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Continuum Model of T-cell Avidity: Understanding Autoreactive and Regulatory T-Cell Responses in Type 1 Diabetes

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Abstract

Type 1 diabetes (T1D) is an autoimmune disease that results from the destruction of insulin-secreting pancreatic β cells, leading to abolition of insulin secretion and onset of diabetes. Cytotoxic $CD4^+$ and $CD8^+$ T cells, activated by antigen presenting cells (APCs), are both implicated in disease onset and progression. Regulatory T cells (Tregs), on the other hand, play a leading role in regulating immunological tolerance and resistant homeostasis in T1D by suppressing effector T cells (Teffs). Recent data indicates that after activation, conventional Teffs transiently produce interleukin IL-2, a cytokine that acts as a growth factor for both Teffs and Tregs. Tregs suppress Teffs through IL-2 deprivation, competition and Teff conversion into inducible Tregs (iTregs). To investigate the interactions of these components during T1D progression, a mathematical model of T-cell dynamics is developed as a predictor of β -cell loss, with the underlying hypothesis that avidity of Teffs and Tregs, i.e., the binding affinity of T-cell receptors to peptide-major histocompatibility complexes on host cells, is continuum. The model is used to infer a set of criteria that determines susceptibility to T1D in high risk (HR) subjects. Our findings show that diabetes onset is guided by the absence of Treg-to-Teff dominance at specific high avidities rather than over the whole range of avidity, and that the lack of overall dominance of Teffs-to-Tregs over time is the underlying cause of the “honeymoon period”, the remission phase observed in some T1D patients. The model also suggests that competition between Teffs and Tregs is more effective than Teff-induction into iTregs in suppressing Teffs, and that a prolonged full width at half maximum of IL-2 release is a necessary condition for curbing disease onset. Finally, the model provides a rationale for observing rapid and slow progressors of T1D based on modest heterogeneity in the kinetic parameters.

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Conflict of Interest:

None.

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Keywords

Mathematical model; immunomodulation; avidity-dependent dominance; honeymoon period; inter- and intra-clonal competition

INTRODUCTION

Cytotoxic CD4⁺ and CD8⁺ T cells play crucial role in protecting target tissues within a host from pathogens by generating the proper immune response(s) using a set of surface molecules on T cells, called T-cell receptors (TCRs). These TCRs typically help T cells recognize foreign antigens expressed on host cells as peptide-major histocompatibility complexes (pMHCs). Effector T cells (Teffs) make biased decisions between foreign (exogenous) antigens that are targeted for eradication and self (endogenous) autoantigens that are tolerated (Altan-Bonnet and Germain, 2005; Irvine et al., 2002). The abundance and diversity of TCR-reactivity to various antigens make some of these T cells, however, susceptible to autoreactivity to self-antigens (Alberts et al., 2008). In normal and healthy conditions, these autoreactive T cells are weeded out in the thymus by means of negative selection (Sakaguchi et al., 2008; Tsai et al., 2011), an essential component of central tolerance. The failure of this process can lead to autoimmune diseases triggered by autoimmune responses against self-molecules (Davis et al., 1998). Though much has been uncovered about the etiology of spontaneous autoimmune diseases, many questions associated with the role of T-cell avidity (a measure of TCR binding affinity to pMHC class I and II) in forming immunological responses in these diseases remain unanswered.

Type 1 diabetes (T1D) in humans and nonobese diabetic (NOD) mice is an autoimmune disorder that results from the destruction of an estimated 90% of insulin-secreting pancreatic β cells (Jaberi-Douraki et al., 2014a; Khadra et al., 2011; Skowera et al., 2008), leading to abolition of insulin secretion crucial for regulating glucose homeostasis. Both CD4⁺ and CD8⁺ cytotoxic T lymphocytes, as well as proinflammatory cytokines secreted by Teffs, macrophages and dendritic cells have been implicated in this disease. Although it is unclear what triggers autoimmune destruction of β cells, there is a strong evidence that defective clearance of apoptotic bodies of dead β cells by macrophages following the naturally occurring apoptotic wave is the cause (Finegood et al., 1995; Marée et al., 2008). It has been further hypothesized that autoimmune destruction is maintained through the uptake of dead β cells by antigen presenting cells (APCs), such as mature dendritic cells (Liblau et al., 2002; Zhang et al., 2002) and macrophages (Georgiou et al., 1995), and the subsequent processing of their proteins into pMHCs (Tsai and Santamaria, 2013; Zhang et al., 2002) needed for T-cell activation and the triggering of polyclonal autoimmune responses. Cytokines (such as interleukin IL-1 and tumour necrosis factor TNF) secreted by CD4⁺ T cells and APCs also play a direct role in the activation of these (and other) immune cells and in the destruction of β cells (Cardozo et al., 2005; Homann and Eisenbarth, 2006; Kopito and Ron, 2000; Nepom, 2008).

The binding of TCRs to pMHCs occurs over a broad range avidity (Mallone et al., 2005; Reijonen et al., 2004) that is correlated with the pathogenic potential of T cells (Amrani et

al., 2000). Experimental evidence suggests that, during T1D progression, T cells undergo a process of avidity maturation (Standifer et al., 2009), regulated by tolerance and competition (Amrani et al., 2000). Tregulatory CD4⁺CD25⁺FoxP3⁺ T cells (Tregs), a set of immunomodulatory cells that comprise 5–10% of peripheral CD4⁺ T cells (Thornton and Shevach, 2000), play a crucial role in this process. They intervene by averting the activation and proliferation of autoreactive T cells (Sakaguchi et al., 1995) via primarily four independent mechanisms; namely, (i) local-tissue competition for growth/survival factors by the consumption of proinflammatory cytokine interleukin IL-2 secreted by T cells; (ii) directly through intra-clonal competition, cell-to-cell contact, and local secretion of suppressive cytokines (Scheffold et al., 2007; Sojka et al., 2008); (iii) modulation of APCs (Vignali et al., 2008); and (iv) conversion of T cells into inducible Tregs (iTregs) when invigorated with proper stimulating factors (Pandey and Lenardo, 2008; Pandey et al., 2007), such as the essential cytokine TGF- β (Zhao et al., 2014).

Recent data suggest that Tregs function in both secondary lymphoid organs and tissues, and that these different microenvironments may contain specialized subsets of these cells with distinct mechanisms of action (Pesenacker et al., 2014). Foxp3 transcription factor is considered a master regulator and the most reliable marker for Treg cells (Corthay, 2009). The plasticity, or ability of Tregs to lose their regulatory function by depleting Foxp3 is an innate property of these cells (Murai et al., 2010; Okada et al., 2014). A reduced expression of Foxp3 in activated Treg population has been found to cause defects in IL-2 signaling and reduced expression of a deubiquitinase important for Foxp3 stability (Bending et al., 2014). Although Tregs need the biochemical signalling molecule IL-2 to survive and perform their tasks in maintaining peripheral tolerance (Thornton et al., 2004), it is highly unlikely that they secrete IL-2 themselves, so their endurance and longevity depend upon IL-2 production by neighbouring cells. This means that they are paracrine cells in the immediate extracellular environment. At the same time the lymphocyte-released IL-2 constitutes a proliferation factor for the Th17 subtype of antigen-stimulated T helper cells, engaging in intra-clonal rivalry with Tregs for IL-2. Unlike Tregs though, IL-2 is an autocrine Th17 cytokine (Malek, 2008). In other words, the paracrine/autocrine growth factor IL-2 not only promotes T-cell assault, this chemical messenger also appears to hinder autoimmune responses (Duprez et al., 1985). Establishing how these dual negative and positive feedbacks exerted by IL-2 on β -cell survival remains incompletely understood.

