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Review Article

Autoimmune responses in T1DM: quantitative methods to understand onset, progression, and prevention of disease

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Understanding the physiological processes that underlie autoimmune disorders and identifying biomarkers to predict their onset are two pressing issues that need to be thoroughly sorted out by careful thought when analyzing these diseases. Type 1 diabetes (T1D) is a typical example of such diseases. It is mediated by autoreactive cytotoxic $CD4^+$ and $CD8^+$ T-cells that infiltrate the pancreatic islets of Langerhans and destroy insulin-secreting β-cells, leading to abnormal levels of glucose in affected individuals. The disease is also associated with a series of islet-specific autoantibodies that appear in high-risk subjects (HRS) several years prior to the onset of diabetes-related symptoms. It has been suggested that T1D is relapsing-remitting in nature and that islet-specific autoantibodies released by lymphocytic B-cells are detectable at different stages of the disease, depending on their binding affinity (the higher, the earlier they appear). The multifaceted nature of this disease and its intrinsic complexity make this disease very difficult to analyze experimentally as a whole. The use of quantitative methods, in the form of mathematical models and computational tools, to examine the disease has been a very powerful tool in providing predictions and insights about the underlying mechanism(s) regulating its onset and development. Furthermore, the models developed may have prognostic implications by aiding in the enrollment of HRS into trials for T1D prevention. In this review, we summarize recent advances made in determining T- and B-cell involvement in T1D using these quantitative approaches and delineate areas where mathematical modeling can make further contributions in unraveling certain aspect of this disease.

Majid Jaberi-Douraki[a], Shang Wan (Shalon) Liu[a], Massimo Pietropaolo[b] and Anmar Khadra[a]

[a]Department of Physiology, McGill University, Montreal, Quebec, Canada; and [b]Laboratory of Immunogenetics, University of Michigan, Ann Arbor, MI, USA

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Corresponding author: Anmar Khadra,
Department of Physiology,
McGill University,
McIntyre Medical Building (Rm 1120),
3655 Promenade Sir William Osler,
Montreal, QC H3G 1Y6,
Canada.
Tel: +1 (514) 398-1743;
fax: +1 (514) 398-7452;
e-mail: anmar.khadra@mcgill.ca

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There are diverse autoimmune disorders that affect human health; type 1 diabetes (T1D) in humans and animal models such as the non-obese diabetic (NOD) mouse, is one of these diseases that target insulin-secreting β-cells in the pancreatic islets of Langerhans. There is general agreement in the scientific community that the disease is triggered by various factors in genetically predisposed individuals, that it is mediated by autoreactive β-cell-specific helper $CD4^+$ and cytotoxic $CD8^+$ T-lymphocytes that infiltrate the islets and destroy up to 90% of the total β-cell population (1–5) The destruction of β-cells ultimately leads to the reduction of insulin secretion and eventually the induction of abnormally high levels of blood glucose in these individuals, i.e., clinical diabetes. It has been hypothesized that (i) reduced expression of self-antigen(s) in the thymus or extrathymic lymphoid organs may lead to T1D by impairing negative selection (6–8); and that (ii) defective clearance of apoptotic β-cells by macrophages is the main trigger of this disease (9–11). The subsequent activation and recruitment of T-cells to the islets, along with the increased release of proinflammatory cytokines, granzyme B, and perforin by these immune cells (12, 13), eventually drive β-cell destruction and increase the workload on surviving β-cells. This, in turn, is suggested to elevate stress in the

endoplasmic reticulum (ER), the compartment where various proteins including insulin are synthesized, exacerbating β-cell loss (14–16).

Naïve T-cells that leave the thymus, upon the failure of negative selection, are activated and differentiated into effector T-cells in the lymph nodes by antigen presenting cells (APCs) that express islet-specific autoantigens. Activation of $CD8^+$ and $CD4^+$ T-cells is determined by T-cell receptor (TCR) interaction with peptide-major histocompatibility complexes (pMHC) class I (17) and class II (18), respectively, on APCs. T-cell recognition of β-cells uses similar mechanisms, requiring TCR interaction with pMHC class I, and perhaps class II (19), molecules on the surface of β-cells. The polyclonal nature of the immune responses against multiple autoantigens (20) along with the broad spectrum of avidities (a measure of TCR-binding affinity) associated with each autoantigenic specificity make this disease a very complex one to analyze (Fig. 1). In fact, during T1D progression, autoreactive T-cells undergo a process of 'avidity maturation' (3, 20, 21), reflecting an increase in the avidity of T-cells during the course of the autoimmune response, and signifying a gain in their pathogenic potential. This process is regulated by both T-cell competition and tolerance (20). All these factors make identifying and designing therapeutic strategies for the disease, such as the monoclonal antibody-based immunosuppressive approaches (22–24) and autoimmune-specific nanovaccines (25, 26), a very challenging task.

