Supporting Information

Hao et al. 10.1073/pnas.1417789111

SI Text

Parameter Estimations

Eq. 1.

- M_0: The number of macrophages in the lung is 15×10^5 cells/mL (1) so that their density is $M_0=1.5\times10^{-3}$ g/mL.
- λ_{MT_α} and λ_{MI_γ}: In experiments reported in ref. 2, macrophages were used to inhibit the growth of *Legionella pneumophila.* The macrophages were then activated either by IFN-γ or by TNF-α. We write the equation for colony-forming unit (CFU) of *L. pneumophila* in the form

$$\frac{d\,\mathrm{CFU}}{dt}=\lambda\,\mathrm{CFU}-dM_A\frac{\mathrm{CFU}}{\mathrm{CFU}+K},$$

where M_A is the density of the activated macrophages, and K is a constant. The doubling time of *L. pneumophila* is 2 h (3), so that $\lambda=8.32\ \mathrm{d}^{-1}$. In the case of inhibition by macrophages that were not activated by either IFN-γ or TNF-α, we have $M_A=M$ and, as reported in ref. 2, the CFU increased from 2×10^4 units (U)/mL to 10^6 U/mL after 1 d and to 5×10^6 U/mL after 2 d ($\mathrm{U}=2\times10^{-5}$ mg). Using Newton's method, we get $K=4.48\times10^{-2}$ g/ml and $dM=0.23\ \mathrm{g\cdot mL^{-1}\cdot d^{-1}}$.

In the case of inhibition by macrophage activated by TNF-α, we have

$$M_A=\left(1+\lambda_{MT_\alpha}\frac{T_\alpha}{T_\alpha+K_{T_\alpha}}\right)M.$$

It was found in ref. 2 that, after 2 d, the CFU, initially at 2×10^4 U/mL, increased to 10^6 U/mL when $T_\alpha=10^2$ U/mL; to a smaller level, 5×10^5 U/mL when $T_\alpha=10^3$ U/mL; and to an even smaller level, 4×10^5 U/mL when $T_\alpha=10^4$ U/mL. Using these three data in the dynamics of CFU and applying Newton's method, we get three slightly different values for λ_{MT_α}, with average $\lambda_{MT_\alpha}=0.49$.

In the case of inhibition by macrophage-activated by IFN-γ, we have

$$M_A=\left(1+\lambda_{MI_\gamma}\frac{I_\gamma}{I_\gamma+K_{I_\gamma}}\right)M.$$

In the experimental data in ref. 2, the CFU decreased from 2×10^4 U/mL to 10^4 U/mL when $I_\gamma=10$ U/mL. Using again Newton's method, we find that $\lambda_{MI_\gamma}=0.65$.

- λ_{MG}: It is reported in ref. 4 that the inhibition of bacterial growth by macrophages activated by GM-CSF is approximately twice the inhibition by macrophage-activated by IFN-γ. Hence we take $\lambda_{MG}=2\lambda_{MI_\gamma}=1.3$.

Eq. 2.

- K_{T_r}: We assume that the inhibition by Treg reduces the production of Th1 by half if Treg is at the "average" density in asthma, reported to be 2×10^{-2} g/cm^3 (5), so that $K_{T_r}=2\times10^{-2}$ g/cm^3.
- $K_{I_{10}T_1}$: We assume that the inhibition of IL-12 Th1 activation by IL-10 [expressed by $1/(1+I_{10}/K_{I_{10}T_1})$] is larger than the inhibition of macrophage IL-12 production by IL-10 [expressed by $1/(1+I_{10}/K_{I_{10}})$]. By ref. 6, $K_{I_{10}}=2\times10^{-7}$ g/mL, and we take $K_{I_{10}T_1}=(1/10)K_{I_{10}}=2\times10^{-8}$ g/cm^3.
- λ_{TI_2}: In ref. 7 it was shown that 10^6 CD25 P14 T cells stimulated by 0.2 ng/mL of IL-2 increased to 2×10^6 cells in 7 d. Using the equation

$$\frac{dT}{dt}=\lambda_{TI_2}\frac{I_2}{K_{I_2}+I_2}T_1-d_TT$$

with $K_{I_2}=5\times10^{-11}$ g/mL (5, 8), we get

$$T_1(7)=T_1(0)\,e^{7\left(\lambda_{TI_2}\times0.8-d_T\right)}.$$

Since $d_T=7.71\times10^{-3}\ \mathrm{d}^{-1}$ (9, 10), we get $\lambda_{TI_2}=0.13\ \mathrm{d}^{-1}$.

Eq. 5.

- $\lambda_{I_\gamma T_1}$: We assume that T cells produce more IFN-γ than macrophages and take $\lambda_{I_\gamma T_1}=2\lambda_{I_\gamma M}$.

