Supplemental Materials: Depletion of TGF-β1 Increases Bacterial Clearance by Cytotoxic T Cells in a Tuberculosis Granuloma

Table S1. Parameters and parameter ranges used to generate baseline containment simulations

Table S2. Significant PRCC values for TGF- β 1 parameters introduced in this version of GranSim at day 200 PI

Figure S1. Decreased secretion of TGF-β1 by macrophages results in increasing percentage of effector cytotoxic T-cells at day 200.

Figure S2. Gating strategy for flow cytometry studies.

Table S1. Parameters and ranges used to generate baseline containment simulations

Parameter name	Value or range	Units				
Mtb parameters						
Growth rate intracellular Mtb	1.003	cells				
Growth rate extracellular Mtb	1.001	cells				
Death rate of extracellular Mtb in caseum	1.5	cells				
	Core model parameters					
Diffusion time step	60	seconds				
Molecular time step	6	seconds				
Diffusion smoother time step	1.2	seconds				
Number of smoother steps	0	n/a				
Number of host cells causing caseation	10	n/a				
Time to heal caseation	[1642, 2462]	days				
Threshold for TNFα induced apoptosis	[1393, 2089]	molecules				
Rate of TNFα induced apoptosis	[1.17e-6, 1.76e-6]	1/seconds				
Minimum number of molecules allowing chemotaxis	[0.514, 0.77]	molecules				
Maximum number of molecules allowing chemotaxis	[374, 562]	molecules				

Diffusivity of TNFα	5.2e-8	cm ² /s			
Diffusivity of IL10	5.2e-8	cm ² /s			
Diffusivity of active TGF-β1	5.2e-8	cm ² /s			
Diffusivity of chemokines	5.2e-8	cm ² /s			
Degradation rate of TNEss	0.00158	molecules/molecular time			
Degradation rate of TNFα	0.00136	step			
Degradation rate of IL10	0.00048	molecules/molecular time			
Degradation rate of 1E10	0.00040	step			
Degradation rate of inactive	[9.28e-6, 1.39e-5]	molecules/molecular time			
TGF-β1	[9.286-0, 1.396-3]	step			
Degradation rate of active	[9.00.4.0.0012]	molecules/molecular time			
TGF-β1	[8.0e-4, 0.0012]	step			
	Macrophage parameters				
Fraction of grid					
compartments with a	[0.024, 0.036]	n/a			
macrophage					
Number of time steps before					
a resting macrophage can	2	n/a			
move					
Number of time steps before					
an activated macrophage can	16	n/a			
move					
Number of time steps before					
an infected macrophage can	[112, 168]	n/a			
move					
Synthesis rate of TNFα	1.5	molecules/diffusion time			
$(MacTNF\alpha_{synth})$	1.3	step			
Synthogic rate of CCL 2	6	molecules/diffusion time			
Synthesis rate of CCL2	U	step			
Synthesis rate of CCI 5	6	molecules/diffusion time			
Synthesis rate of CCL5	υ	step			
Synthesis rate of CCL9	12	molecules/diffusion time			
Symmesis fact of CCL9	12	step			
Synthesis rate of IL10 by an	0.3	molecules/diffusion time			
activated macrophage	0.3	step			
Synthesis rate of IL10 by and	0.02	molecules/diffusion time			
infected macrophage	₩.02	step			
Synthesis rate of Inactive	[1.4e-4, 2.12e-4]	molecules/diffusion time			
TGF-β1 by macrophages	[1.45-4, 2.125-4]	step			
		•			

Number of bacteria a resting	1	n/a		
macrophage can phagocytose	1	11/ 4		
Probability of resting				
macrophage killing bacteria	[0.23, 0.35]	n/a		
$(MacKill_{baseline})$				
Threshold for intracellular				
bacteria causing chronically	[8,12]	bacteria		
infected macrophages				
Threshold for intracellular				
bacteria causing macrophage	[13, 20]	bacteria		
to burst				
Number of bacteria an				
activated macrophage can	[4, 6]	n/a		
phagocytose				
Fraction of inactive TGF-β1				
activated by a mac	[7e-5, 1e-4]	n/a		
$(Activation_{fraction})$				
Amount of TGF-β1 that				
inhibits macrophages	[0.01, 1]	molecules		
$(TGF\beta 1max_{Mac})$				
Fraction of active TGF-β1 in		n/a		
a compartment bound by a	[1.1e-5, 1.7e-5]			
mac				
Probability of an activated				
macrophage healing a	[0.0128, 0.0129]	n/a		
caseated compartment in its	[0.0126, 0.0127]	11/ α		
Moore neighborhood				
	T cell parameters			
Probability of a T cell				
moving to the same	[0.05, 0.08]	n/a		
compartment as a	[0.03, 0.00]	II/ a		
macrophage				
Probability of a T cell				
moving to the same	0.08	n/a		
compartment as a T cell				
Synthesis rate of TNFα by	0.15	molecules/diffusion time		
IFNγ-producing T-cell	0.13	step		
IFNγ-producing T-cell				
probability of inducing	[0.0152, 0.0228]	n/a		
Fas/FasL mediated apoptosis				

