SUPPLEMENTARY MODELING METHODS

The overall structure of the multi-scale agent-based model for the immune response to Mtb infection in the lung as well as the detailed description of processes at each scale, including the stochastic cellular/tissue scale ABM and the deterministic ODE model of TNF/TNFR associated molecular processes, are presented. Figure 1 in the main text indicates how these models exist separately and how they are linked. All parameter definitions and values are listed in Supplementary Tables S1, S2 and S5.

Overall structure of the multi-scale ABM

The multi-scale ABM was developed based on four considerations: an environment, agents (immune cells), ABM rules that govern the agents and their interactions, and the time-step (Δt) used to update events. The environment represents a two-dimensional section of lung parenchyma as a 100 × 100 square lattice that simulates an area of 2 mm × 2 mm. Each grid micro-compartment is thus scaled to the approximate size of a single human macrophage, 20 μm in diameter. Discrete agents (macrophages and T cells) are recruited from specific micro-compartments on the lattice that represent vascular sources. Cells move on the lattice and interact with each other and the environment based on the ABM rules that are defined based on known biological activities. Due to the size difference between macrophages and T cells, up to two T cells are permitted to enter the same micro-compartment (with probability T_{moveT}). A T cell may also move into the same micro-compartment as a macrophage (with probability T_{moveM}). This model of cell spacing is a compromise between a realistic spatial representation and computational

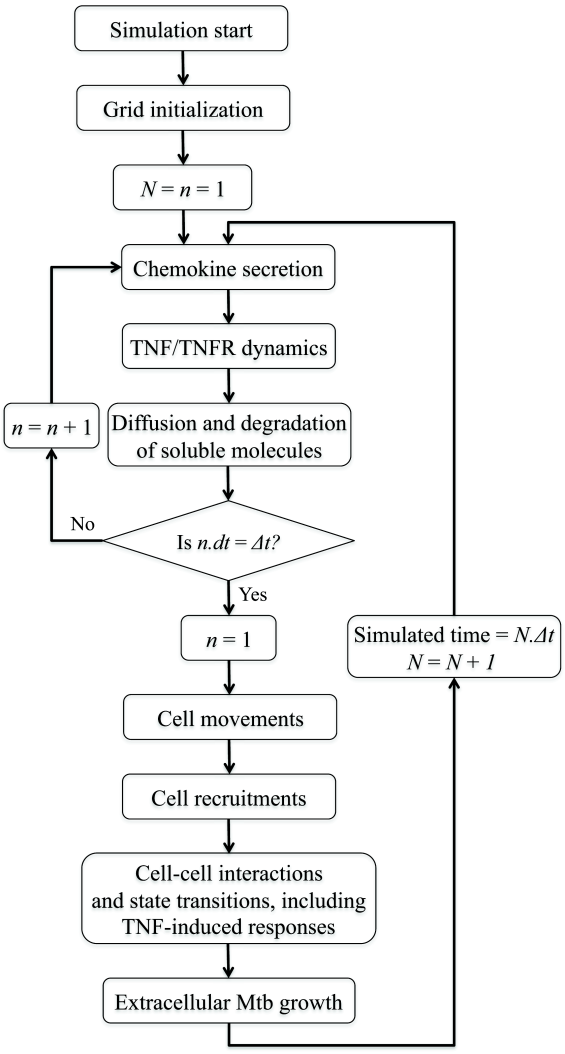
tractability and is consistent with observations on macrophage and T cell dynamics during development of mycobacterial granulomas that show granuloma-associated T cells squeeze through cell junctions created by a dense macrophage network (1).

Extracellular Mtb and soluble molecules, including chemokines (CCL2, CCL5 and CXCL9/10/11), soluble TNF (sTNF) and shed TNFR2 are simulated as continuous entities that can reside anywhere on the lattice. Extracellular Mtb grow in each micro-compartment. Soluble molecules diffuse among micro-compartments. Caseation represents inflammation of and damage to the lung parenchyma from macrophage cell death. In the ABM, caseation is defined to occur when a specific number (N_{caseum}) of infected or activated macrophages die in a micro-compartment. When a micro-compartment becomes caseated, any T cell present in the micro-compartment is killed and no further cells are permitted to enter the micro-compartment.

