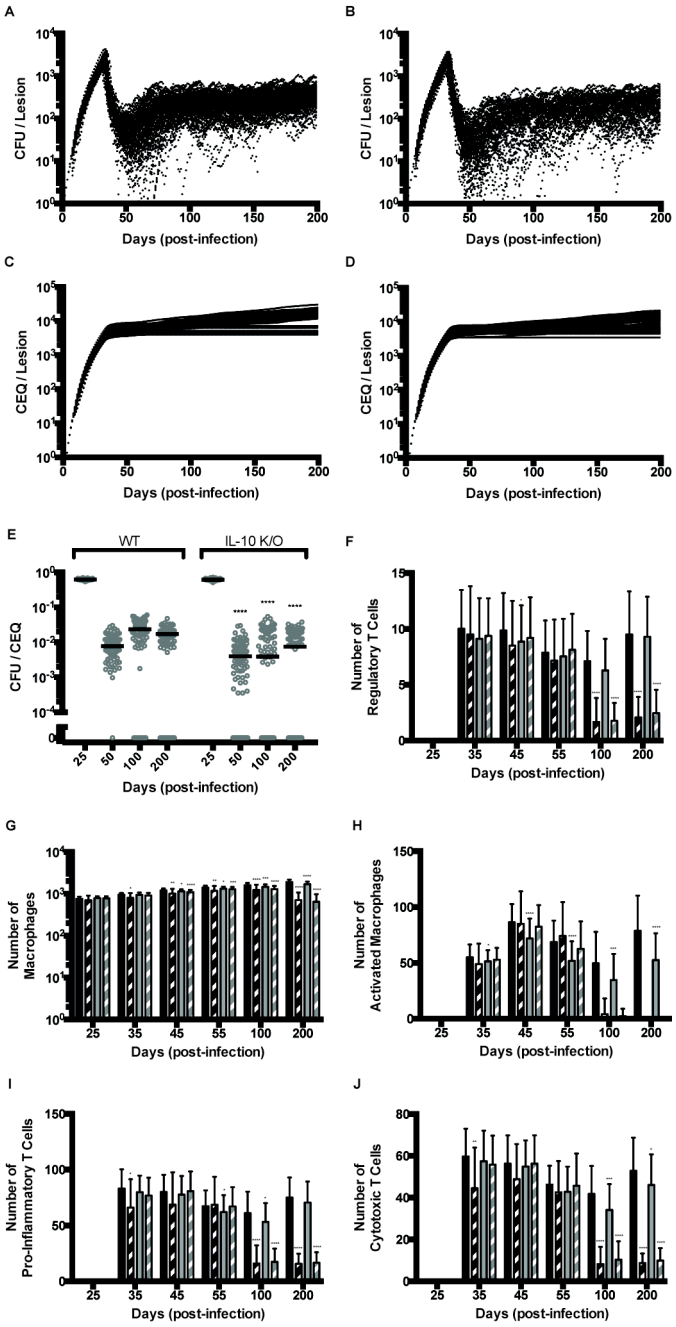
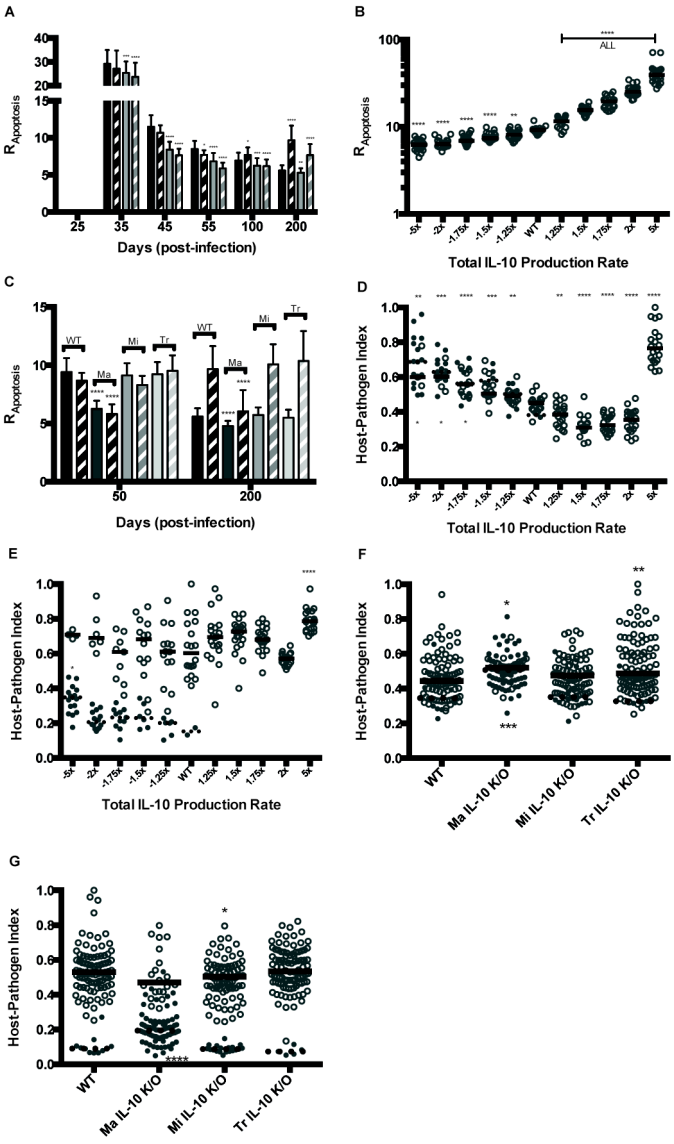