Eq. 6.

- $\lambda_{T_\beta T_1}$: According to ref. 11, 2×10^6 Th1 cells produced 12 pg/mL of TGF-β. Assuming steady state, we have

$$\lambda_{T_\beta T_1}T_1-d_{T_\beta}T_\beta=0.$$

Because $d_{T_\beta}=3.33\times10^2\ \mathrm{d}^{-1}$ (12), we get $\lambda_{T_\beta T_1}=4.2\times10^{-10}\ \mathrm{d}^{-1}$.

- $\lambda_{T_\beta T_r}$: According to ref. 11, The production of TGF-β by Treg is 2.2 times more than the production by Th1 cells. Hence we get $\lambda_{T_\beta T_r}=2.2\lambda_{T_\beta T_1}=9.24\times10^{-10}\ \mathrm{d}^{-1}$.
- $\lambda_{T_\beta M}$: According to ref. 13, 10^6 alveolar macrophages produced 40 pg/mL of TGF-β. Assuming steady state, we have

$$\lambda_{T_\beta M}M_A-d_{T_\beta}T_\beta=0.$$

Because $d_{T_\beta}=3.33\times10^2\ \mathrm{d}^{-1}$ (12), we get $\lambda_{T_\beta M}=3.86\times10^{-7}\ \mathrm{d}^{-1}$.

Eq. 7.

- $\lambda_{I_{12}^{40}I_\gamma}$: According to ref. 6, alveolar macrophages incubated with IFN-γ produced three times more IL-12 p40 than without IFN-γ. Hence $\lambda_{I_{12}^{40}I_\gamma}=3$.

Eq. 8.

- $\lambda_{T_\alpha M}$: In our model, the equation for TNF-α secretion by (inactivated) macrophages is

$$\frac{dT_\alpha(t)}{dt}=\lambda_{T_\alpha M}M-d_{T_\alpha}T_\alpha,$$

and, if M is fixed, then

$$T_\alpha(t)=\frac{\lambda_{T_\alpha M}M-e^{-d_{T_\alpha}t}(\lambda_{T_\alpha M}M-T_\alpha(0)d_{T_\alpha})}{d_{T_\alpha}}.$$

Productions of TNF-α by macrophages are reported in ref. 14 with 10^6 macrophages. After 1 d, T_α increased from 0 to 5×10^{-8} g/mL. Taking $M=10^{-3}$ g/mL, $T_\alpha(0)=0$, and

$d_{T_\alpha} = 55.45\ \mathrm{d}^{-1}$ (15), we get $\lambda_{T_\alpha M} = 2.72 \times 10^{-3}\ \mathrm{d}^{-1}$. Alternatively, in ref. 16, 10^6 alveolar macrophages produced 66 ng/mL of TNF-α, so that $\lambda_{T_\alpha M} = 3 \times 10^{-3}\ \mathrm{d}^{-1}$. By taking the average, we get $\lambda_{T_\alpha M} = 2.86 \times 10^{-3}\ \mathrm{d}^{-1}$.

- $K_{I_{13}}$: According to ref. 17, TNF-α production is reduced by 20% when alveolar macrophages are incubated with 5 ng/mL IL-13. Hence we have $1/((1 + 5 \times 10^{-9})/K_{I_{13}}) = 4/5$, which implies that $K_{I_{13}} = 2 \times 10^{-8}\ \mathrm{g/cm^3}$. We assume that IL-13 is more active in lung tissue and take $K_{I_{13}} = 2 \times 10^{-7}\ \mathrm{g/cm^3}$.

Eq. 9.

- $\lambda_{I_2 T_1}$: Experiments with the production of IL-2 by Th1 are reported in ref. 18: With 3×10^5 cells/mL, IL-2 increased from 0 to 26.7 pg/mL (2 h), 435.3 pg/mL (4 h), 662.2 pg/mL (6 h), and 1,1841.2 pg/mL (24 h). In our model, the equation describing the production of IL-2 by Th1 is

$$\frac{dI_2}{dt} = \lambda_{I_2 T_1} T_1 - d_{I_2} I_2.$$

With $d_{I_2} = 2.376\ \mathrm{d}^{-1}$ (19, 20), we find that the choice of $\lambda_{I_2 T_1} = 1.15 \times 10^{-4}\ \mathrm{d}^{-1}$ makes the best fit to these experiments.

Eq. 11.