There are two major types of discrete agents in the model, macrophages and T cells. Macrophages are either resting (M_r, uninfected), infected (M_i; have taken up Mtb), chronically infected (M_{ci}; are unable to clear their intracellular Mtb due to a high number of bacterial load), or activated (M_a; can effectively kill bacteria). Three distinct T cell classes based on their functions are modeled. The T_γ class represents CD4 and CD8 pro-inflammatory T cells; T_c class represents cytotoxic T cells (CTLs); and T_{reg} class represents regulatory T cells.

Cell-cell interactions are governed by ABM rules that are updated within every ABM time-step (Δt = 10 min) and will be discussed in the next section. Single-cell molecular scale processes, including diffusion of soluble molecules on the lattice,

secretion of chemokines from individual cells and TNF/TNFR dynamics at the single-cell level, that generally occur in shorter time-scales compared to cellular interactions, are updated within shorter time-steps (dt = 6 s). Thus, each molecular event is updated 100 times within each ABM time-step, the time in which each cellular scale event is updated once. The overall algorithm of the simulation takes the form outlined as follows and will be presented in detail in the following sections.



Grid initialization

A 100 × 100 two-dimensional grid is created. Periodic boundary conditions for cell movement and Dirichlet boundary conditions (zero outside grid perimeter) for molecular diffusion is used. N_{source} = 50 vascular source locations are distributed on the grid. 49 of the vascular sources are randomly distributed in 7 × 7 approximately equally sized partitions on the grid. One other micro-compartment is randomly selected from the whole grid as the last vascular source. Initial resting macrophages that represent resident alveolar macrophages are randomly placed on the grid. One infected macrophage with one intracellular Mtb is placed at the center of the grid. This is consistent with estimations of the minimum infection dose of Mtb that range from a single bacterium upward (2).

Cellular/tissue scale ABM rules

Cells move, become recruited to the site of infection and respond to local conditions depending on their type and state according to rules that represent known biological activities *in vivo*. ABM rules that govern cell behaviors and interactions are as follows. Because the main goal of this study is to investigate the role of TNF availability and kinetics of TNF-associated molecular scale processes on the outcome of Mtb infection, we discuss TNF-independent chemokine-related processes (such as chemokine secretion, diffusion and degradation) in addition to cellular scale immunological details of the ABM in this section.

Cell movements

1- Macrophages:

Macrophages may stay in place or move in 8 possible directions on the grid based on CCL2 and CCL5 chemokine concentrations in their Moore neighborhood, the nine micro-compartments around the cell location including the micro-compartment occupied by the cell. Speed of movement only depends on the state of macrophages with the highest speed for M_r and the smallest speed (zero) for M_{ci}. The differences among macrophage speeds are shown in the model by time intervals in which each macrophage attempts once to move (t_{moveMr}, t_{moveMi}, t_{moveMa}). There are minimum and maximum (saturating) concentration thresholds (τ_{chem} and s_{chem}) for the effect of each chemokine on the cell movement. Chemokine concentrations below τ_{chem} or above s_{chem} do not have any effect on direction of movement. For simplicity we assume similar threshold values for all chemokines and cell types. Movement is random if chemokine concentrations in the Moore neighborhood are below τ_{chem} or above s_{chem}. Otherwise, CCL2 and CCL5 concentrations in the Moore neighborhood determine a linear probability distribution for movement. We assume a bias for macrophage movement to the micro-compartment with the highest chemokine concentration. Hence, the highest chemokine concentration in the Moore neighborhood is multiplied by a factor 1.5 before calculation of movement probabilities. Movement is blocked by a caseous micro-compartment or macrophage presence and if blocked, no extra attempt for moving is made.

2- T cells:

T cell movements are updated in time intervals of length t_{MoveT} that is determined by the speed of T cell migration *in vivo*. Movement of T_γ cells depends on CCL2, CCL5 and CXCL9/10/11 concentrations in the Moore neighborhood. T_c cells move based on CCL5 and CXCL9/10/11 concentrations and T_{reg} cells move based on CCL5 concentrations. The details of T cell chemotactic movements are similar to what was described for macrophages. T cell movement is blocked by caseation. However, T cell movement to a micro-compartment that contains one macrophage or one T cell is possible with reduced probabilities, T_{moveM} and T_{moveT}, respectively.

