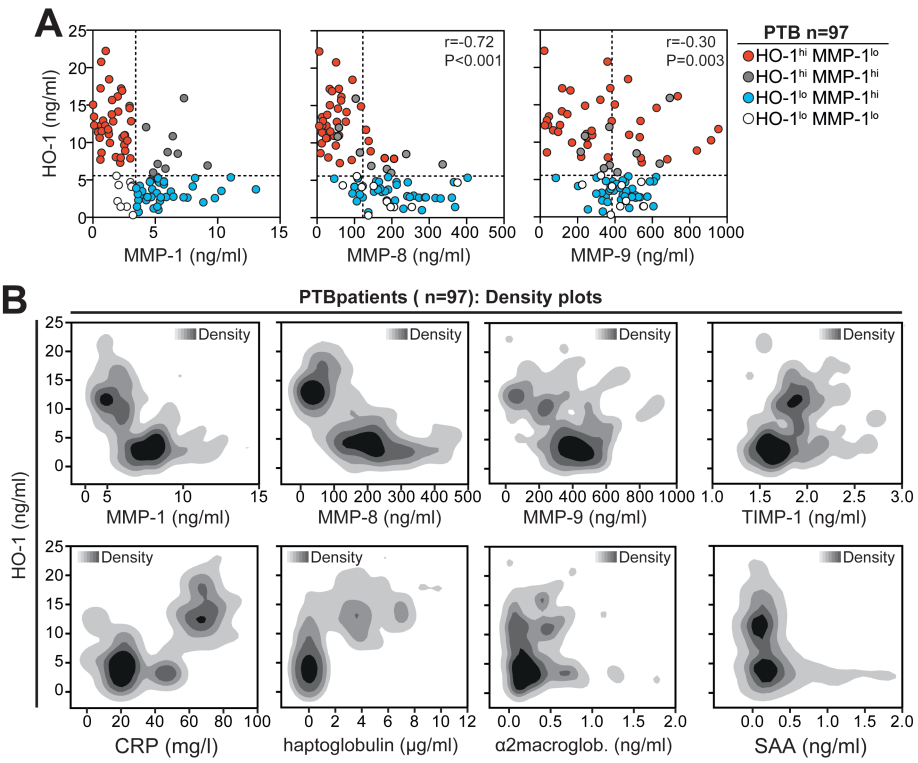
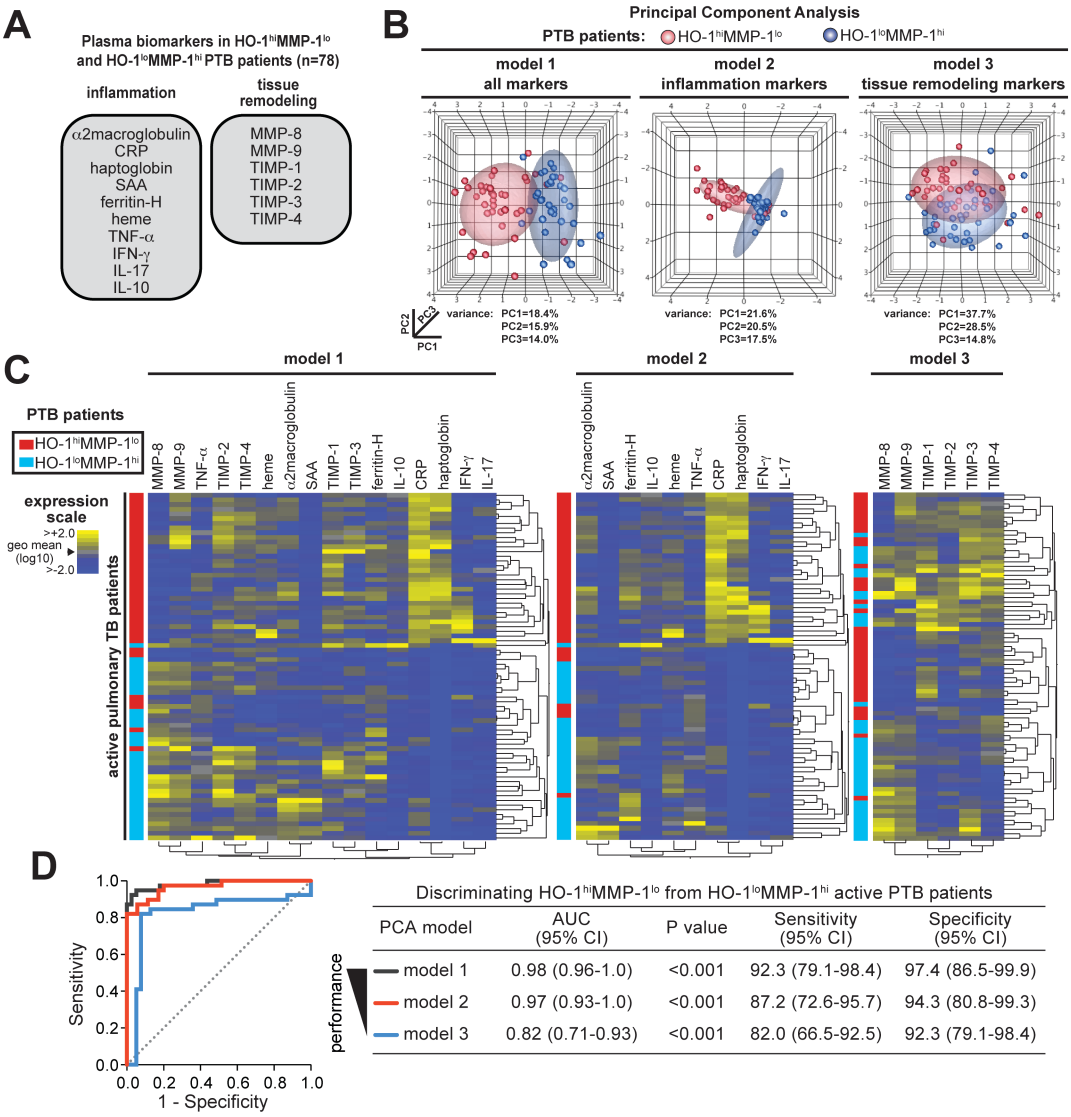
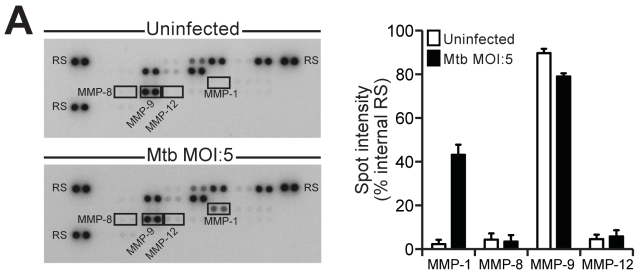