- $\lambda_{I_{10} M}$: According to ref. 21, 10^6 alveolar macrophages produce (in vitro) 3,200 pg/mL of IL-10. Using the steady-state equation

$$\lambda_{I_{10} M} M_A - d_{I_{10}} I_{10} = 0,$$

with $d_{I_{10}} = 16.64\ \mathrm{d}^{-1}$ (22), we get $\lambda_{I_{10} M} = 5.32 \times 10^{-5}\ \mathrm{d}^{-1}$. We assume that in lung tissue, alveolar macrophages are more active than in vitro and take $\lambda_{I_{10} M} = 2 \times 10^{-3}\ \mathrm{d}^{-1}$.

Eq. 12.

- $\lambda_{I_{13} M}$: In ref. 23, 10^6 alveolar macrophages under LPS in systemic sclerosis produce 1.25 ng/mL of IL-13. However, the concentration of IL-13 in BALF was twice as much in sarcoidosis as in systemic sclerosis. Using the steady-state equation

$$\lambda_{I_{13} M} M - d_{I_{13}} I_{13} = 0,$$

with $I_{13} = 2.5 \times 10^{-9}$ g/mL, $d_{I_{13}} = 12.47\ \mathrm{d}^{-1}$ (24), we get $\lambda_{I_{13} M} = 3.98 \times 10^{-5}\ \mathrm{d}^{-1}$. We assume that in lung tissue, alveolar macrophages are more active and take $\lambda_{I_{13} M} = 3.98 \times 10^{-4}\ \mathrm{d}^{-1}$.

Eq. 13.

- d_{CR} and d_{CH}: We assume that internalization rates of CCL20, d_{CR} and d_{CH} are equal. We further assume that when C, T_r, and T_{17} are sufficiently large, namely,

$$C = K_C, T_r = K_{T_r}, \text{ and } T_{17} = K_{T_r},$$

the loss by internalization is the same as the loss due to degradation, so that

$$2 d_{CR} \frac{K_C}{K_C + K_C} K_{T_r} = d_C K_C.$$

Then with $d_C = 1.73\ \mathrm{d}^{-1}$ (19), we get $d_{CR} = d_{CH} = 1.73 \times 10^{-6}\ \mathrm{d}^{-1}$.

- $\lambda_{CT_{17}}$: We assume that the production of CCL20 by Th17 is less than the production by activated macrophage and take $\lambda_{CT_{17}} = \frac{1}{5} \lambda_{CM}$.

Other Parameters. To determine all of the remaining parameters, we use the expression of cytokines in healthy lung tissue reported by Crouser et al. (25) and summarized in Table S1. We also use the following facts in steady-state lung tissue: The ratio of Th1 to Th17 in the healthy case is 10 (26), i.e., $T_{17} = T_1/10$, and the ratio of Treg to Th17 is ∼5 (27), i.e., $T_r = T_1/2$; furthermore, the production of IFN-γ by macrophage is approximately half of that by Th1 cells (28), so that $\lambda_{I_\gamma M} = (1/2)\lambda_{I_\gamma T_1}$. Using these relations and inserting the data from Table S1 into the steady-state equations of the model for the healthy case (namely, when $f = 0$), we obtain 14 equations for concentrations of Th1 cells (T_1), for T_β, and for the 12 unknown parameters ($\lambda_{I_\gamma T_1}, \lambda_{T_{17}}, \lambda_{I_{12}^{40} M_A}, \lambda_{I_{12}^{70} M_A}, \lambda_{T_\alpha I_\gamma}, \lambda_{GM}, \lambda_{I_{13}}, d_{I_{10} M}, \lambda_{T_r I_2}, \lambda_{CM}, d_T$, and d_M). Solving for these unknowns, we find the concentration of the T cells to be

$$T_1 = 1.074 \times 10^{-2}, T_r = 5.372 \times 10^{-3}, T_{17} = 1.074 \times 10^{-3}, \\ T_\beta = 1.55 \times 10^{-10}.$$

The values of the 12 unknown parameters listed above are given in Tables S2 and S3.

Sensitivity Analysis. The parameters chosen are those whose baseline was somewhat crudely estimated whereas at the same time they seem to play an important role in the development of the granuloma. Specifically, we chose all of the 15 production rate parameters from the third column of Table S2.

Following the sensitivity analysis method described in ref. 29, we performed Latin hypercube sampling and generated 100 samples to calculate the partial rank correlation coefficients (PRCC) and P values with respect to the radius of granuloma after 100 d. The PRCCs are shown in Fig. S1, and all of the P values (not shown here) are less than 0.01. We see that the production rates of IFN-γ by Th1 cells ($\lambda_{I_\gamma T_1}$), IL-2 by Th1 cells ($\lambda_{I_2 T_1}$), and IL-12 p40 by macrophages ($\lambda_{I_{12}^{40} M}$) are highly positively correlated with the growth of the granulomas, whereas the production rates of TGF-β by Treg ($\lambda_{T_\beta T_r}$), TGF-β by Th1 cells ($\lambda_{T_\beta T_1}$), IL-10 by macrophages ($\lambda_{I_{10} M}$), and IL-13 by macrophages ($\lambda_{I_{13} M}$) are highly negatively correlated with the growth of the granulomas.

