Supporting Information

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SI Methods

Migration Inhibitory Factor Immunohistochemistry. For migration inhibitory factor (MIF) immunohistochemistry on *Mycobacterium tuberculosis*-infected lungs, tissue sections from formalin-fixed lungs were deparaffinized, and antigen retrieval was performed using the Target Retrieval Solution (Dako). After blocking nonspecific antibody binding (10% goat serum) and endogeneous peroxidase activity (Dual Endogenous Enzyme Block; Dako), sections were incubated with 1:200 dilution of goat polyclonal anti-MIF IgG (Santa Cruz Biotechnology) overnight at 4 °C. Staining was visualized by developing with the Liquid DAB + Substrate Chromogen System (Dako) for 10 min.

Transcriptome Analysis. Bone marrow-derived macrophages (BMDMs) from WT and *Mif*$^{-/-}$ mice (pooled from three animals per genotype) were prepared and infected with *Mycobacterium bovis* (or mock infected with PBS) in triplicate as described previously. Four hours after invasion, total RNA was isolated using the RNeasy kit (Qiagen). The quality of RNA was verified by agarose gel electrophoresis. Afterward, cDNA and then cRNA were prepared and cRNA hybridized to the MouseWG-6 BeadChip (Illumina) according to the manufacturer's instructions. The hybridized chips were scanned using the Illumina BeadArray reader and the images analyzed with Beadstudio software. Data were downloaded into Partek Genomic Suite for analysis. Principal component analysis was used to determine the relationships between the samples in the four groups—WT mock infected, WT *M. bovis* infected, *Mif* $^{-/-}$ mock infected, and *Mif* $^{-/-}$ *M. bovis* infected. Selected immune response genes were extracted from the full transcriptional profile analysis by a combination of statistical testing of absolute and relative changes in expression across the different experimental conditions, controlling for false discovery in multiple testing. Statistical analysis between experimental groups was performed using the Student *t* test with genes with a false discovery rate of <0.05 and a fold change of >1.3 being considered differentially expressed. Gene expression data will be available upon publication.

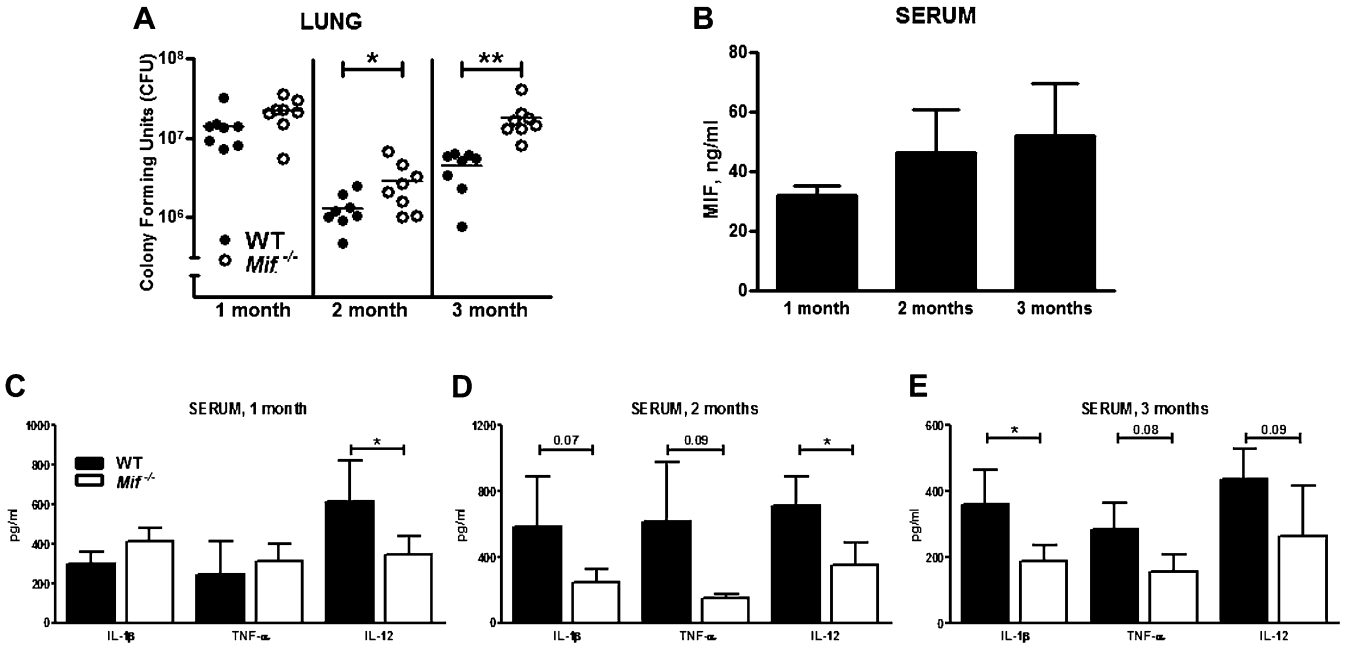


Fig. S1. *Mif*$^{-/-}$ animals have higher bacterial load and impaired systemic production of the inflammatory cytokines in the setting of *M. tuberculosis* infection. (*A*) *Mif*$^{-/-}$ animals infected by areosolized *M. tuberculosis* had higher pulmonary bacterial load than their WT counterparts. (*B*) In the WT mice, MIF was detected in the serum over the course of infection. (*C–E*) Measuring IL-1β, TNF-α, and IL-12 in the serum demonstrated a trend toward decreased levels of these cytokines in the *Mif* $^{-/-}$ animals, and the defect became more pronounced as the infection progressed. $n \geq 4$ per group, experiments repeated at least twice, and mean ± SEM reported. **P* ≤ 0.05, ***P* ≤ 0.01.