Cell recruitments

1- Macrophages:

Resting macrophages are recruited every time-step from vascular sources based on available TNF and chemokine concentrations in each vascular source, provided that the vascular source is not caseated nor blocked by a macrophage or two T cells. For a macrophage to be recruited from a vascular source, the following condition must be met. If ω_{recTNF}.[sTNF] + $\omega_{recCCL2}$.[CCL2] + $\omega_{recCCL5}$.[CCL5] > τ_{recMac}, M_r recruitment occurs with a probability M_{recr}; where [sTNF], [CCL2] and [CCL5] are the numbers of sTNF, CCL2 and CCL5 molecules in the vascular source micro-compartment, respectively.

2- T cells:

Recruitment of T cells begins after a delay (t_{delay}) that represents the time required for activation of the adaptive immune response following Mtb infection. T cell recruitment occurs for all vascular sources at every time-step with a probability T_{recr}. If T cell recruitment is allowed, then T cells of each class are recruited based on TNF and chemokine concentrations in each vascular source as described below, provided that the vascular source is not caseated or blocked by two T cells or one macrophage and another T cell. For a T_γ to be recruited, the following condition must be met. If ω_{recTNF}.[sTNF] + $\omega_{recCCL2}$.[CCL2] + $\omega_{recCCL5}$.[CCL5] + $\omega_{recCXCL9/10/11}$.[CXCL9/10/11] > $\tau_{recTgam}$, T_γ recruitment is permitted with a probability $T_{recTgam}$. Otherwise, T_c recruitment can occur. If ω_{recTNF}.[sTNF] + $\omega_{recCCL5}$.[CCL5] + $\omega_{recCXCL9/10/11}$.[CXCL9/10/11] > $\tau_{recTcyt}$, T_c recruitment is permitted with a probability $T_{recTcyt}$. Otherwise, T_{reg} recruitment can occur. If ω_{recTNF}.[sTNF] + $\omega_{recCCL5}$.[CCL5] > $\tau_{recTreg}$, T_{reg} recruitment is permitted with a probability $T_{recTreg}$.

Cell-cell interactions and state transitions

All cell-cell interactions and state transitions described below are updated every time-step for all cells.

1- Cell death due to age:

All macrophages that are initially distributed or recruited on the grid are assigned a lifespan selected from a uniform distribution between zero and max_{ageMac}. T cells are also assigned a lifespan randomly distributed between zero and $max_{ageTcell}$. M_a has a shortened

lifespan of $max_{ageActive}$. At death, M_r and T cells are removed from the grid. At death, M_i and M_{ci} are removed from the grid and intracellular Mtb from dead cells are dispersed uniformly in the Moore neighborhood including the micro-compartment originally occupied by the cell. M_a death contributes to caseation of the micro-compartment.

2- ABM rules for M_r:

There is a chance of STAT-1 activation in a time-step as a result of interaction between a M_r and IFN-γ producing T_γ cells with a probability ($n_{Tgam}.P_{STAT1}$); where, n_{Tgam} is the number of T_γ cells surrounding the M_r in the Moore neighborhood including the micro-compartment occupied by the M_r.

M_r is able to uptake or to kill extracellular Mtb that reside in the same micro-compartment. If the number of extracellular Mtb (B_{ext}) ≤ N_{rk}, M_r kills them. Otherwise, it either kills N_{rk} of the extracellular Mtb with probability P_k or becomes infected (M_i) after uptake of N_{rk} of the extracellular Mtb as its initial intracellular Mtb.

If both STAT1 and NF-κB are activated in a M_r and it is not already down-regulated by a T_{reg}, it becomes activated (M_a). If the remaining lifespan of such an activated macrophage is greater than $max_{ageActive}$, it will be shortened to $max_{ageActive}$.