Supplementary Figure S1. A. Simulated temporal CFU data for WT lesions. B. Simulated temporal CFU data for IL-10 K/O lesions. Dots represent individual lesions at the specified time point. C. Simulated temporal CEQ data for WT lesions. D. Simulated temporal CEQ data for IL-10 K/O lesions. E. CFU/CEQ for WT and IL-10 K/O lesions, including both sterile and non-sterile lesions. F. Regulatory T cells. G. Total macrophages. H. Activated macrophages. I. Pro-Inflammatory T cell. J. Cytotoxic T cells. Dots represent individual lesions at the specified time point. Both sterile and non-sterile lesions are included. Non-sterile lesions are displayed as solid bars and sterile lesions are displayed as striped bars. Bars are representative of mean values with error bars showing SD. For all panels: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$, N = 100.



Supplementary Figure S2. $R_{Apoptosis}$ is defined as the ratio of infected macrophage apoptosis/necrosis to resting macrophage apoptosis/necrosis (1, 2). Thus, it is a metric of 'good' apoptosis to 'bad' apoptosis. A. $R_{Apoptosis}$ for WT (black bars) and IL-10 K/O (grey bars) lesions. Non-sterile lesions are displayed as solid bars and sterile lesions are displayed as striped bars. Bars are representative of mean values with error bars showing SD. B. $R_{Apoptosis}$ for different levels of total IL-10 production (5-fold reduction to 5-fold increase) at 50 days post-infection. Dots represent individual lesions. Lines indicate the median values. C. $R_{Apoptosis}$ for WT, IL-10 K/O, Ma IL-10 K/O, Mi IL-10 K/O, Tr IL-10 K/O lesions at 200 days post-infection. Both sterile and non-sterile lesions are included. Non-sterile lesions are displayed as solid bars and sterile lesions are displayed as striped bars. Bars are representative of mean values with error bars showing SD. The modified Host-Pathogen Index is defined as the scaled measure (between 0 and 1) of lesion function based on the CFU and healthy macrophage apoptosis/necrosis levels (3). Lower values indicate better lesion function. D, E. Host-Pathogen Index for different levels of total IL-10 production (5-fold reduction to 5-fold increase) at 50 and 200 days post-infection, respectively. Dots represent individual lesions. Lines indicate the median values. F, G. Host-

Pathogen Index for WT, IL-10 K/O, Ma IL-10 K/O, Mi IL-10 K/O, Tr IL-10 K/O lesions at 50 and 200 days post-infection, respectively. Solid lines indicate the median values for non-sterile lesions. Dotted lines indicate the median values for sterile lesions. Open circles are non-sterile lesions. Closed circles are sterile lesions. For all panels: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$, N = 100. Significance values above the data points are for non-sterile lesions while significance values below the data points are for sterile lesions.