During T1D progression and until the clinical onset of the disease, elevation in glucose may prompt endoplasmic reticulum (ER) stress (along with oxidative and mitochondrial stresses) in pancreatic β cells (Marchetti et al., 2007), and inflammatory signalling such as through IL-1 β , causing a two-folded effect (Mandrup-Poulsen et al., 2010). The study of the National Institutes of Health Diabetes Care and Complications Trial (DCCT) (Group, 1998) also revealed that the deterioration in β -cell function is less acute in patients receiving intensive insulin therapy when compared to control group receiving conventional therapy. In fact, it has been observed that such deterioration can be temporarily halted, during the so called honeymoon period that could last for up to 24 months and occasionally more than two years (Abdul-Rasoul et al., 2006; Böber et al., 2001; Robles et al., 2002), through metabolic therapies at the time of initial overt T1D (Aly and Gottlieb, 2009; Atkinson et al., 2011). The interface between intermediary metabolism and autoimmunity may be concomitant with

neogenesis and recovery of endogenous pancreatic β cells (Bottino et al., 2009; Van der Windt et al., 2009). Examining such interaction(s) to elucidate the root causes of the honeymoon period is of clinical relevance to treating the disease.

The complexity of the processes underlying T1D progression and the difficulty in examining them experimentally make the use of quantitative *in silico* methods to study this disease very compelling. These approaches have been previously applied to increase our understanding of immunological responses and self-tolerance in other contexts (Borghans and De Boer, 1995; Borghans et al., 1998; Kim et al., 2007; Nevo et al., 2004). Mathematical models, mostly comprised of ordinary differential equations, were developed to achieve this goal. In T1D, similar approaches have been applied to investigate the role of macrophages in disease onset (Marée et al., 2006; Marée et al., 2008), as well as the role T-cell avidity and killing efficacy in the formation of autoimmune response(s), T-cell cycles and autoantibody release in high risk (HR) subjects (Jaberi-Douraki et al., 2014a; Jaberi-Douraki et al., 2014b; Jaberi-Douraki et al., 2014; Khadra et al., 2009; Khadra et al., 2011). These studies were later extended (Jaberi-Douraki et al., 2014b) to determine how T-cell-dependent autoimmune destruction of β cells compares to β -cell apoptosis induced by ER-stress caused by an increase in metabolic demand on surviving β cells. The study revealed that targeting this pathway for therapeutic purposes, by enhancing the unfolded protein response (UPR) in β cells to increase insulin secretion and inhibit ER-stress (Marchetti et al., 2007), may not be successful due to the dominance of autoimmune destruction. The avidity in these models was quantified using the “effective dissociation” of pMHCs from TCRs (Mammen et al., 1998) and was assumed to be discrete by considering competing clones of T cells.

Here we assume more complex processing for the binding avidities, activation and proliferation of T cells in order to relate regulatory T-cell distributions to that of Teff cell populations. This is achieved by developing a continuum avidity model of integro-differential equations that describes the dynamics of Teffs, Tregs, β cells, IL-2 and autoantigen processing. The model provides important insights about the interactions of these components in health and disease.

MATHEMATICAL MODEL

In our previous work, we have developed a series of mathematical models comprised of system of ordinary differential equations to study the role of avidity and killing efficacy of Teffs in forming autoimmune responses in T1D. These predictive models provided important insights into the implication of both T-cell cycles on autoantibody release and “non-recursive” endoplasmic reticulum (ER) stress in exacerbating autoimmune destruction of β cells (Jaberi-Douraki et al., 2014a; Jaberi-Douraki et al., 2014b; Khadra et al., 2009; Khadra et al., 2011). In these models, T-cell avidity was assumed to be discrete with finite number (at most three) of competing clones of T cells. Here, we extend these studies by assuming that ER-stress is recursive, by taking into account the continuum nature of T-cell avidity and by developing an integro-differential equation model to analyze the effect of immunomodulation, exerted by Tregs on Teffs in the presence of the autocrine/paracrine factor of IL-2, on β -cell survival. The model excludes the unconfirmed role of plasma cells in the destruction of β cells, and only focuses on the dynamics of T cells to provide

predictive criteria for susceptibility to T1D and to answer important basic questions about the disease.

Model description

Based on the scheme of Figure 1, our model is composed of the following key components: insulin-secreting β cells (β); autoreactive effector T cells (T), including the two classes of $CD8^+$ and $CD4^+$ T cells that are reactive to the whole pool of islet-specific autoantigens and possessing a continuum spectrum of avidities; islet-specific regulatory T cells (T_r) with the same range of avidities and autoantigenic specificities as effector T cells; interleukin IL-2 (I) released by effector T cells; and a pool of β -cell specific autoantigens (P) taken up by APCs and expressed as pMHC for T-cell stimulation and activation. The initiation of this autoimmune response can be triggered by various factors, including the naturally occurring apoptotic wave shown in β cells (Finegood et al., 1995) that is marked by the fragmentation of nuclear DNA. To account for such trigger(s), we assume that the variables T , T_r , I and P have non-trivial initial conditions.

According to this model (depicted in Figure 1), Teff and Treg pools are expected to have heterogeneous dynamic structures guided by avidity. Based on the fact that T-cell activation depends sigmoidally on autoantigen level on APCs (Standifer et al., 2009) with EC_{50} that is reciprocally correlated with avidity, we may describe the dynamics of both populations of T cells by the two integro-differential equations

$$\begin{aligned} \frac{\partial T(t, k)}{\partial t} &= \sigma_T(k) \frac{P}{P+k} \\ &+ \alpha_T(k) \eta_T I T(t, k) \frac{P}{P+k} \\ &- \delta_T(k) T(t, k) \\ &- \varepsilon T(t, k) \int_0^K \omega(s) (T(t, s) + T_r(t, s)) ds \\ &- \theta T(t, k) \int_0^K \rho_{T_r}(s) T_r(t, s) ds \end{aligned} \quad (1)$$

$$\begin{aligned} \frac{\partial T_r(t, k)}{\partial t} &= \sigma_{T_r}(k) \frac{P}{P+k} \\ &+ \alpha_{T_r}(k) \eta_{T_r} I T_r(t, k) \frac{P}{P+k} \\ &- \delta_{T_r}(k) T_r(t, k) \\ &- \varepsilon T_r(t, k) \int_0^K \omega(s) (T(t, s) + T_r(t, s)) ds \\ &+ \lambda(k) \rho_{T_r}(k) T(t, k) T_r(t, k), \end{aligned} \quad (2)$$

where $T = T(t, k)$ and $T_r = T_r(t, k)$ are the population sizes of Teffs and Tregs at a given time t and measured avidity k^{-1} , respectively ($k = EC_{50} \in [0, K]$, and K is the minimal avidity attained by T cells as described in the Supplementary Material), $P = P(t)$ is the

