**SUPPLEMENTARY MATERIALS (Online Only)**

**ABM Rules**

**World.** The —world“ is a square grid, 120 x 120 patches, with origin in the center of the grid. X and Y coordinates thus take values in the range of -60 to 60. The tissue region is a circle of diameter 55 centered at the origin.

**Time scale.** We assumed in the model that 1 unit of simulated time represents 0.069 day, or about 1.6 hours. The time resolution of the simulation is in the millisecond range, thus much smaller than a time unit. This assumption results in complete healing (defined as return of the damage variable to baseline) in the normal scenario by ~30 days. All of the dynamics of cells and cytokines are therefore appropriately scaled to give realistic time courses.

**Lifespans and Half-lives**. The lifespan was assumed to be 1-3 days for neutrophils, 4-6 days for macrophages and 5-7 days for fibroblasts. Cytokine half-lives were assumed to be 2-3 days. We note the half life of latent TGF-β1 is much larger than the half life of activated TGF-β1 (73). Activated fibroblasts proliferate every three days.

**Initialization.** We arbitrarily set the total number of resting neutrophils and macrophages to 80 each, and the number of resting fibroblasts was set to 30. The location and age of these cells was randomly distributed in both blood and tissue. The initial total amount of damage was set to M\*M, where M is a number set by the user. In our simulations, we set M = 16. This damage was randomly distributed inside the disk centered at the origin of the domain and with diameter equal to M. The initial number of platelets p(x,y) was spatially distributed according to the formula (100/(1+x^2+y^2)), where (x,y) are grid coordinates. This type of distribution for the platelets is crucial for the initialization of the inflammatory process. The initial values of IL-1β, TNF, activated TGF-β1, IL-10, and collagen were set to zero. The initial amount of latent TGF-β1 was set to 10.

**Activation.** In this simulation, neutrophils and macrophage are chemoattracted by platelets (41) as well as TNF (41) while fibroblasts are chemoattracted by TGF-β1 (41). In actuality, platelets release several growth factors in addition to TGF-β1, such as PDGF, transforming growth factors α (TGF-α), epidermal growth factor (EGF), and insulin-like growth factor œI (IGF-I) to activate macrophages and neutrophils (41). However, in our model we do not include all of these growth factors, but rather assume, for simplicity, that platelets can activate those inflammatory cells in the following way: Macrophages are activated by platelets if the number of platelets is greater than (100 /(1+M\*M))/(1+P1), where M represents the magnitude of the damage, and are activated by TNF if TNF > 0.1 and P1 represents the potency of chemoattraction by platelets. At baseline, P1 = P2 = 0. Neutrophils are activated by platelets if the number of platelets is greater than (100/(1+M\*1.7)\*(M\*1.7))/(1+P2), where M represents the magnitude of the damage, and are activated by TNF if TNF > 0.2. P2 represents the potency of chemoattraction of neutrophils by platelets. At baseline, P1 = P2 = 0. For the studies depicted in Tables 1 and 2, only the activation portion (not the random walk; see below) is modulated. Fibroblasts are activated by TGF-β1 if TGF-β1>0.2 and damage is present.

**Cell motion: chemoattraction and stochastic motion**

The motion of all agents is due to both chemoattraction and random walk. First, neutrophils and macrophage are chemoattracted by platelets (38) as well as TNF (38) while fibroblasts are chemoattracted by TGF-β1 (38). Second, every unit time, the direction of cells is randomly directed motion. For the studies depicted in Tables 1 and 2, only the chemoattractant portion (not the random walk) is modulated.

**Mediators**

**1.TNF:**

1. Produced by activated macrophages and activated neutrophils. Inhibited by TGF-β1 and IL10 and elevated by TNF and IL1-β (41). In the TNF-overproducing simulation, for activated macrophages, the dynamics of TNF are calculated by the equation: TNF = TNF + 0.044 \* ( 1 / ( 0.1 + TGF \* 100 + IL-10 / 100 ) ) \* ( 1 + TNF + IL1-beta / 10 ) ) ). For activated neutrophils, the dynamics of TNF are calculated by the equation: TNF = TNF + 2.2\* (1 / (0.1 + TGF \* 100 + IL-10 / 100) ) \* ( 1 + TNF + IL1-beta / 10 ) ) ). In the simulation of TNF-overproducing with anti-TNF antibody treatment, for activated macrophages, these dynamics are calculated by the equation: TNF = TNF + 0.0293 \* ( 1 / (0. 1 + TGF \* 100 + IL-10 / 100 ) ) \* ( 1 + TNF + IL1-beta / 10 ) ) ). For activated neutrophils, these dynamics are calculated by the equation: TNF = TNF + 1.467\* (1 / (0.1 + TGF \* 100 + IL-10 / 100 ) ) \* ( 1 + TNF + IL1-beta / 10 ) ) ). In the simulation of TGF-β1-under-production with anti-TNF antibody treatment, for activated macrophages, these dynamics are calculated by the equation: TNF= TNF + 0.0067 \* ( 1 / (0. 1 + TGF \* 100 + IL-10 / 100 ) ) \* ( 1 + TNF + IL1-beta / 10 ) ) ). For activated neutrophils, these dynamics are calculated by the equation: TNF = TNF + 0.33\* (1 / (0.1 + TGF \* 100 + IL-10 / 100 ) ) \* ( 1 + TNF + IL1-beta / 10 ) ) ). In the other simulations, for activated macrophages, these dynamics are calculated by the equation: TNF = TNF + 0.02 \* ( 1 / ( 0.1 + TGF \* 100 + IL-10 / 100 ) ) \* ( 1 + TNF + IL1-beta / 10 ) ) ). For activated neutrophils, these dynamics are calculated by the equation: TNF = TNF + ( 1 / ( 0.1 + TGF \* 100 + IL-10 / 100 ) ) \* ( 1 + TNF + IL1-beta / 10 ) ) ).
2. Biological function: Inhibit the expression of TGF-β1 and IL-10 in activated macrophages. Stimulate the expression of TNF and IL-1β in activated macrophages and neutrophils. Activate latent TGF-β1, macrophages, and neutrophils (42).
3. TNF diffuses in the following sense: periodically (every 0.1 unit time) each patch shares 100 percent of the value of the patch with its 8 neighboring patches.