Supplemental Table I. Changes to ABM Rules/Parameters and NHP Data used in Model Calibration

Changes in ABM Rules From (3)

Previous Rule	New Rule	Reason/References
Non-replicating *Mtb* trapped in caseated compartments can only be killed by hypoxia at a specified death rate.	Additionally, non-replicating *Mtb* trapped in caseated compartments in the Moore neighborhood of an activated macrophage can be killed at a reduced rate of activated macrophage killing ($1/10^{th}$).	Realistically *in-vivo* movement of cells is not constrained to binary (yes/no) decisions (e.g. cell squeezing). Thus, we allow activated macrophages to access compartments in their Moore neighborhood to alleviate artifacts of movement restrictions.
Maximal rates of T cell recruitment are allowed as soon as T cell recruitment is begins.	A time delay now exists such that T cell recruitment rates increase linearly to the maximum rates over the specified time interval.	(4)
Once a compartment becomes caseated due to passing a threshold of death events it stays caseated for the entire simulation.	Activated macrophages have an associated probability of initiating a healing event. If the compartment is marked for healing there is an associated time with the healing process. Once the time interval is passed the compartment changes from caseated to non-caseated.	(5–7)
Regulatory T cells modulate their deactivation capacity based on the relative bound IL-10 and bound TNF molecules on the cells surface.	Now, regulatory T cells have a baseline deactivation capacity. When IL-10 production is deleted from regulatory T cells the deactivation capacity is up regulated by a specified factor.	(8, 9)
Lie-type operator splitting (first order accurate) was employed to separate the coupled reaction/diffusion PDEs into three different problems.	Strang-type splitting (second-order accurate) is now employed to separate the coupled reaction/diffusion PDEs into three different problems.	Increases the accuracy of the splitting technique allowing for larger solution time steps for each of the three different problems.
Each pro-inflammatory T cell was given a probability of activating macrophage STAT1 though IFN-γ at each time step.	Pro-inflammatory T cells are now classified by the ability to secrete IFN-γ and activate STAT1 based on a specified probability when it is born.	Although the previous rule gives correct percentages of T cells secreting IFN-γ at any specific time point the population of IFN-γ secreting T cells changes with every time step when the probability is re-evaluated. Thus, the new rule identifies IFN-γ secreting and non-secreting T cells upon birth and the classification persists over the entire life span of the T cell.
All pro-inflammatory and cytotoxic T cells are capable of producing TNF-α	Pro-inflammatory and cytotoxic T cells are now classified by the ability to secrete TNF-α based on a specified probability when it is born.	(Unpublished data – Personal Communication J. Flynn, University of Pittsburgh)

NHP Data Used to Calibrate GranSim From (10–13)

NHP ID	Days Post-Infection of Necropsy	Number of Non-Sterile Lesions	Number of Sterile Lesions

8709	26	9	0
7010	27	35	1
8109	27	5	0
6810	28	18	0
7709	28	16	0
7809	28	11	0
8809	28	16	1
7210	29	22	0
7110	30	8	0
2412	83	13	1
17111	84	16	2
2512	85	21	2
3609	89	7	3
9611	93	12	0
19608	136	7	6
8509	139	6	3
6409	140	4	0
21208	173	10	2
8609	173	16	10
9711	175	10	5
9209	187	5	11
7009	194	4	11
9511	198	3	3
5610	209	2	4
23210	211	26	3
21310	230	22	15
5008	247	4	0
10808	267	2	1
22210	267	9	19
21410	267	13	9
21508	271	3	6
4808	296	1	2

ABM Parameters and Changes in Values of ABM Parameters From (3)

Parameter	**Parameter Description**	**Previous Value**	**New Value**
α_{Bi} (per 10 min)	Intracellular Mtb growth rate	1.4×10^{-3}	3×10^{-3}
α_{Be} (per 10 min)	Extracellular Mtb growth rate	7×10^{-4}	1.25×10^{-3}
N_{caseum}	Number of cell deaths required for caseation	15	10
t_{heal} (days)	Healing time of caseated compartment	---	16
τ_{chem} (molecules)	Minimum chemokine concentration threshold	2	1
s_{chem} (molecules)	Saturating chemokine concentration threshold	2000	400
r_{CCL2} (molecules/s)	Full secretion rate of CCL2 by macrophages	4.14	6
r_{CCL5} (molecules/s)	Full secretion rate of CCL5 by macrophages	4.14	6
r_{CXCL9} (molecules/s)	Full secretion rate of CXCL9/10/11 by macrophages	8.28	12
B_{actM}	Number of extracellular Mtb activating NF-κB in a mac	239	200