autoantigen expression level at time t and $I = I(t)$ is IL-2 concentration at time t . According to these equations, T-cell turnover is given by $\delta_x(k)x$, T-cell escape from the thymus by $\sigma_x(k)P/(P+k)$ and IL-2-dependent T-cell replication by $\alpha_x(k)\eta_k I x(t, k)P/(P+k)$ (assumed to follow Michaelis-Menten kinetics in their dependence on P , and), where $x = T, T_r$, $\delta_x(k)$ are T-cell turnover rates, $\sigma_x(k)$ are the maximum rates of thymic input, $\alpha_x(k)$ are the maximum replication rates of T cells and η_k are the consumption rates of IL-2 by T cells. The T-cell activation in Eqs. (1) and (2), expressed in terms of escape from thymus and replication, is assumed to follow Michaelis-Menten kinetics in its dependence on P , whereas IL-2-dependent T-cell replication is assumed to follow mass-action kinetics on its dependence on I . The formalism used in the former is based (i) on experimental evidence (Standifer et al., 2009), showing that T-cell activation by dendritic cells pulsed with T1D specific peptides is sigmoidal, and (ii) on previously published work (Jaberi-Douraki et al., 2014a; Jaberi-Douraki et al., 2014b; Khadra et al., 2009). The mass-action formalism used in the latter, however, is a linear approximation of the Michaelis-Menten kinetics that describes IL-2 effects on T cells; it reduces the number of parameters used and produces a valid approximation in which IL-2 concentration is assumed very small (in the range of fM-pM) (Busse et al., 2010). The two terms $\varepsilon T(t, k) \int_0^K \omega(s) (T(t, s) + T_r(t, s)) ds$ and $\varepsilon T_r(t, k) \int_0^K \omega(s) (T(t, s) + T_r(t, s)) ds$ in Eqs. (1) and (2) represent T-cell homeostasis attributed to symmetric but non-uniform intra- and inter-clonal competition (arising from limited physical space) between and within Teff and Treg pools. Here ε represents the rate of the competition, whereas the weight function $\omega(k)$ conveys its non-uniform nature. The suppression of Teffs by Tregs, via apoptosis, deactivation and/or transdifferentiation into inducible regulatory T cells (iTregs) is described by $\theta T(t, k) \int_0^K \rho_{T_r}(s) T_r(t, s) ds$, where ρ_{T_r} is the rate of Teff suppression and $\theta = 1 \text{ ml/ng}$ is a scaling factor that keeps the units and definitions of other parameters (here and elsewhere) consistent with those previously published (Jaberi-Douraki et al., 2014a; Jaberi-Douraki et al., 2014b; Khadra et al., 2009). As a result, a fraction $\lambda(k) \in [0, 1]$ of suppressed Teffs that turn into iTregs increase the pool size of Tregs, at a given avidity k^{-1} , by a factor $\lambda(k)\rho_{T_r}(k)T(t, k)T_r(t, k)$. In our simulations, we use k^{-1} as a measure of T-cell avidity and the two quantities

$$\Omega(t) = \theta \int_0^K T(t, s) ds \quad \text{and} \quad \Omega_r(t) = \theta \int_0^K T_r(t, s) ds \quad (3)$$

as measures of Teff- and Treg-accumulation, respectively.

Since interleukin IL-2 secreted only by Teffs (e.g., T helper cells) is a growth factor for both Teffs and Tregs, the cytokine simultaneously exerts negative and positive feedbacks on the dynamics of T cells. We describe this dual role of IL-2 in heightening/suppressing the autoimmune response by the following equation

$$\frac{dI}{dt} = \theta \int_0^K \left(\sigma_I T(t, s) + \alpha_1 T(t, s) \frac{P}{P+s} \right) ds - \delta_I I - \theta I \int_0^K \left(\eta_T(s) T(t, s) + \eta_{T_r}(s) T_r(t, s) \right) ds, \quad (4)$$

where $\theta \int_0^K \sigma_I T(t, s) ds$ and $\theta \int_0^K \alpha_I T(t, s) \frac{P}{P+s} ds$ represent the total amount of IL-2 secreted by Teffs at a basal level (with a maximum rate constant σ_I) and induced by autoantigen stimulation (with a maximum rate constant α_I), respectively, δ_I is IL-2 degradation with a degradation rate δ_I , and $\theta I \int_0^K \eta_x(s) x(t, s) ds$ represents IL-2 consumption by Teffs ($x = T$) and Tregs ($x = T_r$) with consumption rates $\eta_x(k)$. Note here that the peptide-induced release of IL-2 by Teffs is assumed to depend sigmoidally on autoantigen expression on APCs.

The dynamics of β cells, on the other hand, is governed by renewal (due to replication/neogenesis) and loss (due to homicide/suicide). The former is assumed to depend on the number of surviving β cells, whereas the latter is assumed to depend on both the number of Teffs (homicide) and on the rates of ER-stress/UPR signalling cascade (suicide). T-cell mediated β -cell destruction occurs via cell-to-cell contact and/or by the release of proinflammatory cytokines. Based on this, the dynamics of β cells can be described by

$$\frac{d\beta}{dt} = \ell \frac{\beta}{k_\beta + \beta} - \left(\kappa \int_0^K \psi(s) T(t, s) ds + E_r(\beta, U_{pr}) \right) \beta, \quad (5)$$

where $\ell \beta / (k_\beta + \beta)$ represents the density-dependent β -cell growth due to replication and neogenesis with a maximum rate ℓ and a half-maximum growth $k_\beta \left(\kappa \int_0^K \psi(s) T(t, s) ds \right) \beta$ represents β -cell loss (homicide) attributed to autoimmune destruction by Teffs with a maximal killing efficacy rate κ and relative killing efficacies ψ (assumed to be monotonically decreasing function of k to reflect the positive correlation between avidity and killing efficacy of Teffs), and $E_r(\beta, U_{pr})$ represents the rate of β -cell loss (suicide) attributed to ER-stress. Because β -cell homicide is assumed to increase the metabolic demand on surviving β cells, causing a rise in ER-stress in these cells and a subsequent triggering of UPR signalling cascade to restore protein homeostasis and normal insulin synthesis (Jaberi-Douraki et al., 2014b), the term $E_r(\beta, U_{pr})\beta$ is assumed to incorporate both the negative feedback of ER-stress and the positive feedback of UPR (U_{pr}) on β -cell growth. In other words, we assume that $E_r(\beta, U_{pr})$ satisfies the following three criteria:

1. $\lim_{\beta \rightarrow 0} E_r(\beta, U_{pr})$ is finite, which means that ER-stress plateaus by reaching its maximum level;
2. $\lim_{\beta \rightarrow \infty} E_r(\beta, U_{pr}) \beta = 0$ (i.e., ER-stress-induced β -cell death is biphasic);
3. $\lim_{\beta \rightarrow \infty} E_r(\beta, U_{pr}) = 0$, which indicates that ER-stress is negligible in the absence of β -cell loss.

To meet these criteria, we let

$$E_r(\beta, U_{pr}) = a_e \frac{k_e^n}{k_e^n + U_{pr} + \beta^n}, \quad (6)$$

where a_e is the maximum rate of ER-stress or β -cell suicide, $n = 2$ is the Hill coefficient, k_e is the half-maximum activation of ER-stress in the absence of the effect of UPR, and U_{pr} is the inhibition exerted by UPR signalling on ER-stress. To account for the biphasic nature of ER-stress, we assume that

$$U_{pr}(E_r) = a_u \frac{E_r(\beta, U_{pr})\beta}{k_u^2 + E_r(\beta, U_{pr})^2 \beta^2}, \quad (7)$$

where a_u is the UPR activation factor and k_u is its saturation threshold. By substituting Eqn. (7) into (6), we obtain the recursive expression

$$E_r(\beta, U_{pr}) = a_e \frac{k_e^2}{k_e^2 + a_u \frac{E_r(\beta, U_{pr})\beta}{k_u^2 + E_r(\beta, U_{pr})^2 \beta^2} + \beta^2} \quad (8)$$

that was previously simplified (Jaberi-Douraki et al., 2014b) by making U_{pr} in Eqn. (7) depend on $E_r(\beta, 0)$, an assumption that we do not make here (i.e., the recursive nature of Eqn. (8) is maintained). Notice that according to Eqn. (7), U_{pr} is biphasic with

$U_{pr}(0) = \lim_{\beta \rightarrow \infty} U_{pr} = 0$, a physiologically reasonable outcome in view of the fact that UPR is negligible at both high and low β -cell numbers.

The last component of the model is the pool of β -cell specific autoantigens. This pool is generated by APC-uptake of dead β cells and the processing of their proteins (e.g., insulin, glutamic acid decarboxylase, islet antigen 2, and zinc transporter 8) into autoantigenic peptides expressed as pMHCs on the surface of APCs. The dynamics of this pool is given by

$$\frac{dP}{dt} = \gamma \left(\kappa \int_0^K \psi(s) T(t, s) ds + E_r(\beta, U_{pr}) \right) \beta - \delta_p P, \quad (9)$$

where δ_p is the degradation rate of pMHC and γ is the autoantigen production per β cell killed by autoimmune destruction or ER-stress.