producing T-cell to secrete TNFα [0.048, 0.072] n/a Probability of IFNγ-producing T-cell to secrete TNFα [0.288, 0.432] n/a Synthesis rate of TNFα by cytotoxic T-cell killing a macrophage 0.015 molecules/diffusion time step Probability of a cytotoxic T-cell killing a macrophage all associated Mtb [0.012, 0.18] n/a Probability of cytotoxic T-cell to secrete TNFα [0.056, 0.084] n/a Synthesis rate of IL10 by regulatory T-cell 0.739 molecules/diffusion time step Synthesis rate of TGF- β 1 by regulatory T cell [0.0067, 0.0101] molecules/diffusion time step Probability a regulatory T cell will deactivate an activated macrophage [0.011, 0.016] n/a Amount of TGF- β 1 that inhibits T cells (TGF β 1 max _{Tcell}) [0.01, 0.1] molecules Maximum macrophage recruitment probability [0.112, 0.168] n/a Maximum IFNy-producing T cell recruitment probability [0.112, 0.168] n/a	Probability of IFNγ-							
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T cell recruitment probability [0.112, 0.168] n/a	recruitment probability	[0.112, 0.100]	11/ α					
I cell recruitment probability	Maximum IFNγ-producing	[0 112 0 168]	n/a					
3.6 ·	1 2	[0.112, 0.100]	11/ α					
1 100/9 01/1 1 1/9	Maximum cytotoxic T cell	[0 079 0 12]	n/a					
recruitment probability [0.075, 0.12]	recruitment probability	[0.07), 0.12]	11/ α					
Maximum regulatory T cell [0.0232, 0.0348] n/a		[0 0232 0 0348]	n/a					
recruitment probability * Indicates estimated parameters. All other parameters derived from prior work (70)		11/ α						

^{*} Indicates estimated parameters. All other parameters derived from prior work (70).

Table S2: Significant PRCC values for TGF- $\beta1$ parameters introduced to this version of *GranSim* at day 200 PI. p > 0.001

	Parameters
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		Degradation Rate of Active TGF-β1	Degradation Rate of Inactive TGF-β1	Synthesis of Inactive TGF-β1 by Macs	Fraction of TGF-β1 Activated by Macs	Macrophage TGF-β1 Binding Rate	Maximum TGF-β1 Bound by a T cell	TGF-β1 Inhibition of Cytotoxic T cells	Synthesis of Inactive TGF-β1 by Regulatory T Cells
	# Total Macs							0.09	
	# Resting Macs							0.08	
	# Infected Macs		0.08					0.10	
	# Chronically Infected Macs								
	# Activated		0.07					0.08	
	Macs		0.07		0.00			0.00	
	# Dead Macs # Total IFNg+				-0.09				
	T cells							0.08	
	# Active IFNg+ T cells							0.08	
	# Down Regulated IFNg+ T cells								
	# Dead IFNg+ T cells								
	# Total Cytotoxic T cells							0.09	
	# Effector Cytotoxic T cells		0.09						
	# Total Regulatory T cells							0.07	
Outputs	# Intracellular		0.08					0.09	
o	Mtb # Extracellular Mtb							0.09	
	# Non- replicating Extracellular Mtb							0.09	
	Total CFU		0.08					0.10	
	Total CEQ		0.09					0.16	
	# Mtb Killed by Apoptosis		0.09					0.17	
	# Mtb Killed by Cytotoxicity		0.08					0.13	
	# Mtb Killed by Fas/Fas-ligand		0.08					0.16	
	# Mtb Killed by Macs # Mtb Killed in		0.09					0.13	
	# Mtb Killed in Caseation							0.14	
	Total TAG		0.08					0.14	
	Total TNF							0.08	
	Total CCL2							0.08	
	Total CCL5							0.10	
	Total CXCL9							0.10	
		Parameters						•	
		Degradation Rate of	Degradation Rate of	Synthesis of	Fraction of	Macrophage TGF-β1	Maximum TGF-β1	TGF-β1 Inhibition	Synthesis of Inactive