1. Wallace WA, Gillooly M, Lamb D (1992) Intra-alveolar macrophage numbers in current smokers and non-smokers: A morphometric study of tissue sections. *Thorax* 47(6): 437–440.
2. Skerrett SJ, Martin TR (1996) Roles for tumor necrosis factor alpha and nitric oxide in resistance of rat alveolar macrophages to Legionella pneumophila. *Infect Immun* 64(8):3236–3243.
3. Horwitz MA, Silverstein SC (1981) Interaction of the Legionnaires' disease bacterium (Legionella pneumophila) with human phagocytes. I. L. pneumophila resists killing by polymorphonuclear leukocytes, antibody, and complement. *J Exp Med* 153(2): 386–397.
4. Blanchard DK, Michelini-Norris MB, Pearson CA, McMillen S, Djeu JY (1991) Production of granulocyte-macrophage colony-stimulating factor (GM-CSF) by monocytes and large granular lymphocytes stimulated with Mycobacterium avium-M. intracellulare: Activation of bactericidal activity by GM-CSF. *Infect Immun* 59(7): 2396–2402.
5. Ceyhan BB, Enc FY, Sahin S (2004) IL-2 and IL-10 levels in induced sputum and serum samples of asthmatics. *J Investig Allergol Clin Immunol* 14(1):80–85.
6. Isler P, de Rochemonteix BG, Songeon F, Boehringer N, Nicod LP (1999) Interleukin-12 production by human alveolar macrophages is controlled by the autocrine production of interleukin-10. *Am J Respir Cell Mol Biol* 20(2):270–278.
7. Mueller K, Schweier O, Pircher H (2008) Efficacy of IL-2- versus IL-15-stimulated CD8 T cells in adoptive immunotherapy. *Eur J Immunol* 38(10):2874–2885.
8. Friedman A, Turner J, Szomolay B (2008) A model on the influence of age on immunity to infection with Mycobacterium tuberculosis. *Exp Gerontol* 43(4): 275–285.
9. Hellerstein M, et al. (1999) Directly measured kinetics of circulating T lymphocytes in normal and HIV-1-infected humans. *Nat Med* 5(1):83–89.
10. Vrisekoop N, et al. (2008) Sparse production but preferential incorporation of recently produced naive T cells in the human peripheral pool. *Proc Natl Acad Sci USA* 105(16):6115–6120.

11. Li MO, Wan YY, Flavell RA (2007) T cell-produced transforming growth factor-beta1 controls T cell tolerance and regulates Th1- and Th17-cell differentiation. *Immunity* 26(5):579–591.
12. Wakefield LM, et al. (1990) Recombinant latent transforming growth factor beta 1 has a longer plasma half-life in rats than active transforming growth factor beta 1, and a different tissue distribution. *J Clin Invest* 86(6):1976–1984.
13. Khalil N, Corne S, Whitman C, Yacyshyn H (1996) Plasmin regulates the activation of cell-associated latent TGF-beta 1 secreted by rat alveolar macrophages after in vivo bleomycin injury. *Am J Respir Cell Mol Biol* 15(2):252–259.
14. Hallsworth MP, Soh CP, Lane SJ, Arm JP, Lee TH (1994) Selective enhancement of GM-CSF, TNF-alpha, IL-1 beta and IL-8 production by monocytes and macrophages of asthmatic subjects. *Eur Respir J* 7(6):1096–1102.
15. Oliver JC, et al. (1993) Cytokine kinetics in an in vitro whole blood model following an endotoxin challenge. *Lymphokine Cytokine Res* 12(2):115–120.
16. Galve-de Rochemonteix B, Nicod LP, Dayer JM (1996) Tumor necrosis factor soluble receptor 75: The principal receptor form released by human alveolar macrophages and monocytes in the presence of interferon gamma. *Am J Respir Cell Mol Biol* 14(3): 279–287.
17. Hauber HP, Gholami D, Meyer A, Pforte A (2003) Increased interleukin-13 expression in patients with sarcoidosis. *Thorax* 58(6):519–524.
18. Lai YP, Lin CC, Liao WJ, Tang CY, Chen SC (2009) CD4+ T cell-derived IL-2 signals during early priming advances primary CD8+ T cell responses. *PLoS ONE* 4(11): e7766.
19. Hao W, Friedman A (2014) The LDL-HDL profile determines the risk of atherosclerosis: A mathematical model. *PLoS ONE* 9(3):e90497.
20. Balestrino M (2009) *Cytokine Imbalances in Multiple Sclerosis: A Computer Simulation* (M.Eng Projects) Available at ecommons.library.cornell.edu/handle/1813/11726. Accessed July 25, 2014.
21. Toossi Z, et al. (1996) Decreased production of TGF-beta 1 by human alveolar macrophages compared with blood monocytes. *J Immunol* 156(9):3461–3468.
22. Le T, Leung L, Carroll WL, Schibler KR (1997) Regulation of interleukin-10 gene expression: Possible mechanisms accounting for its upregulation and for maturational differences in its expression by blood mononuclear cells. *Blood* 89(11):4112–4119.
23. Hancock A, Armstrong L, Gama R, Millar A (1998) Production of interleukin 13 by alveolar macrophages from normal and fibrotic lung. *Am J Respir Cell Mol Biol* 18(1):60–65.
24. Khodoun M, et al. (2007) Differences in expression, affinity, and function of soluble (s) IL-4Ralpha and sIL-13Ralpha2 suggest opposite effects on allergic responses. *J Immunol* 179(10):6429–6438.
25. Crouser ED, et al. (2009) Gene expression profiling identifies MMP-12 and ADAMDEC1 as potential pathogenic mediators of pulmonary sarcoidosis. *Am J Respir Crit Care Med* 179(10):929–938.
26. Dolff S, et al. (2011) Disturbed Th1, Th2, Th17 and T(reg) balance in patients with systemic lupus erythematosus. *Clin Immunol* 141(2):197–204.
27. Huang H, et al. (2013) Imbalance between Th17 and regulatory T-cells in sarcoidosis. *Int J Mol Sci* 14(11):21463–21473.
28. Darwich L, et al. (2009) Secretion of interferon-gamma by human macrophages demonstrated at the single-cell level after costimulation with interleukin (IL)-12 plus IL-18. *Immunology* 126(3):386–393.
29. Marino S, Hogue IB, Ray CJ, Kirschner DE (2008) A methodology for performing global uncertainty and sensitivity analysis in systems biology. *J Theor Biol* 254(1):178–196.