N_{burst}	Number of intracellular Mtb that leads to M_{ci} bursting	20	15
N_{ak} (per 10 min)	Number of extracellular Mtb killed by M_a	3	5
t_{moveMa} (hour)	Time interval for M_a movement	7.8	2.3
M_{recMax}	Maximum recruitment probability for M_r recruitment	0.09	0.20
$\tau_{recMacTNF}$	TNF threshold for M_r recruitment	0.014	0.05
h_{MacTNF}	Half-saturation of TNF for M_r recruitment	0.5	0.55
P_{heal}	Probability of healing a caseated compartment by M_a	---	0.014
$P_{Fas/FasL}$	Probability of Fas/FasL apoptosis by T_γ	0.0095	0.02
$P_{cytKill}$	Probability of T_c killing M_i or M_{ci}	0.0098	0.01
T_{moveM}	Probability of T cell moving to a mac-containing location	0.027	0.07
$P_{IFN\text{-}Tgam}$	Probability of a T_g secreting IFN-γ	---	0.35
$P_{IFN\text{-}Range}$	Range of probability of a T_g secreting IFN-γ	---	0.10
$P_{IFN\text{-}Moore}$	Probability of a T_g activating STAT1 through IFN-γ in its Moore neighborhood	---	0.25
$P_{TNF\text{-}Tcyt}$	Probability of a T_c secreting TNF	---	0.07
$P_{TNF\text{-}Tgam}$	Probability of a T_g secreting TNF	---	0.07
$P_{Deact\text{-}Treg}$	Probability of T_r deactivation of agents	---	0.015
$F_{Deact\text{-}Treg}$	Factor that describes increase in probability of T_r deactivation in the absence of IL-10	---	2.72
$t_{recEnabled}$ (days)	Time T cell recruitment is enabled	---	28
$t_{recDealy}$ (days)	Time delay in maximal T cell recruitment	---	5
$T_{recTgamMax}$	Maximum recruitment probability for T_γ recruitment	0.0713	0.096
$\tau_{recTgamTNF}$	TNF threshold for T_γ recruitment	0.014	0.1
$h_{TgamTNF}$	Half-saturation of TNF for T_γ recruitment	0.3	0.4
$T_{recTcytMax}$	Maximum recruitment probability for T_c recruitment	0.0505	0.08
$\tau_{recTcytTNF}$	TNF threshold for T_c recruitment	0.014	0.1
$h_{TcytTNF}$	Half-saturation of TNF for T_c recruitment	0.3	0.4
$T_{recTregMax}$	Maximum recruitment probability for T_{reg} recruitment	0.0221	0.024
$\tau_{recTcytTNF}$	TNF threshold for T_c recruitment	0.014	0.1
$h_{TcytTNF}$	Half-saturation of TNF for T_c recruitment	0.3	0.4
$k_{NF\kappa B}$ ((#/cell)$^{-1}$s^{-1})	Rate constant for TNF-induced NFκB activation in macrophages	1.41×10^{-8}	1.62×10^{-8}
k_{apopt} ((#/cell)$^{-1}$s^{-1})	Rate constant for TNF-induced apoptosis in all cell types	3.45×10^{-10}	2.22×10^{-9}
$\tau_{NF\kappa B}$ (#/cell)	Cell surface sTNF/TNFR1 threshold for TNF-induced NFκB activation	65	81
τ_{apopt} (#/cell)	Internalized sTNF/TNFR1 threshold for TNF-induced apoptosis	1728	2028
s_{apopt} (#/cell)	Saturation concentration of internalized sTNF/TNFR1 for TNF-induced apoptosis	4022	4691
$s_{NF\kappa B}$	Saturation fraction of sTNF/TNFR1 for TNF-induced NFκB activation	0.43	0.541
$k_{synthMacInf}$ (#/cell.s)	Full synthesis rate of soluble IL10 by infected macrophages	0.061	0.02
$k_{synthMacAct}$ (#/cell.s)	Full synthesis rate of soluble IL10 by activated macrophages	0.41	0.30

All NHPs were infected with the Erdman strain of *Mycobacterium tuberculosis* except 7010 and 7210 which were infected with barcoded Erdman strains from (11).

Supplemental Table II. Uncertainty and Sensitivity Analysis Partial Rank Correlation Coefficients of IL-10 Parameters