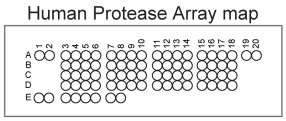
Supplemental Figure 1. Dichotomous expression of HO-1 and markers of inflammation and tissue remodeling in plasma from active TB patients

(A) Values from individuals with active TB from India (n=97) were colored according to the expression profile of HO-1 and MMP-1 in plasma samples. The individuals were then marked in Spearman correlation graphs between HO-1 and MMP-8 or MMP-9 to test if they would also exhibit similar patterns of expression. **(B)** Density plots of the correlations between HO-1 and other biomarkers of inflammation and tissue damage are shown to illustrate the different patterns of expression between these markers in PTB patients shown in **(A)**. Darker areas in the plots represent higher number of individuals.



Supplemental Figure 2. HO-1^{hi}MMP-1^{lo} and HO-1^{lo}MMP-1^{hi} TB patients can be better distinguished by their plasma protein expression profile of inflammatory biomarkers than by tissue remodeling markers.
(A) List of the plasma biomarkers of inflammation or tissue remodeling measured in Indian patients with active PTB patients exhibiting either HO-1^{hi}MMP-1^{lo} (n=39) or HO-1^{lo}MMP-1^{hi} (n=39) expression profile (See Supplemental Table 1 for details). **(B)** Principal component analyses including different combinations of plasma biomarkers was employed to assess the contribution of each combination to distinguish HO-1^{hi}MMP-1^{lo} from HO-1^{lo}MMP-1^{hi} active PTB patients. Normal contour ellipsoids were used to show limits of each group (coverage area = 50%). The percentage of variance from the principal components (PC) shown in different three-dimensional graphs is described below each graph. **(C)** Unsupervised cluster analyses (Ward's method) were employed using the different combinations of markers shown in the diverse PCA models displayed in **(A)**. PTB patients exhibiting either HO-1^{hi}MMP-1^{lo} or HO-1^{lo}MMP-1^{hi} were listed in rows and each biomarker was placed in a different column. The squares in the heat maps represent values below or above the geometric mean levels (Log10) of a given biomarker in the study population. **(D)** ROC curve analyses were performed to estimate in a quantitative way the performance of the different combinations of markers used in the PCA and cluster analyses in segregating HO-1^{hi}MMP-1^{lo} from HO-1^{lo}MMP-1^{hi} PTB patients.