The fully dimensioned model (also called the continuum avidity model) presented here makes three simplifying assumptions: (i) it excludes islet-specific B cells from the model because they play minimal role in the destruction of β cells; (ii) it applies quasi-steady state approximation (QSS) on the pool of T1D-specific proinflammatory cytokines, such as tumour necrosis factor, IL-1 β and interferon gamma (but not IL-2), by making it proportional to the population size of Tffs at steady state; (iii) it assumes that the population size of APCs is constant embedded in the parameter values of the model; and (iv) insulin secretion and glucose metabolism are not included explicitly in the model.

Model parameters

The continuum avidity model was initially nondimensionalized to generate parameter combinations that are easier to compute numerically, then the outcomes of the nondimensionalized model were scaled back to their original dimensioned form to produce

the figures shown in the paper. Parameter values and distributions used in the simulations are listed in Table 1. The references used to estimate these parameters are also listed in Table 1. In brief, parameter values were estimated using a combination of experimental data, obtained from human subjects (T1D patients and first degree relatives) and animal models (nonobese diabetic mouse), and steady state analysis. Kinetic parameters of Teffs and Tregs were determined using previous estimates (Jaberi-Douraki et al., 2014a; Khadra et al., 2009; Kim et al., 2007) and other *in vitro* studies of T1D-specific Teffs and Tregs (co-)cultures (Pandiyani and Lenardo, 2008; Pandiyani et al., 2007; Scheffold et al., 2007) (see Supplementary Material for more details). Kinetic parameters of IL-2 release, on the other hand, were estimated using *in vitro* T-cell data (Busse et al., 2010; Feinerman et al., 2010a). Avidity ranges under various conditions were determined by matching the *in vivo* time evolution of T1D cumulative risk in human subjects (Pietropaolo et al., 2012) to model simulations (Figure S1) and fitting *in vitro* data of various clones of T1D-specific autoreactive T cells (Han et al., 2005; Skowera et al., 2008; Standifer et al., 2009) to steady state solutions. Parameters associated with β -cell dynamics were determined using previous estimates (Khadra et al., 2009) and other published data on islet literature (Dor et al., 2004; Khadra and Schnell, 2015). The parameters that are expected to follow certain patterns in their dependency on k were randomly selected according to the distributions listed in Table 1 and rearranged with respect to k based on their expected dependency.

Statistical methods

Most mathematical models are comprised of input factors and parametric quantities that are in principle not known with an adequate degree of confidence. This is attributed to natural variation and uncertainty within the physiological system under investigation, error in instruments and measurements, or, as in the case for T1D, due to the impediment in sampling experimental data (i.e., deficiency in current experimental techniques). This can be resolved mathematically by conducting sensitivity analysis to assess the level of uncertainty associated with each component of the model. Latin Hypercube Sampling (LHS) (Marino et al., 2008), an efficient sampling-based approach belonging to the Markov Chain class of sampling methods, is applied in combination with a binomial distribution for the probability density function to address this problem. The sensitivity analysis is conducted by randomizing the parameters associated with T-cell competition $\alpha(k)$, to reflect the non-uniformity of competition between T cells (including Teffs and Tregs), and the rate of Teff suppression by Tregs ρ_{T_r} , which depends on $\alpha(k)$. Selecting the weight function $\alpha(k)$ for randomization is based on the fact that the model is less sensitive to moderate perturbations in other parameters (results not shown), as well as based on a recent study (Jaberi-Douraki et al., 2014b) showing that T-cell dynamics within a discrete T-cell avidity model is more sensitive to perturbation in the rate of competition than other parameters. The goal here is to show how randomization and heterogeneity in the continuum avidity model (1) – (9) affect model dynamics in a multi-dimensional parameter space.

Software

In this paper, the continuum avidity model (1) – (9) is investigated dynamically using numerical techniques. We use the software package MATLAB (Mathworks, Natick, MA

and C++) to perform time-series simulations, parameter estimation, sensitivity, and population model analysis.

RESULTS

Minor variations in T-cell competition can lead to major changes in disease outcomes

Experimental observations revealed that first degree relatives (FDRs) of T1D patients exhibit various levels of susceptibility to T1D and rapidity to disease onset (Morran et al., 2015; Morran et al., 2010). To determine the underlying cause(s) of this “heterogeneity”, we studied how variations in inter- and intra-clonal competition between T effs and Tregs, expressed by the weight function $\omega(k)$, in the continuum avidity model can affect the dynamics of T cells, β cells and IL-2. Such variations can result from genetic differences within one group of FDRs of a T1D patient.

By running 500 randomization trials of the weight function $\omega(k)$, within the range [0.5, 1.5] ng/ml (see Table 1), using the uniform distribution and LHS method, while keeping other parameters of the model fixed, a sample of 500 high risk (HR) simulated “individuals” is generated to compare their temporal profiles. As shown in Figure 2, the time evolution of the total population size of T effs Ω (panel A), fraction of surviving β cells relative to their initial population size given by β/β_0 (panel B), total population size of Tregs Ω_r (panel C), and IL-2 concentration (panel D), for the 500 simulated “individuals” plotted collectively as heat-maps, exhibit time-dependent changes that vary between them. These heat-maps are colour-coded according to the colour-bars (in logarithmic scale, except for the fraction of surviving β cells β/β_0) adjacent to each panel. Panel A shows that a significant rise in T effs (shown as red) for a simulated “individual” over 10 years is typically accompanied by a significant loss in surviving β cells (shown as blue) in panel B, an expected outcome in view of the fact that high accumulation of effector T cells leads to greater autoimmune as well as ER-stress-dependent destruction of β cells. The simulated “individuals” that exhibit no elevation in T effs (shown as blue in panel A), on the other hand, are accompanied by a minor loss in β cells (shown as red in panel B). Given that the only difference between “individuals” within the first (“likely-diabetic”) and the second (“non-diabetic”) groups is the randomization of $\omega(k)$, which directly alters the inter- and intra-clonal competition between T cells for each “individual”, it is surprising to observe such major changes in disease outcomes between them. One may suggest that peripheral tolerance, exerted and maintained by the accumulation of Tregs, or lack thereof, is the main cause for observing the discrepancy between these two groups. Examining panel C shows that, although the elevation in Tregs in the second “non-diabetic” group is playing protective role in blocking the autoimmune destruction of β cells, this role is not as effective since some cases in the first “likely-diabetic” group also exhibit elevations in Tregs. Furthermore, IL-2 profiles in all of these 500 HR simulated “individuals” (within the “likely-diabetic” and “non-diabetic” groups), displayed in panel D, exhibit transient elevations in their concentration levels, suggesting that other factors involving T effs, Tregs and IL-2 may be playing a role in distinguishing between the “likely-diabetic” and “non-diabetic” cases. We will show in the next sections that T-cell avidity is actually the key to explaining such outcomes.

Figure 2 shows that the onset of T1D-specific autoimmune responses does not always translate into clinical manifestation of the disease. The destruction of β cells caused by these responses must be prominent for the symptoms to appear and for the HR simulated “individuals” to become fully diabetic. In other words, critical thresholds for diabetes (labelled CTs), determined by the fraction of surviving β cells, must be crossed for the clinical symptoms of T1D to appear. We expect these thresholds (typically between 10–30% of the initial population size of β cells) and the pace of reaching them to vary between “individuals”, making them either rapid or slow progressors of T1D (Morran et al., 2010). To illustrate these ideas, we randomized the CTs of the 500 HR simulated “individuals” used in Figure 2 within the interval [0.1, 0.3] using exponential distribution, and quantified the cumulative risk of diabetes, or the cumulative number of “individuals” that cross the CT for diabetes, for 10 years (Supplementary Figure S1, solid line). We found that although 75% of “individuals” cross the CT and become type 1 diabetic in a manner similar to what have been observed previously (Morran et al., 2010), they do not do so at the same pace; some are fast in reaching the clinical disease (within few years) and some are slow (longer than 10 years).