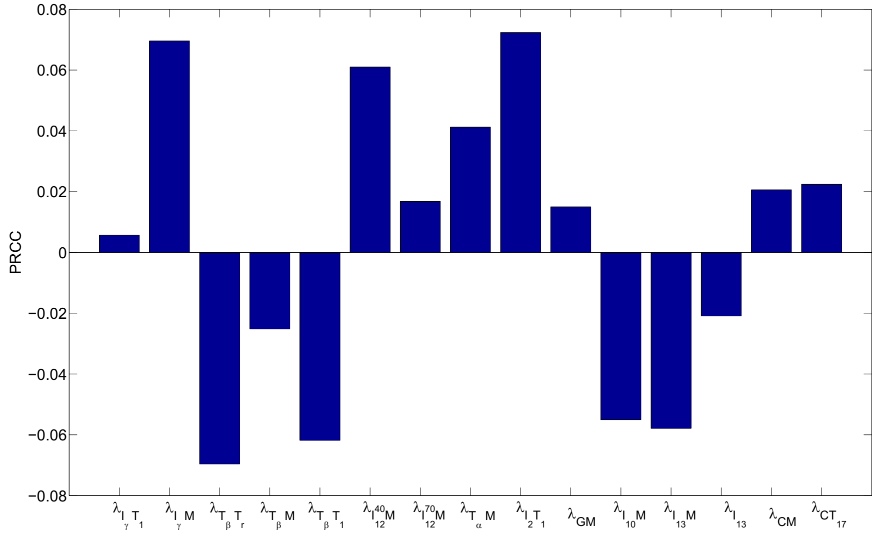

Fig. S1. The PRCC of parameters for sensitivity analysis.

Table S1. Lung tissue cytokine concentration

Cytokine	Value	Cytokine	Value
IL-2	5.2×10^{-7} g/mL	IL-10	1.82×10^{-7} g/mL
IL-12(p40)	4.94×10^{-6} g/mL	IL-12(p70)	1.04×10^{-7} g/mL
IL-13	6.5×10^{-8} g/mL	GM-CSF	3.12×10^{-7} g/mL
CCL20	4.81×10^{-6} g/mL	TNF-α	1.56×10^{-7} g/mL
IFN-γ	3.9×10^{-8} g/mL		