Furthermore, in T1D, islet autoantibodies manufactured by mature B-cells of the immune system are directed against one or more host self-proteins and can serve as reliable surrogate predictive markers of the disease (27–31). The measurement of these autoantibodies is now a clear prerequisite in screening for individuals at risk of developing hyperglycemia and clinical diabetes requiring insulin for treatment, and one of the most potent risk determinants (32–35). It has been proposed that the presence of two or more autoantibodies to islet autoantigens [such as insulin, glutamic acid decarboxylase 65 (GAD65), or islet-autoantigen 2 (I-A2)] should be used as entry criteria for intervention trials (36, 37). However, the design of these trials, such as TrialNet, should be based on the understanding that over 50% of relatives who were positive for autoantibodies might not develop insulin requirement within 5 yr (27, 28, 38, 39). Therefore, predicting the rate of progression to clinical disease is still difficult and requires alternative ways to assist in the screening process. Several well-defined epidemiological studies are currently available around the world and these at risk populations represent the groundwork from which antibody risk determinants can be applied and refined. These studies include the Bart's Windsor study (40), the Joslin-Denver (35, 41, 42), Pittsburgh (43), Seattle (44), Gainesville (45), and a number of other important family studies (46, 47). T1D is the quintessential model for the application of autoantibody markers in the prediction of a selective immune-mediated tissue damage, and this concept can be theoretically extended to other chronic autoimmune diseases.

Developing predictive mathematical models to understand the immunological processes underlying the onset and progression of T1D is an alternative and powerful method to achieve this goal. Typically, these models are expressed as ordinary differential equations (ODEs) that describe the temporal dynamics of the population sizes of immune cells, as well as the concentrations of autoantigens and autoantibodies implicated in the disease. They are either analyzed theoretically using mathematical methods or simulated numerically using computational tools to examine their short- and long-term (steady-state) behavior. It is anticipated that these models, when perfected and validated against experimental data, can eventually serve as diagnostic tool(s) of the disease in clinical settings.

In this review, we summarize recent findings associated with MHC class II genetic susceptibility in T1D, and present an overview of the literature on modeling different aspects of the disease. We highlight how these mathematical models were utilized to make predictions and important insights about the various components implicated in the disease. We also propose new directions in the investigation of T1D progression and treatment using these theoretical approaches.

Single pMHC class II complex is critical for T1D

Peptide binding and presentation by MHC class II is essential for $CD4^+$ T-cell activation. Peptides are typically anchored onto the MHC class II binding cleft through their amino acid side chains at four positions, termed pockets P1, P4, P6, and P9, which also interact with the flanking alpha helices of the MHC molecule to stabilize the pMHC complex (48). Comparison of MHC class II alleles in genome-wide single-nucleotide polymorphism (SNP) studies showed surprisingly conserved MHC sequences with the exception of a few amino acid alterations in the flanking alpha helices. Disease-promoting alleles of the gene encoding for the human MHC class II β chain have amino acid alterations characterized by the replacement of a positively charged residue, such as aspartic acid (ASP) near the P9 position of the peptide-binding pocket, with a non-charged amino acid serine (SER) or alanine (ALA) (49, 50). This results in a net-positively charged P9 pocket, as SER and ALA cannot neutralize the charge imparted by the opposing

