Supplementary Information

ABCD of IA: A multi-scale agent-based model of T cell activation in inflammatory arthritis

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Additional Model Details and Justifications

Cell Movement

Cell movement and motility is important for determining the rate of interactions between T cells and dendritic cells in the lymph node. To implement cell motion we used a random walk model on a fixed lattice assuming an average T cell speed of ~14 μm/min, consistent with measured values.[1] Using this speed, we determined the probability that a T cell would move into a given voxel in an extended three-dimensional Moore neighborhood with a radius of two voxels in each direction. This neighborhood was chosen as it represents a range of distances with an average step size of ~14.1 microns, with the longest steps ranging to ~20.8 μm. As dendritic cells move much slower than T cells and affix to the reticular network, we assumed that the dendric cells were stationary after being recruited to a random voxel, as has previously been done in models of deep cortical units (DCUs) of lymph nodes.[2]

T cell Activation, and Proliferation

Upon binding to a cognate antigen presented by dendritic cells, the T cell receptor (TCR) activates and promotes downstream intracellular signaling. As others have previously reported, T cell signaling can be modeled via a signal integration mathematical model [3]. In this model, the T cell stimulation signal accumulates through repeated DC encounters, representing the buildup of key intracellular species involved in T cell activation signaling cascades [4,5]. At the same time, the signal can degrade, representing the breakdown or transport of these same species via active and passive mechanisms [6,7]. If the accumulated activation signal reaches certain thresholds, the T cell reaches certain stages of activation that are imprinted. In the presented ABM, T cells have three distinct phases of activation based on stimulation level and follows previously reported in vivo and

computational reports [3,8,9]. T cells that have not yet reached the first threshold are considered to be naïve T cells and have highly transient contacts with DCs, moving rapidly and sampling the lymph node unit. Once they pass the first stimulation threshold, T cells maintain longer contact with DCs and upregulate co-inhibitory markers. In this second phase the T cells become susceptible to suppression but are not considered fully mature. When T cells pass a second threshold, DC interactions again speed up and T cells are considered mature and capable of proliferating and egressing from the lymph node. After reaching the mature state, a T cell must both have a sufficient integrated TCR signal and contact a DC to begin proliferation. Once the T cell receives a signal to proliferate, it takes approximately 18 hours for the proliferation to occur, and the T cell creates a clone which has the same affinity for the antigen and is already considered mature. The level of signal built up in the T cell is split evenly between the existing T cell and the newly split clone. To begin a new proliferation cycle, the mature cells must reach the signal threshold again.

T cell Affinity

The total signal induced by a single T cell-to-DC interaction is a function of the contact time, the total avidity of the T cell-DC contact, and the antigen density presented on the DC. Here, we use a simplified model in which the DCs are assumed to have a uniform, high presentation of antigen, so the signal is a function of TCR affinity and contact time. T cell affinities were assigned by sampling from Maxwell distributions. To model high disease susceptibility, a right shifted Maxwell distribution was used, representing a higher frequency of high affinity TCRs. Conversely, a left shifted Maxwell distribution represented reduced disease susceptibility via a lower frequency of high affinity TCRs. T cells were not considered “cognate” or “non-cognate” as in several reported ABMs, but a specific T cell’s ability to achieve a proliferative state in the model was

based on the amount of stimulation it received during all interactions with DCs as previously outlined.

Trafficking of DCs to LN

The movement of DCs to the LN is not well characterized in models of active inflammation, and timelines may be highly species dependent. Here, we instead in vitro reports of antigen concentrations relevant for activating T cells in DC:T cell co-culture assays. We used published data that reported T cell activation level as a function of peptide pulsed onto DCs and converted this into a probability that an activated, antigen-presenting DC would drain to a lymph node based on antigen concentration at the distal site.[10,11] The antigen concentrations used here induce significant immune response and are comparable to bolus antigen concentrations administered in antigen-induced arthritis models in vivo.[12]

T cell Recruitment and Antigen Concentration

The model is initiated with an amount of antigen present in the model joint compartment. This results in the movement of DCs as outlined above. The antigen rapidly drains away from the joint based on reported values in terms of molecular weight.[13] As T cells mature and proliferate in the LN, some T cells are recruited to the joint compartment based on probability. For simplicity, a differential equation is then used to determine the concentration of antigen present in the joint compartment as a function of the number of T cells present in the joint compartment. This method is comparable to tumor papers that model T cell killing of tumor cells, but use a differential equation to determine rate of T cell recruitment based on tumor cell death rate.[14] After residing in the joint compartment for a set time, T cells are assumed to die and no longer contribute to the rate of antigen production.

Function of IaAPCs

As we are interested not only in the transition to chronic RA, but in how we might prevent this transition, we also tested hypothetical immunomodulatory artificial antigen presenting cells (IaAPC) alter T cell activation and proliferation kinetics in the lymph node. The detailed inter- and intra-cellular mechanism of T cell suppression and exhaustion by co-inhibitory factors such as PD-L1 is the topic of several computational studies, particularly in the context of cancer.[14–16] A common theme in the intracellular mechanisms is the inhibition of signaling downstream of the TCR. Here, we implement rules consistent with these findings in which T cell stimulus via TCR signaling is temporarily dampened following the interaction of a T cell with a iaAPC. However, based on prior reports, many co-inhibitory receptors are only upregulated on T cells following initial stimulating events.[17] To capture this aspect, T cells are not susceptible to iaAPC inhibition until they reach a certain stimulation threshold. For simplicity, after a T cell begins expression of co-inhibitory receptors that T cell and any clones are assumed to constitutively express the co-inhibitory receptors.