Table S2. Parameter descriptions and values

Parameter	Description	Value and source
D_M	Diffusion coefficient of macrophage	8.64×10^{-7} cm^{-2}·d^{-1} (1, 2)
D_{T_1}	Diffusion coefficient of Th1 cell	8.64×10^{-7} cm^{-2}·d^{-1} (1, 2)
D_{T_r}	Diffusion coefficient of Treg cell	8.64×10^{-7} cm^{-2}·d^{-1} (1, 2)
$D_{T_{17}}$	Diffusion coefficient of Th17 cell	8.64×10^{-7} cm^{-2}·d^{-1} (1, 2)
D_{I_γ}	Diffusion coefficient of IFN-γ	1.08×10^{-2} cm^{-2}·d^{-1} (3)
D_{T_β}	Diffusion coefficient of TGF-β	4.32×10^{-2} cm^{-2}·d^{-1} (3)
D_{I_2}	Diffusion coefficient of IL-2	1.08×10^{-2} cm^{-2}·d^{-1} (3)
$D_{I_{10}}$	Diffusion coefficient of IL-10	1.08×10^{-2} cm^{-2}·d^{-1} (3)
$D_{I_{12}}$	Diffusion coefficient of IL-12	1.08×10^{-2} cm^{-2}·d^{-1} (3)
$D_{I_{13}}$	Diffusion coefficient of IL-13	1.08×10^{-2} cm^{-2}·d^{-1} (3)
D_G	Diffusion coefficient of GM-CSF	1.728×10^{-2} cm^{-2}·d^{-1} (3)
D_C	Diffusion coefficient of CCL20	1.728×10^{-2} cm^{-2}·d^{-1} (3)
D_{T_α}	Diffusion coefficient for TNF-α	1.29×10^{-2} cm^{-2}·d^{-1} (3)
λ_{MI_γ}	Activation rate of macrophages by IFN-γ	0.69 (4, 5) & estimated
λ_{MG}	Activation rate of macrophages by GM-CSF	1.3 (4, 5) & estimated
λ_{MT_α}	Activation rate of macrophages by TNF-α	0.32 (4, 5) & estimated
$\lambda_{TI_{12}}$	Activation rate of Th1 cells by IL-12	6×10^{-4} d^{-1} (3)
λ_{TI_2}	Activation rate of Th1 cells by IL-2	0.13 d^{-1} (6) & estimated
$\lambda_{T_r I_2}$	Activation rate of Treg cells by IL-2	1.76×10^{8} d^{-1} (7) & estimated
$\lambda_{T_{17}}$	Activation rate of Th17 cells	3.55×10^{7} d^{-1} (7) & estimated
$\lambda_{I_r T_1}$	Production rate of IFN-γ by Th1 cells	2.34×10^{-6} d^{-1} (7) & estimated
$\lambda_{I_r M}$	Production rate of IFN-γ by macrophages	1.17×10^{-6} d^{-1} (7) & estimated
$\lambda_{T_\beta T_1}$	Production rate of TGF-β by Th1 cells	4.2×10^{-10} d^{-1} (8) & estimated
$\lambda_{T_\beta T_r}$	Production rate of TGF-β by Treg cells	9.24×10^{-10} d^{-1} (8) & estimated
$\lambda_{T_\beta M}$	Production rate of TGF-β by macrophages	3.86×10^{-7} d^{-1} (9) & estimated
$\lambda_{I_{12}^{40} M_A}$	Production rate of IL-12 p40 by macrophages	3.78×10^{-3} d^{-1} (7) & estimated
$\lambda_{I_{12}^{70} M_A}$	Production rate of IL-12 p70 by macrophages	9.64×10^{-4} d^{-1} (7) & estimated
$\lambda_{T_\alpha M}$	Production rate of TNF-α by macrophages	2.86×10^{-3} d^{-1} (10, 11) & estimated
$\lambda_{T_\alpha I_\gamma}$	Production rate of TNF-α by IFN-γ	10.24 (7) & estimated
$\lambda_{I_2 T_1}$	Production rate of IL-2 by Th1 cells	1.15×10^{-4} d^{-1} (12)
λ_{GM}	Production rate of GM-CSF by macrophages	8.65×10^{-4} d^{-1} (7) & estimated
$\lambda_{I_{13}}$	Production rate of IL-13 by Th2 cells	2.12×10^{-7} g·mL^{-1}·d^{-1} (7) & estimated
$\lambda_{I_{13} M}$	Production rate of IL-13 by macrophages	3.98×10^{-4} d^{-1} (13) & estimated
$\lambda_{I_{10} M}$	Production rate of IL-10 by macrophages	2×10^{-3} d^{-1} (9) & estimated
λ_{CM}	Production rate of CCL20 by macrophages	4.86×10^{-3} d^{-1} (7) & estimated
$\lambda_{CT_{17}}$	Production rate of CCL20 by Th17	9.71×10^{-4} d^{-1} (7) & estimated