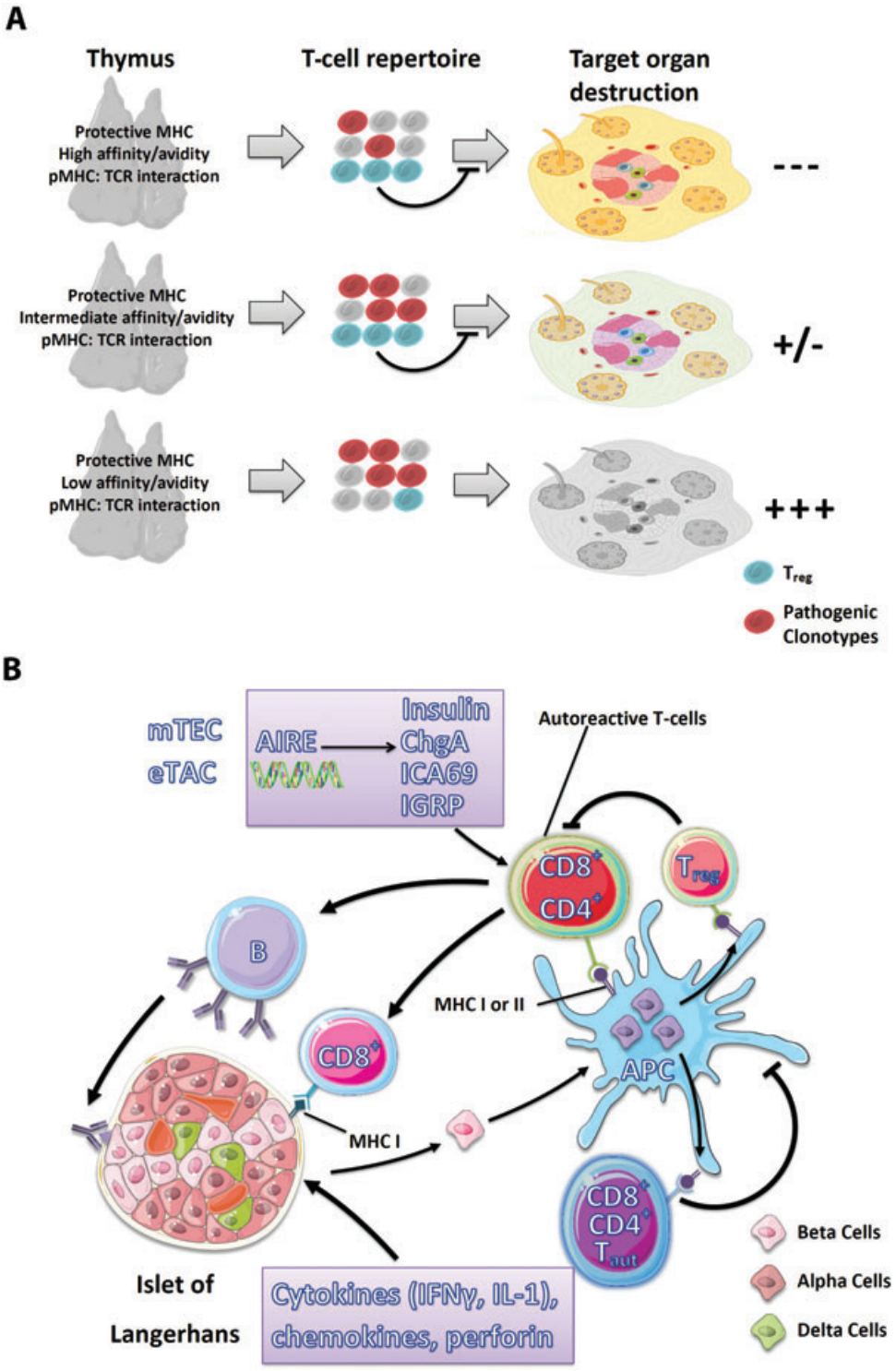

Fig. 1. (A) A scheme showing the effect of high/intermediate/low avidity/affinity T-cell receptor–peptide-major histocompatibility complexes (TCR-pMHC) interaction. High affinity/avidity interaction leads to deletion of most autoreactive T-cells, creating a T-cell repertoire that is low in pathogenic and high in regulatory T-cells (T_{regs}), resulting in healthy state without islet destruction. Intermediate affinity/avidity interaction results in a T-cell repertoire contain not only a higher portion of pathogenic T-cells, but also a high number of T_{regs}. This results in limited islet destruction, because the T_{regs} limit the destructive effects of the pathogenic T-cells. Low avidity/affinity interaction results in T-cell pool containing many autoreactive T-cells with few T_{regs}. This results in autoimmune state where most islets are destroyed. (B) A scheme showing the various components of the autoimmune response in T1D including the Copenhagen model. The uptake of β-cell specific proteins by antigen presenting cells (APCs) triggers APC recruitment and activation. This in turn leads to the activation of various classes of islet-specific $CD4^+$ and $CD8^+$ T-cells [i.e., T_h-lymphocytes, T_{regs} and autoregulatory T-cells (T_{aut})], as well as B-cells. High-avidity cytotoxic T-lymphocytes destroy β-cells by either secreting harmful cytokines or by inducing apoptosis via cell-to-cell contact. Mature B-cells release islet-specific autoantibodies that may appear prior to disease onset.

alpha helix. Alignment of the murine disease-protective I-Aβ chain and the disease-promoting counterpart I-$A\beta^{g7}$ (the only MHC class II chain in NOD mice) show similar amino acid alterations. Interestingly, it was shown in studies of MHC class II polymorphism that transgene expression of the protective I-Aβ allele in NOD mice completely ablated the development of diabetes (51).