To provide a more detailed description of how these slow and fast progressors of T1D evolve over time, we plotted in Figure 3 a histogram of the fraction of surviving β cells in the 500 HR simulated “individuals” at 3 different time points: 1 year (panel A), 5 years (panel B) and 10 years (panel C) after the start of the autoimmune attack. The figure shows that there are two propagating peaks (waves) of “individuals” that shift to the left, or the lower end of surviving β cells, over time. The left most peak (panels A–C) represents the rapid progressors of T1D, whereas the middle peak (panels A–C) corresponds to slow progressors. The propagation of these peaks over time will of course depend on the rate of β -cell destruction by T cells given by κ (i.e., T-cell killing efficacy). In fact, decreasing the default value of κ to 10^{-9} (cell-day) $^{-1}$ confers a cumulative risk of 50% for diabetes (Supplementary Figure S1, dashed-dotted line), whereas increasing it to 10^{-7} (cell-day) $^{-1}$ confers a cumulative risk of 100% (Supplementary Figure S1, dashed line) within 10 years of follow-up. These outcomes are consistent with experimental studies of FDRs screened positive for conventional and novel β -cell specific autoantibodies (such as GAD65 and IA-2FL, respectively) (Morran et al., 2010).

β -cell survival and the honeymoon period

At the clinical onset of T1D, most patients retain some insulin secretory capacity, as exemplified by the so-called honeymoon period of the disease (Group, 1998; Pietropaolo, 2013). During this period, patients often experience minimal difficulty in maintaining near-normal glucose control, but that capability is eventually lost in most cases.

To determine if the continuum avidity model, which does not include the dynamics of insulin secretion and glucose metabolism explicitly, can produce the honeymoon period, we plotted in Figure 4 the time courses of 4 representative profiles of fractional β -cell survival from the 500 HR simulated “individuals” with randomly selected CT. [A larger sample of 20 HR simulated “individuals” is plotted in Supplementary Figure S2 for comparison.] The profiles show that it is possible to have “individuals” with minor loss in β cells (panel A),

major loss in β cells without crossing the CT and becoming symptomatic (panel B); major loss in β cells accompanied by several crossings of the CT (in the form of a cycle) during the remission phase of the disease (panel C); or significant loss in β cells that crosses the CT very rapidly leading to diabetes onset.

Figure 4 shows that, although β -cell renewal and ER-stress parameters are identical for all simulated “individuals”, including the 4 presented here, variations in T-cell competition can alone generate considerable differences in β -cell loss between them. In fact, panel C shows that it is possible to observe the honeymoon period (when the fraction of surviving β cells is above the CT during remission) in the absence of metabolic therapies. The frequency of such outcomes ranges between 5–10%, which is considerably lower than the 43–56% or the 25–100% seen in newly diagnosed children receiving insulin therapy (Abdul-Rasoul et al., 2006). This suggests that some of these T1D patients are intrinsically capable of undergoing the remission phase without therapy because of mechanism(s) independent of insulin and glucose metabolism. In the next sections, we show that the onset of partial remission in these cases (that possess identical expressions for β -cell dynamics) is likely due to a combination of two avidity-dependent factors: partial Treg immunomodulation and average avidity maturation decline.

Based on our simulations, it is possible to adjust the frequency of “individuals” exhibiting the honeymoon period to a higher level (up to 30%) by altering the rate of β -cell loss κ (i.e., Teff killing efficacy) and/or ER-stress kinetics in pancreatic β cells (results not shown). These results suggest potential pathways by which metabolic therapies exert their influences.

Effects of Teff-to-Treg dominance on disease outcomes

A notable characteristic of the continuum avidity model is the presence of Tregs that exert suppressive effects on Teffs and their cytotoxic activities through several immunomodulatory pathways. These Tregs possess the same range of avidity as that of Teffs, making their interaction with Teffs very complex and not intuitive. The presence of these peculiar “likely-diabetic” cases with elevated level of Tregs in Figure 2 makes it imperative to understand how Tregs exert their immunomodulatory function within this system.

One way of achieving this is done by considering a new measure, called the time-averaged ratio of Teffs-to-Tregs, defined by

$$\log \left(\frac{\langle T \rangle_t}{\langle T_r \rangle_t} \right) = \log \left(\frac{\int_0^{10} T(t, k) dt}{\int_0^{10} T_r(t, k) dt} \right), \quad (10)$$

and analysing its behaviour as a function of k (the half-maximum activation) for the 4 HR simulated “individuals” of Figure 4. Figure 5(A) and (B) show that the two non-diabetic “individuals” of Figure 4(A) and (B) that maintain a fraction of surviving β cells above the CT, respectively, exhibit one common feature in their time-averaged ratio: the presence of a large negative peak at low k values (around $k \approx 1.5 \times 10^4$ ng/ml in Figure 5(A) and $k \approx 8.8$

$\times 10^4$ ng/ml in Figure 5(B)) indicating the dominance of Tregs over Teffs at a high avidity. This dominance was sufficient to protect β cells from major destruction beyond the CT caused by autoimmunity and ER-stress induced apoptosis. These “individuals” remain healthy (or asymptomatic) even in the presence of a prominent positive peak at higher k values in Figure 5(B), representing Teff-dominance at a significantly lower avidity. This positive peak is responsible for the major part of the non-pathogenic β -cell loss in Figure 4(B).

Interestingly, for the other two “individuals” shown in Figure 4(C) and (D), the large negative peak of Treg-dominance is either no longer present at low values of k as in Figure 5(C), and/or is not pronounced, as in Figure 5(D), respectively. Instead, these negative peaks occur at moderate values of k (around $k \approx 15.8 \times 10^4$ ng/ml in Figure 5(C) and $k \approx 9.8 \times 10^4$ ng/ml in Figure 5(D)), and are accompanied by very prominent positive peaks of Teff-dominance occurring at slightly higher k values. As a result, these two “individuals” show significant and pathogenic loss in β cells that is more pronounced in panel D than in C of Figure 4. The latter is due to the absence of a pronounced negative peak in Figure 5(D) and the presence of positive peak at a lower k value ($k \approx 28.5 \times 10^4$ ng/ml in Figure 5(C) versus $k \approx 13.3 \times 10^4$ ng/ml in Figure 5(D)).

It is important to point out that, by plotting the ratios of the total populations of Teffs-to-Tregs, $T(t, k) / T_r(t, k)$ (in logarithmic scale) with respect to k in Supplementary Figure S3 at five distinct time points: 30 days (gainsboro-grey curves), 3 months (light-grey curves), 6 months (dark-grey curves), 1 year (grey curves), and 10 years (black curves) after the start of the autoimmune attack, we find that these ratios in the 4 simulated “individuals” of Figure 4 are dynamic. Indeed, the negative and positive peaks that we see in these plots become more gradually pronounced with time, suggesting that “avidity maturation” can be interpreted as a time-dependent increase in the dominance of Teffs over Tregs at a given avidity. This new interpretation implies that avidity maturation depends on T-cell number, not on time-dependent changes in TCR binding affinity, and that it occurs at specific values of avidity (k^{-1}) rather than over the whole range of avidity.

T-cell avidity and the honeymoon period

Quantifying the time-averaged ratio of Teffs-to-Tregs, defined by Eqn. (10), was valuable in identifying the immunological responses leading to diabetes or its absence in the 500 HR simulated “individuals”. Treg-to-Teff dominance at specific avidities was the key in determining such outcomes. Although the kinetics of β cells in all of these “individuals” have been chosen to be identical, major differences are still observed in their β -cell profiles, particularly in the two diabetic cases of Figure 4(C) and (D). The use of the time-averaged ratio in this context is insufficient to explain how these differences are generated and/or how the honeymoon period, characterized by a temporary recovery in the fraction of surviving β cells above the CT, is formed.