3- ABM rules for Mi:

Intracellular Mtb (B_{int}) replicate in M_i every time-step according to the following equation:

$$B_{\text{int}}(t+\Delta t) = (1+\alpha_{Bi})B_{\text{int}}(t) \qquad (1)$$

M_i is able to uptake but not kill extracellular bacteria from its micro-compartment with a probability ($P_{uptakeMi}$) that is computed as a function of B_{int} as follows:

$$P_{uptakeMi} = (N_c - B_{\text{int}})/100 \quad (2)$$

M_i takes up N_{rk} of extracellular bacteria if $B_{ext} > N_{rk}$. Otherwise, it takes up all extracellular bacteria that are available in the micro-compartment. If the number of intracellular Mtb (B_{int}) exceeds a threshold N_c, the M_i becomes chronically infected (M_{ci}).

There is a chance of STAT-1 activation in a time-step as a result of interaction between a M_i and IFN-γ producing T_γ cells with a probability ($n_{Tgam}.P_{STAT1}$) where, n_{Tgam} is the number of T_γ cells surrounding the M_i in the Moore neighborhood (including the micro-compartment occupied by the M_i). If both STAT1 and NF-κB are activated in a M_i and it is not already down-regulated by a T_{reg}, it becomes activated (M_a). If the remaining lifespan of such an activated macrophage is greater than $max_{ageActive}$, it will be shortened to $max_{ageActive}$.

4- ABM rules for M_{ci}:

Intracellular Mtb (B_{int}) replicate in M_{ci} every time-step according to Equation 1. If the number of intracellular Mtb exceeds a threshold (N_{burst}), M_{ci} bursts and its intracellular Mtb are evenly distributed to the Moore neighborhood surrounding the M_{ci} (including the micro-compartment occupied by the cell). M_{ci} bursting contributes to caseation of the micro-compartment.

5- ABM rules for M_a:

M_a is capable of effectively killing extracellular Mtb. Each time-step, M_a kills N_{ak} of the extracellular Mtb in its micro-compartment.

6- ABM rules for T_c:

If T_c is not already down-regulated by a T_{reg} and there is a M_i or M_{ci} present in the same micro-compartment as T_c, there is a chance of perforin/granulysin-mediated killing of M_i or M_{ci} with probability $P_{cytKill}$. M_i killing by a T_c kills all intracellular Mtb and contributes to caseation of the micro-compartment. In the case of M_{ci} killing, the intracellular Mtb are killed with probability $P_{cytKillClean}$. Otherwise, the intracellular Mtb will be uniformly distributed in the Moore neighborhood (including the micro-compartment occupied by the cell). M_{ci} killing by T_c also contributes to caseation of the micro-compartment.

7- ABM rules for T_γ:

If T_γ is not already down-regulated by a T_{reg} and there is a M_i or M_{ci} present in the same micro-compartment as T_γ, there is a chance of Fas/FasL-induced apoptosis of M_i or M_{ci} with probability $P_{apop/Fas}$. As a result of apoptosis, half of the intracellular Mtb in M_i or M_{ci} will be killed and the other half will be equally distributed in the Moore neighborhood (including the micro-compartment occupied by the cell).

8- ABM rules for T_{reg}:

Regulatory T cells suppress or down-regulate the action of T cells and macrophages through poorly understood mechanisms that may occur by cell contact, secretion of immunosuppressive cytokines or both (3, 4). T_{reg} here down-regulates all cells (macrophages, T_c and T_γ) in its Moore neighborhood including its own micro-

compartment. Down-regulated states last for t_{regMac}, $t_{regTgam}$ and $t_{regTcyt}$ for macrophages, T_c and T_γ cells, respectively. Consequences of T_{reg} down-regulation for each cell type is explained in sections that describe ABM rules for that cell type.