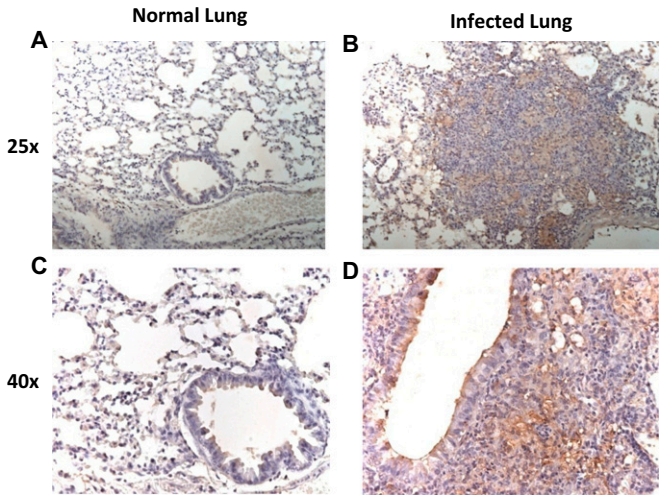


Fig. S2. Immunohistochemistry demonstrates MIF staining within *M. tuberculosis* granuloma structures. (*A* and *C*) In normal lung, MIF staining (brown) was detected within the type II pneumocytes (*A*) as well as the bronchial epithelium (*C*). (*B* and *D*) During *M. tuberculosis* infection, MIF was abundant within parenchymal (*B*) and subepithelial granuloma structures (*D*).

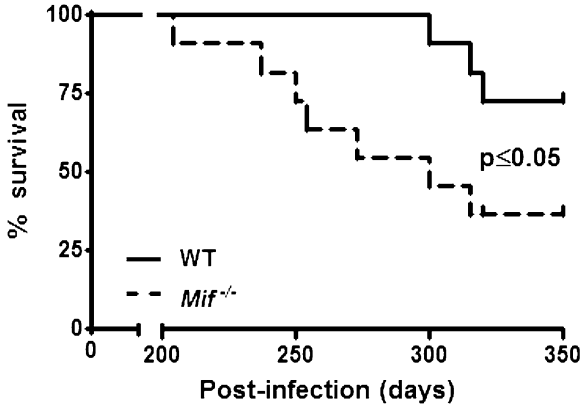
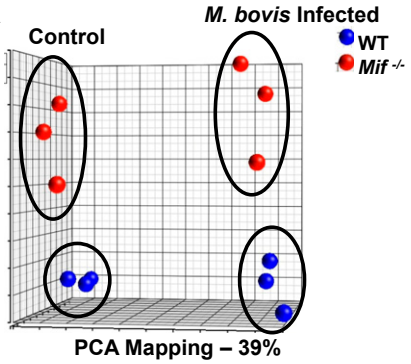


Fig. S3. *Mif*$^{-/-}$ animals succumb more quickly to *M. bovis* infection than their WT counter parts. Seventy-two percent of the WT and 36% of the *Mif*$^{-/-}$ animals survived after 1 y after infection, indicating that infection with *M*. bovis in this system was less virulent than that with *M. tuberculosis*.

A



B

Probe Set	Gene Symbol	Description	Fold Change (*Mif* $^{-/-}$ infected vs. WT infected)	p-value (FDR Adjusted)
ILMN_1239843	**Clec7a**	**Dendritic cell-associated C-type lectin-1 (dectin-1)**	**-1.54**	**0.006**
ILMN_2554110	Entpd4	Ectonucleoside triphosphate diphosphohydrolase 4 (Entpd4)	-1.76	0.011
ILMN_1249336	Mmp13	Matrix metallopeptidase 13	-1.58	0.012
ILMN_2460572	Tlr8	Toll-like receptor 8 (Tlr8)	-1.41	0.013
ILMN_3089584	Cd74	MIF receptor	-1.48	0.019

Fig. S4. Transcriptional microarray was performed to determine gene expression differences in WT and *Mif*$^{-/-}$ BMDMs after *M. bovis* infection. (*A*) Principal component analysis (PCA) of the data obtained showed clustering of the WT, *Mif*$^{-/-}$, control, and infected samples. Transcriptional fold change was calculated for WT and *Mif*$^{-/-}$ *M. bovis*-infected samples, normalized for the respective uninfected controls. The false discovery rate was set <0.05, and we examined genes that were down-regulated >1.3 fold in the *Mif*$^{-/-}$ compared with WT. (*B*) A selection of the highest scoring candidate genes.