Selected Model Outputs at 200 Days Post-Infection

Model Outputs	D_{IL10}	k_{deg}	K_D	k_{on}	k_t	k_{int}	$IL10R_{Mac}$	$IL10R_{Tcell}$	δ_I	γ_I	$F_{Deact\text{-}Treg}$	$k_{synthMacInf}$	$k_{synthMacAct}$	$h_{synthMacAct}$	$k_{synthTcell}$
TNF-Induced Processes															
Apoptosis/Necrosis – M_r	+	+++		---		+++	---	-		+++	+	---	---	+	-
Apoptosis/Necrosis – M_i		+	+	-		+	--		+		---	---	+		+
Apoptosis/Necrosis – M_{ci}				-			-		+		--	---	+		+
Apoptosis/Necrosis – M_a	+	+++		---		+++	---	-		+++	++	---	---	+	-
Apoptosis/Necrosis – T cells	+	+++		---		+++	---			+++		---	---	+	-
Activation – M_r	+	+++		---		+++	---	-		+++	++	---	-	+	-
Activation – M_i			+						+	-	-	---	+		+
T-Cell Outputs															
CTL Killing		---		+++		---	+++			---		+++	+++		++
Fas/FasL Killing		---		+++		---	+++			---		+++	+++		++
Bacterial Outputs															
Intracellular *Mtb*	-	--		++		---	+++			---		+++	+++	-	++
Extracellular *Mtb*		---		+++		---	+++			---	-	+++	+++		+
CFU per Lesion		---		+++		---	+++			---	-	+++	+++		++
CFU/CEQ		---		+++		---	+++			---		+++	+++		+
Cellular-Level Outputs															
M_r		+++		-		+++	-				+++	---			
M_i	-	--		++		---	+++			---		+++	+++	-	++
M_{ci}	-	---		++		---	+++			---		+++	+++	-	++
M_a		+							-	-	+++		+		
T_g						-	+		--	---	+++	+	+		+
T_c						-	+		--	---	+++	++	+		+
T_r									--	---	+++	+	+		
Tissue-Level Outputs															
Caseous Necrosis		-	-	+		---	+++		--	---	+++	+++	+		+
Lesion Size						-	+		-	---	+++	+++	++		
[TNF-α]		+							-	-	+++				
[IL-10]		---				-			-	---	+++	+++	+++		+++
[Chemokines]						-			-	---	+++	+	+++		

Selected Model Outputs at 50 Days Post-Infection

Model Outputs	D_{IL10}	k_{deg}	K_D	k_{on}	k_t	k_{int}	$IL10R_{Mac}$	$IL10R_{Tcell}$	δ_I	γ_I	$F_{Deact\text{-}Treg}$	$k_{synthMacInf}$	$k_{synthMacAct}$	$h_{synthMacAct}$	$k_{synthTcell}$
TNF-Induced Processes															
Apoptosis/Necrosis – M_r	+	+++		---		+++	---			+++		---	---		-
Apoptosis/Necrosis – M_i	+	+		--		+++	---			+++	-	---		+	
Apoptosis/Necrosis – M_{ci}		+		--		+++	--		+		-	---			
Apoptosis/Necrosis – M_a	+	+++		---		+++	---			+++	+	---	---	+	-
Apoptosis/Necrosis – T cells	+	+++		---		+++	---			+++		---	---		-

Activation – M_r	+	+++		---	+++	---		+++	+	---	---		-
Activation – M_i		+	+	-	+++	--		+	-	---			
T-Cell Outputs													
CTL Killing		---		+++	---	+++		---		+++	+		++
Fas/FasL Killing		---		+++	---	+++		---		+++	+		+
Bacterial Outputs													
Intracellular *Mtb*		---		+++	---	+++		---		+++	++		+
Extracellular *Mtb*	-	---		++	---	+++		---		+++	++		+
CFU per Lesion	-	---		+++	---	+++		---		+++	++		+
CFU/CEQ		---		+++	---	+++		---	-	+++	++	-	++
Cellular-Level Outputs													
M_r							+			-		+	
M_i	-	---		++	---	+++		---		+++	++		+
M_{ci}		---		+++	---	+++		---		+++	+		+
M_a		+++		--	+++	---		+++	+++	---	-	+	
T_g							---		+++	+++	-		
T_c							-		+++	+++	-		
T_r									+++	+++	-		
Tissue-Level Outputs													
Caseous Necrosis	+	+++		---	+++	---		+++		---	-	+	-
Lesion Size					--	++		---	+++	+++			
[TNF-α]	+	+++		---	+++	---		+++	++	---	---	+	-
[IL-10]		---		-				-		+++	+++		+++
[Chemokines]			-				-		+++				+

Significant PRCC values are as follows: -/+ $0.005 < p < 0.05$ --/++ $0.0005 < p < 0.005$ ---/+++ $p < 0.0005$
PRCC and significance values calculated from N – 250 simulations with 4 replications each
M_i = Infected Macrophages, M_{ci} = Chronically Infected Macrophages, M_a = Activated Macrophages, M_r = Resting Macrophages, T_g = Pro-inflammatory T cells, T_c = Cytotoxic T cells, T_r = Regulatory T cells
CTL = Cytotoxic, CFU = Colony Forming Units, CEQ = Chromosome Equivalents
Parameters are defined herein or in Cilfone et al. (3)

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