T cell Phenotype Modeling:

The signals in the local microenvironment influence T cell phenotype commitment and function.[18,19] Depending on the composition of the cytokine milieu, T cells may take on pro-inflammatory or anti-inflammatory function, which contributes the rise of distinct pathogenic T cell subsets linked to disease progression in inflammatory arthritis[20,21]. To test the role of inflammatory signaling and T cell phenotype commitment in driving transition to chronic arthritis, we incorporated a T cell phenotype commitment component to the joint compartment, modeled after observations of pro-inflammatory Th17 and anti-inflammatory T_{reg} cell subsets recorded in the murine SKG model of RA.[22–25] For this model, only Th17 and T_{reg} cells are considered, as the

role of additional subsets to the contribution of inflammatory arthritis is less defined in the SKG in vivo model used for calibration, and the majority of profiled cells in the joint exhibit either a Th17 or T_{reg} like phenotype.

In the version of the model that accounts for T cell phenotypes, an inflammation parameter (I) is incorporated into the model to broadly represent the degree of inflammation in the joint milieu as accurate measurements of individual cytokines in the joint remain difficult to obtain experimentally. The level of inflammation determines the probabilistic differentiation of T cells into either a Th17 or T_{reg} phenotype as they are recruited into the joint from the lymph node. Inflammation decays based on a half-life consistent with other models of cytokine decay and/or clearance.[14] Th17 cells contribute to inflammation and antigen production via enhanced tissue damage, while T_{reg} cells inhibit Th17 mediated inflammation. In addition, an abundance of T_{reg} cells relative to Th17 cells acts to enhance tissue regeneration and reduce inflammation.

Changes to the number of T_{reg} in the joint are determined via the equation:

$$\Delta T_{reg} = T_{reg,in} - T_{reg,death} \quad (1)$$

While changes to the number of Th17 are determined via a similar equation:

$$\Delta Th17 = Th17_{in} - Th17_{death} \quad (2)$$

Here, $T_{reg,death}$ and $Th17_{,death}$ are the number of T_{reg} and Th17 that die due to age at a given time step based on the fixed lifespan assumed for all T cells in the joint. The number of infiltrating T_{reg} and Th17 cells, $T_{reg,in}$ and $Th17_{in}$, respectively, migrating to the joint from the lymph node are determined via a combination of stochastic and deterministic processes. First, the number of T cells draining from the lymph node is considered to determine the total number of infiltrating T cells. Then, each T cell is probabilistically assigned to differentiate into a T_{reg} or a Th17 based on

the level of inflammation in the joint. The probability of an infiltrating T cell differentiating into a T_{reg} as a function of inflammation is given by:

$$p_{T_{reg}}(I) = \frac{k_{reg} * K_I}{I + K_I} + p_{T_{reg}{}_{inf,ss}} \quad (3)$$

And conversely, the probability of a T cell differentiating into a Th17 is given by:

$$p_{Th17}(I) = 1 - p_{T_{reg}} \quad (4)$$

Here, $p_{T_{reg}{}_{inf,ss}}$ is the probability of a T cell differentiating into a T_{reg} under chronic inflammatory conditions, while k_{reg} is a constant dependent on the non-inflamed steady state differentiation rate of T cells into T_{reg} vs Th17. K_I serves as a scaling factor to determine the rate of differentiation change relative to inflammation. As inflammation does not have specific units in this model and thus is on an arbitrary scale, K_I was set to 100 to keep inflammation on a similar scale to antigen concentration.

While the scale of inflammation in this model is arbitrary and require parameter sweeps to determine appropriate values in comparison to experimental data, the key parameters of this model, $p_{T_{reg}{}_{inf,ss}}$ and k_{reg}, can be determined directly by comparison to well defined in vivo model disease states. Under high levels of inflammation, which are achieved during chronic inflammation, Equation (3) simplifies to:

$$p_{T_{reg}}(I \to \infty) = p_{T_{reg}{}_{inf,ss}} \quad (5)$$

Using Equation (5) and comparing to experimental results in the in vivo SKG model demonstrates that $p_{T_{reg}{}_{inf,ss}}$ is approximately 0.3.[22,26]

At zero inflammation (normal physiological conditions), the Equation (3) becomes:

$$p_{T_{reg}}(I) = k_{reg} + p_{T_{reg}{}_{inf,ss}} \tag{6}$$

Using this equation, in combination with reports on the non-inflamed (pre-arthritic) steady state ratio of T_{reg} to Th17 in lymphoid organs of SKG mice, we can approximate k_{reg} to be approximately 0.66.[22] These yield ratios of T_{reg}:Th17 of 30:1 in the absence of inflammation, and 3:7 under chronic inflammatory conditions, which is consistent with literature reports. For calculating the change in inflammation (I) and antigen concentration (a) between timesteps, the following equations are used:

$$\Delta I = -Ik_i + \frac{Th17 - T_{reg}}{K_T} \tag{7}$$

And

$$\Delta a = -ak_a + \frac{Th17 - T_{reg}}{K_T} \tag{8}$$

Where k_i and k_a are parameters that relate the rate of decay/clearance of inflammatory species and antigen, respectively. K_T is a scaling factor introduced to approximate the amount of antigen and inflammation induced or prevented per T cell on average over a single timestep. k_i and k_a were chosen based on reported literature values for cytokine clearance and peptide clearance from the joint space, while K_T was chosen via a parameter sweep and comparison to lymph node dynamics.

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