Extracellular Mtb growth

Growth of extracellular Mtb (B_{ext}) in all micro-compartments is calculated based on the following equation:

$$B_{ext}(t+\Delta t) = B_{ext}(t) + \alpha_{Be} B_{ext}(t)\left[1 - \frac{B_{ext}(t)}{1.1K_{be}}\right] \quad (3)$$

Chemokine secretion

M_i, M_{ci}, M_a, NF-κB activated M_r and NF-κB activated M_i are able to secrete chemokines, provided that they are not down-regulated by T_{reg}. The rates of chemokine secretion for different cell types are as follows. M_{ci}, M_a and NF-κB activated M_i are able to secrete chemokines with full secretion rates (r_{CCL2}, r_{CCL5} and r_{CXCL9}) as listed in Supplementary Table S1. NF-κB activated M_r and M_i cells that are not NF-κB activated secrete chemokines with half-full secretion rates ($0.5 \times r_{CCL2}$, $0.5 \times r_{CCL5}$ and $0.5 \times r_{CXCL9}$). Caseated micro-compartments also secrete attractants that attract immune cells. For simplicity, we use quarter-full rates of chemokine secretion to simulate the effect of such attractants ($0.25 \times r_{CCL2}$, $0.25 \times r_{CCL5}$ and $0.25 \times r_{CXCL9}$). Chemokine secretions to the

micro-compartments on the grid are updated in time intervals of *dt*. Secretion of TNF will be discussed in TNF/TNFR dynamics section.

Diffusion and degradation

The equation for diffusion and degradation of chemokines and other soluble molecules, including sTNF and shed TNFR2, can be implemented numerically on the grid by using an iterative finite-difference method. This form of this equation in two dimensions is as follows:

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2}\right) - \delta C \qquad (4)$$

where C is the concentration of diffusing molecule that changes with time (t) in the x and y directions, D is the diffusion coefficient for the molecule in the diffusion environment, and δ is the degradation rate constant. Rewriting this equation using a finite difference approximation for discrete-time discrete-space diffusion on our grid gives:

$$C_{i,j}(t+dt) = (1-\delta dt)C_{i,j}(t) + \frac{\lambda}{4}\{C_{i-1,j}(t) + C_{i+1,j}(t) + C_{i,j-1}(t) + C_{i,j+1}(t) - 4C_{i,j}(t)\} \qquad (5)$$

where $C_{i,j}(t)$ is the concentration of the diffusing molecule in the micro-compartment (i,j) at time t and λ is determined as a function of D, diffusion time-step (dt = 6 s), and lattice spacing through which diffusion occurs (dx = 20 μm):

$$\lambda = \frac{4Ddt}{(dx)^2} \qquad (6)$$

Solution to Equation 5 is stable if $\lambda < 1$. Thus, *dt* and *dx* must be picked accordingly.

Extensions and updates to the ABM rules described by Ray *et al*

In the previous sub-sections we presented the ABM rules describing cellular/tissue scale activities and interactions. As mentioned earlier, this model was first developed by Segovia-Juarez *et al* (5) and later extended by Ray *et al* (6). The differences and extensions of the cellular/tissue scale ABM used in this study compared with the ABM by Ray *et al* are as follows:

1) T_γ cells used to have two different active states. These two states have been merged, as they were not significantly different and introduced unnecessary complexity to the model.

2) In order to have more realistic down-regulatory mechanisms in the model, T_c cells and macrophages according to the published data reviewed in (7), in addition to T_γ cells, can be down-regulated by T_{reg} cells. When down-regulated, T_c cells lose their cytotoxic capabilities for a fixed period of time $t_{regTcyt}$. Following macrophage down-regulation, STAT1 is deactivated and the macrophage does nothing but moves for a fixed period of time t_{regMac}.

3) The extracellular bacteria threshold for NF-κB activation, B_{actM}, has been extended to consider the Moore neighborhood, rather than the local micro-compartment.

4) We assume that a fully activated macrophage can only secrete TNF and chemokines at the maximal rate. Thus, resting macrophages that have been NF-κB activated but have

not been STAT-1 activated now secrete TNF and chemokines at half rate compared with activated macrophages.

5) We did not consider possibility of Mtb uptake by infected macrophages in our previous model. Infected macrophages now have the ability to uptake additional extracellular bacteria; the probability of extracellular Mtb uptake is inversely proportional to the number of intracellular Mtb that reside in the macrophage.

6) TNF-induced NF-κB activation and apoptosis were previously modeled as events that occurred with probabilities of 100% and 4% (approximated via uncertainty analysis) for extracellular TNF concentrations above specific thresholds. Here, we have revised TNF-induced cell responses as will be discussed in detail in later sections.