**2.TGF-β1**:

1. Activated from latent-TGF-β1 by TNF and IL1-β: if TNF>0.2 or IL1-β > 0.2, then TGF =TGF + latent-TGF \* 0.001; latent-TGF=latent-TGF \* 0.999. In the simulations of latent-TGF treatment, the initial value of latent-TGF equals four. In the other simulations, the initial value of latent-TGF equals one.
2. Produced by activated macrophages and activated fibroblasts. Inhibited by TNF (42). In the simulations of TGF-β1-under-production, for activated macrophages, TGF-β1 dynamics are calculated by the equation: TGF=TGF + latent-TGF \* 0.03 / (1 + TNF\*10). For activated fibroblasts, these dynamics are calculated by the equation: TGF=TGF + 0.015 / (1 + TNF/5). In the simulations of TGF-β1-under-production with TGF-β1 activation treatment, for activated macrophages, TGF-β1 dynamics are calculated by the equation: TGF=TGF + latent-TGF \*0.15/ (1 + TNF\*10). For activated fibroblasts, these dynamics are calculated by the equation: TGF=TGF + 0.075 / (1 + TNF/5). In the simulations of TNF-overproducing with TGF-β1 activation treatment, for activated macrophages, TGF-β1 dynamics are calculated by the equation: TGF=TGF + latent-TGF / (1 + TNF\*10). For activated fibroblasts, these dynamics are calculated by the equation: TGF=TGF + 0.5 / (1 + TNF/5). In the other simulations, for activated macrophages, these dynamics are calculated by the equation: TGF=TGF + latent-TGF \* 0.2 / (1 + TNF\*10). For activated neutrophils, these dynamics are calculated by the equation: TGF=TGF + 0.1 / (1 + TNF/5).
3. Biological function: Inhibit expression of TNF and IL-1β in activated macrophages and neutrophils; chemoattract and activate fibroblasts (42).
4. TGF-β1 diffuses in the following sense: periodically (every 0.1 s) each patch shares 100 percent of the value of the patch with its 8 neighboring patches.

**3.IL-1β**:

1. Produced by activated macrophage and neutrophils. Inhibited by TGF-β1 and IL-10 (43). Elevated by TNF and IL1-β. The dynamics of IL-1β are calculated by the equation: IL1beta=IL1-beta + 0.2 / ( 1 + TGF\*2+IL-10/100)\*(1+TNF+IL1-beta).
2. Biological function: Simulate TNF and IL-1β expression in activated macrophages and neutrophils. Increase TGF-β1 activation (11,41,42).
3. IL-1β diffuses in the following sense: periodically (every 0.1 s) each patch shares 100 percent of the value of the patch with its 8 neighboring patches

**4.IL-10**:

1. Produced by activated macrophages. The dynamics of IL-10 are calculated by the equation: IL1-10=IL1-10+1.
2. Biological function: Inhibit TNF (43,74) and IL-1β (43) expression in activated macrophages and neutrophils.
3. IL-10 diffuses in the following sense: periodically (every 0.1 unit time) each patch shares 100 percent of the value of the patch with its 8 neighboring patches.

**5.Collagen**:

1. Produced by activated fibroblasts. Inhibited by TNF and elevated by TGF-β1 (5). In our model, we also required that the amount of collagen produced not exceed the existing amount of damage in the same patch. Collagen dynamics are calculated by the equation: (if damage > 2 \* total-TGF / (1 + total-TNF), collagen=collagen + 2 \* total-TGF / (1 + total-TNF)) else collagen=collagen + damage).
2. Biological function: tissue repair (41,42).

**Source Terms**

In the simulation, there are damage-dependent sources for resting macrophages and resting neutrophils randomly distributed in the tissue and blood. The number of newly created neutrophils is a function of the total amount A of damage: 2\*(A/1500+1) every 0.5 time units until 2.7 days of simulated time are reached. The number of newly created macrophage is a function of the total amount A of damage: A/15000+1 every 2 time units until 20 days of simulated time are reached. There is also a constant source (two cells per every four time units) for resting fibroblasts randomly distributed in the tissue and blood if damage exists.

**Damage:** In addition to initial damage, damage can also be created by TNF if TNF > 0.25. Damage is healed by collagen (if collagen>0. damage=damage œ1.collagen=collagen -1), and it also has 0.2% chance for self-healing every time unit.