approach to tuberculosis (44), and our data demonstrate that part of the mechanism of action of PAS is to down-regulate excessive host inflammatory immune responses by inhibiting PG-driven MMP-1 secretion.

Disclosures

The authors have no financial conflict of interest.

References