1. Kim Y, Lawler S, Nowicki MO, Chiocca EA, Friedman A (2009) A mathematical model for pattern formation of glioma cells outside the tumor spheroid core. *J Theor Biol* 260(3):359–371.
2. Kim Y, Roh S, Lawler S, Friedman A (2011) miR451 and AMPK mutual antagonism in glioma cell migration and proliferation: A mathematical model. *PLoS ONE* 6(12):e28293.
3. Hao W, Friedman A (2014) The LDL-HDL profile determines the risk of atherosclerosis: A mathematical model. *PLoS ONE* 9(3):e90497.
4. Skerrett SJ, Martin TR (1996) Roles for tumor necrosis factor alpha and nitric oxide in resistance of rat alveolar macrophages to Legionella pneumophila. *Infect Immun* 64(8):3236–3243.
5. Horwitz MA, Silverstein SC (1981) Interaction of the Legionnaires' disease bacterium (Legionella pneumophila) with human phagocytes. I. L. pneumophila resists killing by polymorphonuclear leukocytes, antibody, and complement. *J Exp Med* 153(2):386–397.
6. Mueller K, Schweier O, Pircher H (2008) Efficacy of IL-2- versus IL-15-stimulated CD8 T cells in adoptive immunotherapy. *Eur J Immunol* 38(10):2874–2885.
7. Crouser ED, et al. (2009) Gene expression profiling identifies MMP-12 and ADAMDEC1 as potential pathogenic mediators of pulmonary sarcoidosis. *Am J Respir Crit Care Med* 179(10):929–938.
8. Li MO, Wan YY, Flavell RA (2007) T cell-produced transforming growth factor-beta1 controls T cell tolerance and regulates Th1- and Th17-cell differentiation. *Immunity* 26(5):579–591.
9. Toossi Z, et al. (1996) Decreased production of TGF-beta 1 by human alveolar macrophages compared with blood monocytes. *J Immunol* 156(9):3461–3468.
10. Hallsworth MP, Soh CP, Lane SJ, Arm JP, Lee TH (1994) Selective enhancement of GM-CSF, TNF-alpha, IL-1 beta and IL-8 production by monocytes and macrophages of asthmatic subjects. *Eur Respir J* 7(6):1096–1102.
11. Galve-de Rochemonteix B, Nicod LP, Dayer JM (1996) Tumor necrosis factor soluble receptor 75: The principal receptor form released by human alveolar macrophages and monocytes in the presence of interferon gamma. *Am J Respir Cell Mol Biol* 14(3):279–287.
12. Robertson-Tessi M, El-Kareh A, Goriely A (2012) A mathematical model of tumor-immune interactions. *J Theor Biol* 294:56–73.
13. Hancock A, Armstrong L, Gama R, Millar A (1998) Production of interleukin 13 by alveolar macrophages from normal and fibrotic lung. *Am J Respir Cell Mol Biol* 18(1):60–65.

Table S3. Parameters' description and value

Parameter	Description	Value and source
d_M	Death rate of macrophage	$0.49\ d^{-1}$ (1) & estimated
d_T	Death rate of Th1 cell	$1.97\times10^{-1}\ d^{-1}$ (1) & estimated
d_{T_r}	Death rate of Treg cell	$1.97\times10^{-1}\ d^{-1}$ (1) & estimated
$d_{T_{17}}$	Death rate of Th17 cell	$1.97\times10^{-1}\ d^{-1}$ (1) & estimated
d_{I_γ}	Degradation rate of IFN-γ	$0.69\ d^{-1}$ (2)
d_{T_β}	Degradation rate of TGF-β	$3.33\times10^{2}\ d^{-1}$ (3)
$d_{I_{12}}$	Degradation rate of IL-12	$1.188\ d^{-1}$ (2)
d_{T_α}	Degradation rate of TNF-α	$55.45\ d^{-1}$ (4)
d_{I_2}	Degradation rate of IL-2	$2.376\ d^{-1}$ (2, 5)
d_G	Degradation rate of GM-CSF	$4.16\ d^{-1}$ (6)
$d_{I_{13}}$	Degradation rate of IL-13	$12.47\ d^{-1}$ (7)
$d_{I_{10}}$	Degradation rate of IL-10	$16.64\ d^{-1}$ (8)
d_C	Degradation rate of CCL20	$1.73\ d^{-1}$ (2)
d_{CR}	Degradation rate of CCL20 by chemotaxis of Treg	$1.73\times10^{-6}\ d^{-1}$ estimated
d_{CH}	Degradation rate of CCL20 by chemotaxis of Th17	$1.73\times10^{-6}\ d^{-1}$ estimated
χ_C	Chemotactic sensitivity parameter	$10\ cm^{-5}\cdot g^{-1}\cdot d^{-1}$ (2, 9)
M_0	Alveolar macrophage density	$1.5\times10^{-3} g\cdot ml^{-1}.\ d^{-1}$ (10) & estimated
K_M	Alveolar macrophage density	$3\times10^{-3} g\cdot cm^{-3}\cdot d^{-1}$ (10) & estimated
K_{I_γ}	IFN-γ saturation	$2\times10^{-7} g\cdot cm^{-3}$ (11)
K_{T_α}	TNF-α saturation	$5\times10^{-7}\ g/cm^3$ (11)
K_G	GM-CSF saturation	$1\times10^{-6}\ g/cm^3$ (11)
$K_{I_{12}}$	IL-12 saturation	$1.5\times10^{-5}\ g/cm^3$ (1)
$K_{I_{10}}$	IL-10 saturation	$2\times10^{-7}\ g/cm^3$ (12)
$K_{I_{10}T_1}$	IL-10 saturation by Th1 cells	$2\times10^{-8}\ g/cm^3$ (12) & estimated
K_{I_2}	IL-2 saturation	$5\times10^{-7}\ g/cm^3$ (11)
K_{T_r}	Treg cells saturation	$3\times10^{-2}\ g/cm^3$ (13)
$K_{I_{13}}$	IL-13 saturation	$2\times10^{-7}\ g/cm^3$ (14) & estimated
K_C	CCL20 saturation	$2\times10^{-6}\ g/cm^3$ (15)