To address this issue, another measure, called the avidity-averaged ratio of Teffs-to-Tregs, given by

$$R(t) = \log\left(\frac{\Omega}{\Omega_r}\right) = \log\left(\int_0^K T(t, s) ds\right) - \log\left(\int_0^K T_r(t, s) ds\right), \quad t \in [0, 10], \quad (11)$$

is employed to study these differences in the 4 simulated “individuals” of Figure 4. Figure 6(A) and (B) show that the temporal profiles of R for the non-diabetic “individuals” of Figure 4(A) and (B), respectively, are monotonically decreasing functions of time (indicating a loss in the dominance of Teffs-to-Tregs over time), whereas Figure 6(D) shows that R , associated with the diabetic “individual” of Figure 4(D), is monotonically increasing (indicating an increase in the dominance of Teffs-to-Tregs over time). These results are consistent with the observed profiles of β -cell survival shown in Figure 4. In the diabetic case of Figure 4(C), however, R is biphasic with a nadir that is attained precisely during T1D remission. The latter case suggests that the loss and gain in the overall dominance of Teffs-to-Tregs is the key for invoking the honeymoon period in such “individuals” not subjected to metabolic (or insulin) therapies typically used on T1D patients that are newly diagnosed.

Dual role of interleukin IL-2 signalling

As we have indicated earlier, IL-2 secreted by Teffs exerts positive and negative feedbacks on the dynamics of the continuum avidity model by acting as a growth factor for both Teffs (positive feedback) and Tregs (negative feedback). To decipher this dual role of IL-2, we simulated in Figure 7 the temporal profiles of this cytokine over 10 years for the four representative “individuals” we used in Figure 4, respectively. In all cases, we consistently observe an elevation in IL-2 concentration that is comparable in amplitude between “individuals” but mostly differ in their full width at half maximum (FWHM). In fact, by comparing the FWHM of the two non-diabetic cases in panels A and B with the diabetic case in panel D of Figure 7 (as defined by Figure 4), we see that the IL-2 wave is prolonged in the non-diabetic cases when compared to the diabetic ones. This behaviour was consistent throughout the 500 HR simulated “individuals”. This suggests that while IL-2 is an important growth factor for Teffs, its persistent elevation over prolonged period of time during the autoimmune response can have therapeutic effects by initiating better immunomodulatory responses by Tregs.

In the case of “individuals” that exhibit the honeymoon period (as in panel C of Figure 4), the profile of IL-2 release is typically a hybrid between the “non-diabetic” and “diabetic” cases, as shown in Figure 7(C). Whereas FWHM of IL-2 release is prolonged in such cases, the downstroke of IL-2 profile are as steep as those seen in the diabetic cases (such as the one shown in Figure 7(D)).

The above results suggest that it is possible to use the profiles of IL-2 release along with their FWHM as indicators of susceptibility to T1D in FDRs. Measuring the profiles of IL-2 concentration *in vivo* over time, however, is challenging experimentally. One possible way of confirming these results in through the development of co-culture systems involving activated Teff and Treg cells of the same specificity from healthy and newly onset T1D patients to compare their IL-2 profiles.

Key elements of immunological tolerance regulated by Tregs

In the continuum avidity model, two essential components of immunological tolerance exerted by Tregs on Teffs have been described explicitly; namely, (i) the intra-clonal competition (that is T-cell density-dependent), and (ii) Teff induction into iTregs. With IL-2 deprivation, they play crucial role in maintaining the proper immunological responses by Teffs in healthy conditions. Defects or imbalance in these two components may lead to pathological outcomes. Therefore, it is imperative to determine how these two pathways compare to each other in regulating immunological tolerance during T1D.

This point is addressed by studying how the absence of each one of these two components from the model affect the 4-year accumulation of Teffs over the whole range of avidity as measured by the quantity Ω (see Eqn. (3)). Figure 8 shows that the absence of intra-clonal competition alone (dotted line) and the absence of induction into iTregs alone (dashed line) both lead to a pathogenic elevation in the accumulation of Teffs (or an increase in Ω at every time point), averaged over 30 HR simulated “individuals”, when compared to the control case (solid line) that includes both components. Interestingly, the increase in the accumulation of Teffs in the absence of intra-clonal competition is higher than that in the absence of induction, suggesting that Tregs exert immunological tolerance more effectively through competition than through induction. In other words, immunomodulation by Tregs is also regulated by factors, such as limited space and limited number of pMHC binding sites on APCs, which are independent of avidity.

DISCUSSION

At the onset of T1D, patients exhibit abnormally elevated level of glucose excursions in the blood (hyperglycaemia) and multiple islet autoantibodies that are associated with β -cell destruction (Morran et al., 2015). The impediment in sampling experimental data from the pancreatic tissue or the lymphatic system in high risk subjects makes the use of quantitative modelling approaches of pancreatic β -cell destruction an intriguing and fascinating new opportunity to analyse this disease, as well as a promising and an alternative method to unravel the role of pathogenic effector and regulatory T cells along with ER-stress in the immunopathology of the disease. Experimental approaches are conventionally employed to investigate these highly nonlinear processes, but with the emergence of the field of computational biology, it is now feasible to employ such quantitative *in silico* methods, in parallel with experimental techniques, to increase our understanding of how these autoimmune responses are generated and how they affect β -cell survival.

In this study, an object-oriented approach employing a novel integro-differential equation model is adopted to define a set of criteria that determines susceptibility to T1D. The model features two important elements of the disease that have never been considered before; namely, (i) the incorporation of the dynamics of regulatory T cells (Tregs) and IL-2 secreted by effector T cells (Teffs), and (ii) the assumption that Teffs and Tregs are reactive to the same pool of autoantigens and thus possess a continuum range of avidity. It also includes the dynamics of autoreactive Teffs, β cells and the whole pool of β -cell specific autoantigens, and assumes that β -cell destruction caused by autoimmunity induces ER-stress and UPR signalling in surviving β cells. The resulting continuum avidity model is then employed as a

framework to understand how these various components interact with each other during autoimmune responses in T1D, as well as deliver a quantitative structure to investigate the role of Teffs and Tregs in the autoimmune destruction of β cells, along with the role of non-uniform inter and intra-clonal competition in regulating their dynamics. Using a combination of numerical simulations and sensitivity analysis, the study reveals important insights about the immunomodulatory mechanisms by which Tregs mediate their suppressive functions towards Teff- and ER-stress-induced β -cell homicide and suicide during T1D (Atkinson et al., 2011).

Our main findings uncover the role of T-cell avidity in guiding disease outcomes in T1D. More specifically, they show that the lack of dominance of Tregs-to-Teffs at high avidities is what drives Teffs to exert their own destructive processes, provided that they exhibit dominance over Tregs at lower avidities. These results indicate that disease manifestation is not necessarily associated with an overall elevation in the population sizes of effector T cells at the expense of regulatory T cells, but rather with the elevation of Teffs at specific avidities accompanied by the absence of Treg-dominance at high avidities. The existence of such association between T-cell avidity, on one hand, and the interrelation between T1D-specific Teffs and Tregs, on the other, has been already demonstrated experimentally at the level of the thymus during negative selection (Tsai and Santamaria, 2013). In particular, it was shown that an increase in the failure of negative selection is correlated with a rise (a decline) in the population size of high-avidity Teffs (Tregs) in the periphery and an increase in the severity of T1D. This is consistent with our findings showing that the location of Teff dominance with respect to avidity determines how fast β -cell decline is and how rapid clinical T1D is. We posit that this mechanism is what differentiates between rapid and slow progressors of T1D. The time-averaged ratio of Teffs-to-Tregs is used to reach these conclusions.