7) We have revised the user interface for performing our modeling studies so that we can easily visualize and track different aspects of the granuloma, including the structure and molecular concentration gradients, as it forms and is maintained. In order to satisfy the cross-platform requirement, we make use of the Qt framework. Qt is a C++ framework for developing cross-platform applications with a graphical user interface (GUI).

ODEs that govern molecular scale TNF/TNFR dynamics

The binding interactions and reactions controlling TNF/TNFR dynamics at the single-cell level regardless of the cell type are schematically illustrated in the main text (Figure 1B). TNF is first synthesized by TNF-producing cells (M_i, M_{ci}, M_a, NF-κB activated M_r, T_γ and T_c), if not down-regulated by T_{reg} cells, as a membrane-bound precursor form

(mTNF) that can then be processed and released as a soluble form (sTNF) into extracellular spaces. This processing occurs via a cell-associated metalloproteinase called TACE. Two types of TNF receptors (TNFR1 and TNFR2) are synthesized and expressed on the cell surface as free receptors. Soluble TNF (sTNF) reversibly binds to TNFRs on the cell membrane. sTNF-bound cell surface TNFR1 internalizes and sTNF-bound cell surface TNFR2 may undergo internalization or shedding into extracellular spaces (8). Internalized receptors may degrade or recycle to the cell membrane where they can re-bind to sTNF (9). Ligand-free TNFRs also turn over (internalize) (9, 10). Intact sTNF may dissociate from the shed sTNF/TNFR2 complex in the extracellular space (11). We modeled these molecular processes based on mass action kinetics as shown in Supplementary Table S3; model equations are listed in Supplementary Table S4; definitions and values of the rate constants are given in Supplementary Table S2. Note that the rates of mTNF synthesis and release from the cell membrane and TNFR synthesis (k_{Synth}, k_{TACE}, V_{r1} and V_{r2}) are cell type/state-specific as indicated in Supplementary Table S2, but other rate constant values are common between all cells. Note that this ODE model was presented previously (12) and is described here for completeness.

In the multi-scale model described in this work, the rates of mTNF synthesis for different cell types are as follows. M_{ci}, M_a and NF-κB activated M_i are able to synthesize mTNF with a full rate ($k_{synth} = k_{synthMac}$) as shown in Supplementary Table S2. NF-κB activated M_r and NF-κB deactivated M_i express mTNF with a half-full rate ($k_{synth} = 0.5 \times k_{synthMac}$). T_γ cells and T_c cells express mTNF with rates $k_{synthTcell}$ and $0.1 \times k_{synthTcell}$, respectively. T_{reg}-down-regulated cells do not express TNF. TACE activity is also assumed to be cell type-dependent as shown in Supplementary Table S2.

TNF/TNFR dynamics model ODEs are solved for each individual cell on the grid in combination with TNF diffusion and degradation equations using the time-step *dt*. Soluble molecules in the model (sTNF and sTNF/TNFR2$_{shed}$) are expressed as volumetric concentration units (e.g. M), whereas cell-associated species are expressed as # of molecules per cell. Thus, when a membrane-bound molecule releases to the extracellular space (i.e. the micro-compartment occupied by the cell), or when a soluble molecule binds to the cell membrane, a scaling factor (ρ/N_{av}) is required as indicated in Supplementary Table S4, where ρ is the cell density in the micro-compartment and can be computed as $(dx)^{-3}$ assuming that each micro-compartment is a cube of side *dx*.

NF-κB activation and apoptosis

TNF-induced NF-κB activation and TNF-induced apoptosis are modeled, as described in the main text, as Poisson processes with rate parameters computed as functions of molecular concentrations from the ODE model. NF-κB activation is checked once for all M_r and M_i within each ABM time-step (Δt). NF-κB pathway can also be activated in M_r or M_i if the number of extracellular bacteria (B_{ext}) in the Moore neighborhood micro-compartments exceeds a threshold (B_{actM}). TNF-induced apoptosis is checked once for all cells on the grid within each time-step (Δt). If the apoptotic cell is a M_i or M_{ci}, half of the intracellular Mtb in M_i or M_{ci} will be killed as a result of apoptosis and the other half will be equally distributed in the Moore neighborhood including the micro-compartment occupied by the cell.

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