1. Crouser ED, et al. (2009) Gene expression profiling identifies MMP-12 and ADAMDEC1 as potential pathogenic mediators of pulmonary sarcoidosis. *Am J Respir Crit Care Med* 179(10):929–938.
2. Hao W, Friedman A (2014) The LDL-HDL profile determines the risk of atherosclerosis: A mathematical model. *PLoS ONE* 9(3):e90497.
3. Wakefield LM, et al. (1990) Recombinant latent transforming growth factor beta 1 has a longer plasma half-life in rats than active transforming growth factor beta 1, and a different tissue distribution. *J Clin Invest* 86(6):1976–1984.
4. Oliver JC, et al. (1993) Cytokine kinetics in an in vitro whole blood model following an endotoxin challenge. *Lymphokine Cytokine Res* 12(2):115–120.
5. Balestrino M (2009) *Cytokine Imbalances in Multiple Sclerosis: A Computer Simulation* (M.Eng Projects) Available at ecommons.library.cornell.edu/handle/1813/11726. Accessed July 25, 2014.
6. Rafei M, et al. (2007) A GMCSF and IL-15 fusokine leads to paradoxical immunosuppression in vivo via asymmetrical JAK/STAT signaling through the IL-15 receptor complex. *Blood* 109(5):2234–2242.
7. Khodoun M, et al. (2007) Differences in expression, affinity, and function of soluble (s)IL-4Ralpha and sIL-13Ralpha2 suggest opposite effects on allergic responses. *J Immunol* 179(10):6429–6438.
8. Le T, Leung L, Carroll WL, Schibler KR (1997) Regulation of interleukin-10 gene expression: Possible mechanisms accounting for its upregulation and for maturational differences in its expression by blood mononuclear cells. *Blood* 89(11):4112–4119.
9. Kim Y, Lawler S, Nowicki MO, Chiocca EA, Friedman A (2009) A mathematical model for pattern formation of glioma cells outside the tumor spheroid core. *J Theor Biol* 260(3):359–371.
10. Wallace WA, Gillooly M, Lamb D (1992) Intra-alveolar macrophage numbers in current smokers and non-smokers: A morphometric study of tissue sections. *Thorax* 47(6):437–440.
11. Galve-de Rochemonteix B, Nicod LP, Dayer JM (1996) Tumor necrosis factor soluble receptor 75: The principal receptor form released by human alveolar macrophages and monocytes in the presence of interferon gamma. *Am J Respir Cell Mol Biol* 14(3):279–287.
12. Isler P, de Rochemonteix BG, Songeon F, Boehringer N, Nicod LP (1999) Interleukin-12 production by human alveolar macrophages is controlled by the autocrine production of interleukin-10. *Am J Respir Cell Mol Biol* 20(2):270–278.
13. Ceyhan BB, Enc FY, Sahin S (2004) IL-2 and IL-10 levels in induced sputum and serum samples of asthmatics. *J Investig Allergol Clin Immunol* 14(1):80–85.
14. Hauber HP, Gholami D, Meyer A, Pforte A (2003) Increased interleukin-13 expression in patients with sarcoidosis. *Thorax* 58(6):519–524.
15. Francis JN, Sabroe I, Lloyd CM, Durham SR, Till SJ (2008) Elevated CCR6+ CD4+ T lymphocytes in tissue compared with blood and induction of CCL20 during the asthmatic late response. *Clin Exp Immunol* 152(3):440–447.