B

coordinate	analyte/control	isoform specificity	coordinate	analyte/control	isoform specificity
A1, A2	reference spots (RS)	N/A	C3, C4	Kallikrein 6	proform & active
A3, A4	ADAM8	ectodomain	C5, C6	Kallikrein 7	proform & active
A5, A6	ADAM9	ectodomain	C7, C8	Kallikrein 10	proform & active
A7, A8	ADAMST1	proform	C9, C10	Kallikrein 11	proform & active
A9, A10	ADAMST13	active	C11, C12	Kallikrein 13	proform & active
A11, A12	Cathepsin A	proform & active	C13, C14	MMP-1	proform & active
A13, A14	Cathepsin B	proform	C15, C16	MMP-2	proform & active
A15, A16	Cathepsin C	proform & active	C17, C18	MMP-3	proform & active
A17, A18	Cathepsin D	proform & active	D3, D4	MMP-7	proform & active
A19, A20	reference spots (RS)	N/A	D5, D6	MMP-8	proform & active
B3, B4	Cathepsin E	proform & active	D7, D8	MMP-9	proform & active
B5, B6	Cathepsin L	proform & active	D9, D10	MMP-12	proform & active
B7, B8	Cathepsin S	proform & active	D11, D12	MMP-13	proform
B9, B10	Cathepsin V	proform & active	D13, D14	Neprilysin/CD10	ectodomain
B11, B12	Cathepsin X/Z/P	proform & active	D15, D16	Presenilin-1	N-terminal fragment
B13, B14	DPPIV/CD26	ectodomain	D17, D18	Proprotein convertase 9	active
B15, B16	Kallikrein 3/PSA	proform & active	E1, E2	reference spots (RS)	N/A
B17, B18	Kallikrein 5	proform & active	E3, E4	Proteinase 3	active
			E5, E6	uPA/Urokinase	proform & active
			E7, E8	negative control	N/A

Supplemental Figure 3. Expression of matrix metalloproteinases by human macrophages infected with *M. tuberculosis*

(A) Monocyte-differentiated macrophages were infected with H37Rv Mtb strain for 24h and expression levels of 34 proteases in culture supernatants were determined simultaneously using a human protease array kit (Human Protease Array kit, R&D Systems). Left panel shows the intensity of expression of key matrix metalloproteinases relative to the average intensity of the reference spots (RS). **(B)** The detailed map of the human protease array used in this experiment is shown. The results shown involved cells from 2 healthy control donors.

Supplemental Table 1. Expression of plasma biomarkers in Indian patients individuals with active pulmonary tuberculosis.

Disease process	Biomarker	Unit	All PTB (n=97)	HO-1^{hi}MMP-1^{lo} (n=39)	HO-1^{lo}MMP-1^{hi} (n=39)	P-value
Inflammation	α2macroglobulin	ng/mL	2.7 (1.2-5.3)	2.1 (0.9-5.2)	3.4 (2.0-6.3)	0.077
	CRP	mg/L	36.3 (21.2-69.4)	70.0 (58.5-75.8)	23.0 (20.4-41.1)	**<0.001**
	Ferritin-H	ng/mL	234.8 (93.9-414.2)	245.2 (65.2-348.6)	181.5 (87.0-415.6)	0.497
	Haptoglobin	µg/mL	1.3 (0.2-6.4)	3.4 (1.6-5.2)	1.5 (0.3-7.8)	**<0.001**
	Heme	µM	21.7 (15.5-31.0)	20.9 (16.9-29.7)	21.4 (14.4-27.8)	0.704
	IFN-γ	pg/mL	33.9 (29.8-38.1)	36.0 (31.8-80.3)	29.8 (27.8-36.0)	**<0.001**
	IL-10	pg/mL	21.1 (15.9-29.0)	28.3 (24.3-37.2)	17.0 (12.1-19.4)	**<0.001**
	IL-17	pg/mL	27.1 (22.9-35.3)	27.7 (23.6-38.7)	26.5 (22.1-31.2)	0.274
	SAA	pg/mL	125.1 (94.6-231.3)	101.7 (76.2-137.9)	225.9 (119.1-517.9)	**<0.001**
	TNF-α	pg/mL	21.3 (15.0-27.4)	15.8 (12.8-24.0)	22.6 (18.3-28.2)	**0.015**
Tissue remodeling	MMP-8	ng/mL	122.4 (54.1-202.3)	46.6 (24.3-76.9)	190.4 (152.2-272.8)	**<0.001**
	MMP-9	ng/mL	384.2 (255.0-510.8)	275.3 (116.1-533.3)	441.5 (352.2-429.9)	**0.012**
	TIMP-1	ng/mL	180.0 (161.7-199.7)	189.0 (177.2-201.4)	171.3 (157.3-198.6)	**0.028**
	TIMP-2	ng/mL	219.0 (199.4-239.0)	223.5 (203.3-238.0)	216.5 (194.3-241.0)	0.689
	TIMP-3	ng/mL	26.3 (15.9-43.9)	29.8 (11.1-54.6)	25.1 (17.3-39.1)	0.868
	TIMP-4	ng/mL	10.3 (7.7-12.4)	10.5 (8.5-12.3)	10.0 (7.5-12.4)	0.576

Data represent medians and interquartile ranges. The values of each biomarker were compared between patients with simultaneously high concentrations of HO-1 and low levels of MMP-1 (HO-1^{hi}MMP-1^{lo}) and those with low levels of HO-1 and high MMP-1 values in plasma (HO-1^{lo}MMP-1^{hi}) using the Mann-Whitney test. Statistically significant P values are highlighted in bold font.