Another interesting outcome of this study is that the lack of overall dominance of Teffs over Tregs can indirectly trigger disease remission by allowing fraction of surviving β cells to recover and form of a “cycle” around the critical threshold (CT) during the honeymoon period. This latter outcome is an intrinsic property of the model and is independent of metabolic therapies that are typically used in newly diagnosed T1D patients. In other words, the study predicts that a subset of T1D patients that appear to respond to metabolic therapies, such as insulin therapy, are capable of naturally exhibiting this phenomenon on their own without the influence of therapies, due to the overall dominance of Tregs over Teffs as measured by the avidity-averaged ratio R . It was previously suggested that such cycles may repetitively appear during β -cell loss (von Herrath et al., 2007), but the cycle that appears around the CT is perhaps the only one detectable clinically because of its association with temporary relief in symptoms.

In the continuum avidity model, immunomodulation exerted by Tregs is described as a local competition for IL-2 consumption, as an intra-clonal competition between Teffs and Tregs, and as a conversion of Teffs into iTregs. By quantifying each component separately, it was determined that IL-2 profiles in non-diabetic “individuals” exhibit certain kinetics that are quite distinct from those in the diabetic cases. More specifically, the model reveals that the full width at half maximum and the steepness of the downstroke of the IL-2 profile can be

used as indicators for disease outcomes, with the former being longer in non-diabetics and the latter being steeper in diabetics. Furthermore, our study predicts that intra-clonal competition is a more effective pathway for Tregs to suppress Teffs than Teff conversion into iTregs. This means that Tregs are also capable of exerting effective suppression of Teffs in an avidity-independent and antigen non-specific manner. Although this latter result appears to be in disagreement with experimental evidence (Vandenbark and Offner, 2008), suggesting that antigen-specific Treg therapies are more potent than polyclonal Treg therapies in treating autoimmune diseases, it is important to point out that Teff induction into iTregs included in this quantitative study is only one of several ways in which Tregs suppress Teffs in an avidity- and antigen-specific way.

This study provides insights into how the two pools of autoreactive Teffs and Tregs interact during the manifestation of T1D in HR subjects. It provides a list of predictors, based on T-cell, β -cell and IL-2 dynamics, to distinguish between “likely-diabetic” and “non-diabetic” cases, especially in terms of the dynamic profiles of these components and their dependencies on avidity. The model presented also lays the groundwork for conducting future research into the relationship between Teffs and Tregs, on the one hand, and other clones of T cells, on the other. For example, the model can be extended to include low-avidity autoreactive CD4⁺ and CD8⁺ T cells that spontaneously differentiate (during T1D progression) into memory autoregulatory T cells (Taut), capable of blunting autoimmunity (Clemente-Casares et al., 2011; Tsai et al., 2010; Wang et al., 2010). Recent findings have shown that IL-2 promotes the recruitment and function of Tauts, whereas Tregs suppress the generation of Tauts (Shameli et al., 2013). Clinically, these Tauts can be expanded using nanoparticles coated with pMHC class II and I complexes (Clemente-Casares et al., 2011; Khadra et al., 2010b; Sugarman et al., 2013; Tsai et al., 2010). The extended model can thus help unravel the complex homeostatic interplay between all these T-cell pools and to optimize the therapeutic efficacy of nanoparticles in the treatment of the disease.

Last but not least, in this study we introduced the new concept of continuum T-cell avidity within the framework of a novel mathematical model of integro-differential equations that capture this important feature. As a future direction, it would be interesting to combine this approach with classical quantitative methods to analyse flow cytometry data and study their implications on T1D. The mathematical model presented in the paper will be very helpful to account for these large data sets of FACS plots and to provide a platform to validate the hypotheses suggested here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A diagram outlining the different factors involved in the autoimmune destruction of β cells in T1D. CD8⁺ and CD4⁺ autoreactive T cells (Teffs), activated by APCs expressing β -cell specific autoantigens as pMHCs, infiltrate the islets of Langerhans and destroy ~90% of the total population of β cells via cell-to-cell contact or by the release proinflammatory cytokines (e.g., INF γ , TNF, IL-1 β). Islet-specific CD4⁺CD25⁺FoxP3⁺ regulatory T cells (Tregs), on the other hand, are activated by APCs in the presence of the growth factor interleukin IL-2 secreted by Teffs. They play an anti-inflammatory role by depriving Teffs from IL-2, by releasing regulatory cytokines (e.g., granzymes and perforin) that suppress Teffs, by deleting Teffs via cell-to-cell contact, and/or by modulating APCs (blocking maturation or causing apoptosis). In the absence of IL-2, Tregs undergo apoptosis.

Figure 2.

Progression of T1D in 500 HR simulated “individuals” over 10 years of follow-up. The HR simulated “individuals” are generated by randomizing the weight function $\omega(k)$ 500 times within its respective range in Table 1 using the uniform distribution. The time evolution of (A) total number of Tregs (Ω), calculated over the whole range of avidity $[0, K]$; (B) fraction of surviving β cells (β/β_0); (C) total number of Tregs (Ω_t), calculated over the whole range of avidity $[0, K]$; and (D) IL-2 concentration secreted by Tregs, are shown for the 500 HR simulated “individuals” as heat-maps. The colour-bars adjacent to each panel illustrate the correspondence between colours and the level of each one of these components in logarithmic scale (except for the fraction of surviving β cells β/β_0). According to these panels, small variations in clonal competition lead to major changes in disease outcomes.

Figure 3.

Rapid and slow progressors of T1D. Histograms showing the temporal changes in the frequency of the fraction of surviving β cells in 500 HR simulated “individuals” generated in Figure 2, i.e., the changes in the frequency of outcomes shown in Figure 2B over time. Three time points are selected: (A) 1 year (B) 5 years; and (C) 10 years after the start of the autoimmune attack. A subset of 500 HR simulated “individuals” cross the CT for T1D symptoms very rapidly within 1 year (the left peak in panel A), whereas another subset crosses the threshold at a much later time, after 5–10 years (the middle peak in panels A–C).

Figure 4.

Four typical profiles of β -cell loss over 10 years from a sample of 500 HR simulated “individuals”. By randomly selecting CTs for T1D onset in HR simulated “individuals” within the range [0.1, 0.3] using an exponential distribution, we obtain 4 distinct temporal profiles for the fraction of surviving β cells. They are characterised by: (A) a minor loss in β cells that is shy of 10%; (B) a significant loss in β cells that does not cross the CT; i.e., the “individual” remains healthy and asymptomatic; (C) a significant loss in β cells that is accompanied by a remission phase, labelled the honeymoon period, characterized by the presence of a cycle around the CT (seen in 5–10% of HR simulated “individuals”); and (D) a major (> 90%) loss in β cells that crosses the CT rapidly. The duration of the honeymoon period in C is about 2.9 years but the length of this phase depends on the randomly selected CTs for the onset of T1D symptoms.

Figure 5.

The absence of (Treg-to-Teff)-dominance at high avidities is the lead cause of T1D onset. The ratios of Teffs-to-Tregs (each averaged over 10 years) for the 4 distinct cases listed in Figure 4, respectively, are displayed in logarithmic scale. The presence of very pronounced negative (positive) peaks at specific values of k reflects Treg-dominance (Teff-dominance) over Teffs (Tregs). For the 4 cases considered, we either observe (A) a large negative peak at high avidity (accompanied by minor β -cell loss); (B) a large negative peak at high avidity and a large positive peak at moderate avidity (accompanied by significant but non-pathogenic β -cell loss); (C) a large negative peak at moderate avidity and a large positive peak at low avidity (accompanied by significant and pathogenic β -cell loss); or (D) a large positive peak at moderate avidity (accompanied by major and pathogenic β -cell loss). These outcomes are typical for all the 500 HR simulated “individuals”.

Figure 6.