It is expected that modifying the affinity of peptide binding can have significant implications on other aspects of MHC class II mediated processes. For example, it was demonstrated that disease-promoting MHC class II molecules bind a different set of peptides than those that bind to the disease-protective MHCs, with the former favoring the binding (with high affinity) of peptides carrying an acidic side chain at the C-terminus, thereby impairing their binding to certain self-peptides (52, 53). Therefore, it was proposed (52) that negative selection in the thymus is governed by the affinity/avidity of the interaction between pMHC and TCR (Fig. 1A). High affinity interaction of autoreactive T-cells to MHC presented by APCs and epithelial cells in the medulla of the thymus promotes deletion through negative selection and/or the development of regulatory T-cells (T_{regs}). These processes dampen the autoimmune reaction by reducing the size of the pathogenic T-cell population and imparting suppressor function to those that survive. The change in peptide affinity and peptide-binding repertoire in disease-promoting MHCs is thought to decrease the affinity/avidity of this interaction and thus compromise thymic negative selection, leading to the escape of autoreactive T-cells that lack suppressor function from the thymus. In the pancreas, the increased exposure to self-peptides eventually leads to the activation of islet-reactive T-cells and the demise of β-cells.

This hypothesis was supported by studies on the binding of a dominant autoantigenic peptide in NOD mice: the insulin β-chain (B:12–23). It is known that this 12 amino acid peptide can bind the NOD MHC class II I-$A\beta^{g7}$ in four positions or 'registers'. Binding in register 3, where B:14–22 are anchored in the peptide-binding pocket, is the least favorable biochemically due to the charge clash between arginine (ARG) and the positively charged P9 pocket of I-$A\beta^{g7}$. Surprisingly, binding at this register was found to be most immunogenic to Barbara Davis Center for Childhood Diabetes (BDC) 12–4.1 T-cells, the cognate T-cell against insulin B:12–23 (54). It is possible that the low-affinity binding can cause poor or low presentation during negative selection, allowing pathogenic T-cells recognizing self-peptides, to survive. Further, it was shown that T-cells recognizing B:12–23 in register 3 are pathogenic while populations that recognize the same peptide presented in other, more favored registers, are protective and non-disease-promoting (55).

Insulin, despite being one of the primary antigenic targets for T-cells in NOD mice, can only stimulate anti-B:12–23 T-cells when presented by islet-resident APCs (14, 56). In addition, owing to the low-binding affinity of B:12–23 peptide to the immunogenic register, the physiological concentration of insulin in circulation is not enough to lead to any immune stimulation even in NOD mice. In the pancreas, however, APCs can engulf vast amounts of insulin produced by β-cells and present antigens above the threshold of activation for autoreactive T-cells.

Most proteins undergo post-translational modifications (PTMs), a process which has shown some association with autoimmunity. Some PTMs can create new autoantigens or mask antigens normally recognized by the immune system. Differential antigen processing that may result from the PTMs is another process that can affect the onset of autoimmune response. While no direct evidence of PTMs in T1D has been observed, discussion of the effect of PTMs in the context of other autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, and celiac disease, can be found in other reviews (57, 58).

Modeling the role of APCs in T1D

The involvement of APCs, including macrophages, in the onset of T1D remains an outstanding question. It has been suggested that these cells play an important role in phagocytizing dead β-cells that have been destroyed because of external or internal environmental factors, such as the naturally occurring β-cell apoptotic wave observed in rodents and primates during the neonatal period (59, 60). A mechanism underlying this autoimmune process was first proposed by Nerup et al. (61, 62) in the Copenhagen model describing the onset and progression of this disease (see Fig. 1B). The model conjectured that protein uptake by APCs trigger autoantigen processing, pMHC class II expression, and further APC recruitment and activation. This in turn caused monokine secretion by activated APCs, such as interleukin (IL)-1 and tumor necrosis factor (TNF), as well as upregulation of costimulatory signal(s), leading to the induction of cytokine secretion from islet-specific $CD4^+$ helper T-cells (T_h)-lymphocytes, such as IFN, and further APC activation. It was then hypothesized that β-cell destruction (or apoptosis) is caused by either the induction of free radicals by cytotoxic IL-1 release from APCs and/or the upregulation of Fas receptor (a member of the tumor necrosis factor receptor superfamily) expression on β-cell surface and its increased interaction with Fas ligand on infiltrating lymphocytes. One would then expect that these two

latter processes amplify the autoimmune response and cause further damage to the tissue.