		Active TGF-β1	Inactive TGF-β1	Inactive TGF-β1 by Macs	TGF-β1 Activated by Macs	Binding Rate	Bound by a T cell	of Cytotoxic T cells	TGF-β1 by Regulatory T Cells
	Total TAG							0.10	
	Total Active TGFB			0.07				0.09	
	Total Inactive TGFB		-0.28	0.23					0.15
	Total TNFα Induced Mac Apoptosis		0.08					0.13	
	TNFa Induced Resting Mac Apoptosis		0.07					0.11	
	TNFα Induced Infected Mac Apoptosis		0.09					0.14	
Outputs	Total Chronically Infected Mac Apoptosis							0.19	
	TNFα Induced Activated Mac Apoptosis		0.07					0.12	
	TNFα Induced T cell Apoptosis							0.11	
	Fas/FasL Killing		0.08					0.15	
	Cytotoxic Killing							0.12	
	Total Chronically Infected Mac Bursting		0.10					0.15	
	Total Pet Hot							0.08	

Macrophage TGFB binding rate, T cell TGFB binding rate had no significant correlations at day 200 PI*

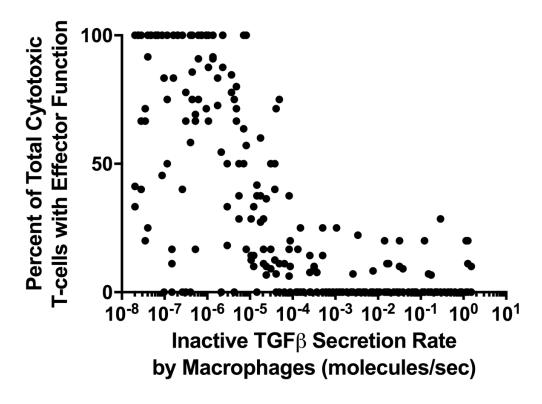


Figure S1: Simulated decreased secretion of TGFβ by macrophages results in increasing percentage of effector cytotoxic T-cells at day 200. 300 granulomas were simulated for 200 days with differing rates of latent TGFβ secretion by macrophages. The rate of secretion by macrophages is plotted against percent of total cytotoxic T-cells that are effector cytotoxic T-cells at day 200.

Effector cytotoxic T-cell activity shows sensitivity to different rates of TGF-β1 secretion.

Cytotoxic T-cell effector activity, and therefore bacterial killing efficiency, is inhibited by TGF- β 1 signaling. In the absence of TGF- β 1, effector cytotoxic T-cells in the granuloma are increased in number. Since macrophages are a major contributor to TGF- β 1 levels in the granuloma, we compare how TGF- β 1 secretion rates by macrophages affects the percent of effector cytotoxic T cells that are in granulomas (Fig. S1). We predict there is a negative correlation between the secretion rate of TGF- β 1 and the percent of effector cytotoxic T cells in the granuloma (Fig. S1). In order to see a meaningful increase in the effector functions of cytotoxic T cells in our simulations, the TGF- β 1 secretion rate by macrophages required a decrease by several orders of magnitude (Fig. S1).

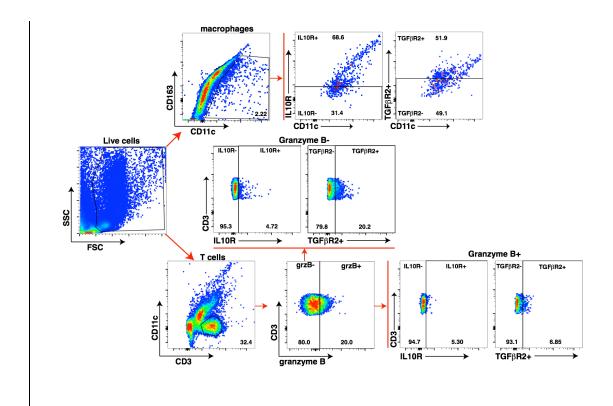


Figure S2: Gating strategy for flow cytometry studies. Granulomas do not contain enough cells for gating controls, and so positive and negative gates were determined by gating on erythrocyte-lysed whole blood (not shown) and these gates were then applied to granuloma samples. Isolated granuloma cells were gated on viable cells to exclude small, low complexity objects that confound analysis and then macrophages and T cells were identified by surface marker expression. Epithelioid macrophages and T cells were identified as CD11c+CD163- and CD3+CD11c- cells, respectively. T cells underwent a second round of gating against granzyme B to differentiate cytotoxic (granzyme B+) and noncytotoxic (granzyme B-) T cells. Subsequent analysis was done by gating each population's primary surface marker (CD11c or CD3) against IL10R or TGFBR2 expression, and comparing the MFI of positive and negative populations.