The overall dominance of Teffs-to-Tregs over time is the key determinant of T1D progression. The temporal profiles of the avidity-averaged ratio (R) of the total number of Teffs (Ω) to Tregs (Ω_r), both calculated over the whole range of avidity $[0, K]$, for the 4 distinct cases of Figure 4, respectively, are shown. These profiles reveal that R can either (A) steadily decline to a negative steady state within 1 year of the autoimmune attack, indicating a rapid progression of Treg-dominance; (B) slowly decline to a very negative steady state (not reached within 10 years of the autoimmune attack), indicating a slow progression of Treg-dominance; (C) decline then steeply increase to a positive steady state (with a nadir that coincides with the honeymoon period), indicating the eventual dominance of Teffs; or (D) steadily increase to a positive steady state within a few months of the autoimmune attack, indicating a rapid progression of Teff-dominance.

Figure 7.

Interleukin IL-2 concentration peaks at the height of the autoimmune attack. The temporal profiles of IL-2 release from Teffs for the 4 distinct cases of Figure 4, respectively, are displayed to elucidate the dual role of this cytokine in stimulating and suppressing the autoimmune response. For the 500 HR simulated “individuals”, two prevailing behaviours in IL-2 profiles are observed with respect to logarithmic time; namely, (i) a gradual rise and decline of IL-2 concentration with a prolonged FLHM in “non-diabetics” exhibiting minor (A) and major (B) β -cell loss; and (ii) a steep decline in IL-2 concentration accompanied by a prolonged (C) or narrow (D) FLHM in “diabetics”. The profile in C is a hybrid between those in A, B and in D.

Figure 8.

Intra-clonal competition between Teffs and Tregs is more effective in suppressing Teffs than Teff-induction into iTregs. The accumulation of the total number of Teffs (Ω), calculated over the whole range of avidity $[0, K]$ and averaged over 30 randomly selected HR simulated “individuals”, is plotted in the presence of both intra-clonal competition and Teff-induction into iTregs (solid line), in the absence of intra-clonal competition (dotted curve) and in the absence of induction (dashed curve). Error bars represent the standard error measurements. Notice that the increase in the accumulation of Teffs without intra-clonal competition is significantly larger than that without induction.

Table 1

Parameters values

Parameters without units are dimensionless, and those without values are randomly selected using the distributions and ranges specified in the table and arranged according to their functional dependency on $k \in [0, K]$, where $K \in [1, 10^3] \times 414.12$ ng/ml. See Supplementary Material for the estimation of some of these parameters.

Parameters	Description	Value	Range	Reference
$\sigma_T(k), \sigma_{T_r}(k)$	Influx rates of Teffs and Tregs from the thymus	Uniform distribution (in cell/day)	[3.55, 183.3]	(Jaberi-Douraki et al., 2014a; Jaberi-Douraki et al., 2014b; Khadra et al., 2009)
$\alpha_T(k), \alpha_{T_r}(k)$	Expansion rates of Teffs and Tregs	Normal distribution (in cell/fM) with mean $16.1 \times 10^7, 3.7 \times 10^7$ and variance $2.5 \times 10^7, 9.3 \times 10^6$	$[2.5, 30] \times 10^7$ $[9.3, 112] \times 10^6$	(Jaberi-Douraki et al., 2014a; Jaberi-Douraki et al., 2014b; Khadra et al., 2010a; Khadra et al., 2010b; Khadra et al., 2011; Kim et al., 2007)
$\delta_T(k), \delta_{T_r}(k)$	Turnover rates of Teffs and Tregs	Exponential distribution (in day ⁻¹) with mean 0.15, 0.2 and variance 0.1	[0.01, 0.3]	(Jaberi-Douraki et al., 2014a; Jaberi-Douraki et al., 2014b; Khadra et al., 2010a; Khadra et al., 2010b; Khadra et al., 2011; Kim et al., 2007)
ε	T-cell competition	5×10^{-6} (cell-day) ⁻¹	–	(Jaberi-Douraki et al., 2014a; Jaberi-Douraki et al., 2014b; Khadra et al., 2009; Khadra et al., 2011)
$\omega(k)$	Weight function to reflect non-uniformity in the competition	Uniform distribution (in ml/ng)	[0.5, 1.5]	(Jaberi-Douraki et al., 2014a; Jaberi-Douraki et al., 2014b)
$\rho_{T_r}(k)$	Rate of Teff suppression by Tregs	$0.1 \varepsilon[\omega(k)]$ (cell-day) ⁻¹ ($[\omega(k)]$ is the magnitude of $\omega(k)$)	$[0.1, 0.2] \times \varepsilon[\omega(k)]$	(Pandiyani and Lenardo, 2008; Pandiyani et al., 2007; Scheffold et al., 2007)
θ	A scaling factor to make the units consistent	1 ml/ng	-	-
$\lambda(k)$	Fraction of suppressed Teff pool transforming into inducible Tregs (iTregs)	0.5	[0.1, 0.8]	(Pandiyani et al., 2007)
$\sigma_I(k)$	Basal rate of IL-2 secretion	1000 molecules/(cell·h) which is equivalent to 0.03985×10^{-3} fM/(cell·day)	$[0.02, 0.08] \times 10^{-3}$	(Busse et al., 2010; Feinerman et al., 2010b)
$\alpha_I(k)$	IL-2 secretion rate by antigen stimulated Teffs	9000 molecules/(cell·h) which is equivalent to 0.35868×10^{-3} fM/(cell·day)	$[0, 0.9] \times 10^{-3}$	(Busse et al., 2010; Feinerman et al., 2010b)
$\delta_I(k)$	IL-2 degradation rate	0.01 day ⁻¹	[0, 0.1]	(Busse et al., 2010)
η_r	IL-2 binding rate to Teffs	0.015×10^{-3} (cell-day) ⁻¹	$[.002, .0213] \times 10^{-3}$	Estimated
η_{r_r}	IL-2 binding rate to Tregs	0.04×10^{-3} (cell-day) ⁻¹	$[0.02, 0.7] \times 10^{-3}$	Estimated
ℓ	Maximal rate of β -cell renewal per day	605 cell/day	[511, 1100]	(Dor et al., 2004; Jaberi-Douraki et al., 2014b)
k_β	Number of β cells required for 50 % maximal renewal	8745 cell	[6875, 12100]	(Dor et al., 2004; Jaberi-Douraki et al., 2014b)
κ	Killing rate of β cells	0.6×10^{-7} (cell-day) ⁻¹	$[10^{-10}, 10^{-7}]$	(Jaberi-Douraki et al., 2014a; Jaberi-Douraki et al., 2014b; Khadra et al., 2009; Skowera et al., 2008)

Parameters	Description	Value	Range	Reference
$\psi(k)$	Relative killing efficacies of Teffs	Uniform distribution (in ml/ng) [rearranged to make ψ a decreasing function of k]	[0.5, 3]	(Jaberi-Douraki et al., 2014a; Jaberi-Douraki et al., 2014b; Khadra et al., 2011)
a_e	Maximal rate of β -cell loss induced by ER-stress	0.005 day^{-1}	$[9.1 \times 10^{-4}, 0.16]$	(Jaberi-Douraki et al., 2014b)
k_e	Saturation threshold for ER-stress	110000 cell	$[6, 19.3] \times 10^4$	(Jaberi-Douraki et al., 2014b)
k_u	UPR saturation threshold	$2.73 \times 10^{-6} \text{ cell/day}$	$[0.55, 4.5] \times 10^{-6}$	(Jaberi-Douraki et al., 2014b)
a_u	UPR activation factor	$2.9 \times 10^6 \text{ cell}^3/\text{day}$	$[1.5, 109] \times 10^5$	(Jaberi-Douraki et al., 2014b)
γ	Peptide accumulation rate	$0.4 \text{ ng}/(\text{cell} \cdot \text{ml})$	–	(Jaberi-Douraki et al., 2014a; Jaberi-Douraki et al., 2014b; Khadra et al., 2011; Skowera et al., 2008)
δ_p	Peptide degradation rate	0.1 day^{-1}	–	(Jaberi-Douraki et al., 2014a; Jaberi-Douraki et al., 2014b; Khadra et al., 2009; Khadra et al., 2011; Skowera et al., 2008)