A mathematical formulation based on the Copenhagen model was developed by Freiesleben De Blasio et al. (63) to test the model and determine if certain components are predominantly responsible for triggering T1D. The model was described in the form of ODEs portraying the rate of change of two interacting populations of macrophages, a resting population not expressing islet-specific pMHCs and an active population expressing pMHCs, along with one population of T_h-lymphocytes, and the total expression level of pMHCs. The model showed that T1D susceptibility is due to dynamic instability in the system as a whole, rather than one single etiological trigger. In fact, it was demonstrated that in healthy conditions, i.e., in the non-disease state, the population sizes of all these immune cells ultimately vanish, but under certain immunological conditions, generated by applying perturbations to the parameters of the system, the healthy state loses stability and the disease is manifested.

Further extensions of the Freiesleben De Blasio model were subsequently reported (64, 65). More specifically, a direct description of β-cells was included (64), instead of considering only the expression level of autoantigen(s). In this study, it was shown that disease dynamics of T1D critically depend on the rate of β-cell turnover (i.e., the difference between β-cell replication/neogenesis and death), which in turn depends on the organ developmental stage of the pancreas. As such, it was suggested that the slow and fast turnover of β-cells are responsible for the age-dependent heterogeneity observed in T1D pathology, an outcome that is in agreement with clinical observations. The oscillatory decline of β-cell number to zero, however, made this modeling study less physiological. A different mathematical model (65) combined the Freiesleben De Blasio model with the β-cell model described glucose and insulin effects on β-cell mass (66). The end result was a model of early stages of the disease that was composed of both an autoimmune and metabolic components. When examining the degenerative and autoimmune-induced loss of β-cells, the study found that depending on the degree of regulation, autoimmunity may play a protective role in the initial response to stressors.

Although the Freiesleben De Blasio model (63) and these follow-up studies (64–66) provided important qualitative insights about the mechanisms underlying susceptibility, they were mostly phenomenological, and represented only an approximation of the real physiological system. For these reasons, several models were subsequently developed to address certain aspects of macrophage complicity in the initiation of the disease (9–11). One of these aspects is the defective clearance of apoptotic β-cells by macrophages, which was further analyzed by developing several Markov state models (67, 68) that described the process of macrophage encounter and engulfment of up to N (=7 or 12) apoptotic cells (Fig. 2). Each state in these models represented the class of macrophages (M_i) with a given number ($i \leq N$) of engulfed apoptotic cells inside them, and the transitions between them were assigned the rate constants k_a, k_e, and k_d. The main focus of both of these studies was to determine what properties of macrophage phagocytosis (including engulfment, degradation, and/or activation) are altered in NOD mice prone to T1D in comparison with wild-type mice, and to quantify the level of impairment. According to these studies, it was found that macrophages from normal (Balb/c) mice engulf apoptotic cells 2.6–5.5 times faster than those in NOD mice (67, 68), and that the digestion of apoptotic cells is not only serial (i.e., the backward digestion rate in Fig. 2 is constant k_d), but also at least two times slower in NOD than in Balb/c macrophages (67). Interestingly, an activation step and an acceleration in subsequent engulfment steps were found to be exhibited in both strains, except that they are smaller in NOD than in Balb/c macrophages (67). These results were obtained by applying steady-state analysis and fitting model simulations to *in vitro* macrophage feeding experimental data that included two measurable quantities: the percent of macrophages that have visible engulfed cells and the average number of engulfed cells per 100 macrophages.

These results were further tested (69) by considering and quantifying variants of the Freiesleben De Blasio model (63) based on parameter values obtained for NOD and (normal) Balb/c mice (68). The goal was to determine whether macrophage defects alone are sufficient for triggering chronic inflammation, or if the apoptotic wave of β-cells (59, 60) is also necessary for initiating T-cell priming associated with full-blown disease. The results revealed that the Freiesleben De Blasio model cannot quantitatively explain these observed results within biologically reasonable parameters, even if other strain-specific variations are included (e.g., differences in macrophage-induced rate of damage to β-cells). However, when the model was modified, by taking into account the ability of necrotic β-cells, i.e., β-cells destroyed by harmful monokines secreted by activated NOD macrophages that failed to promptly remove apoptotic β-cells (70), the results were qualitatively and quantitatively consistent with the observed differences between NOD and Balb/c macrophages. In other words, it was shown that the apoptotic wave can trigger escalating inflammatory response in NOD, but not Balb/c mice. One important feature in this study was the inclusion of a more physiologically reasonable assumption regarding monokines namely that they induce apoptosis in β-cells with saturating kinetics.

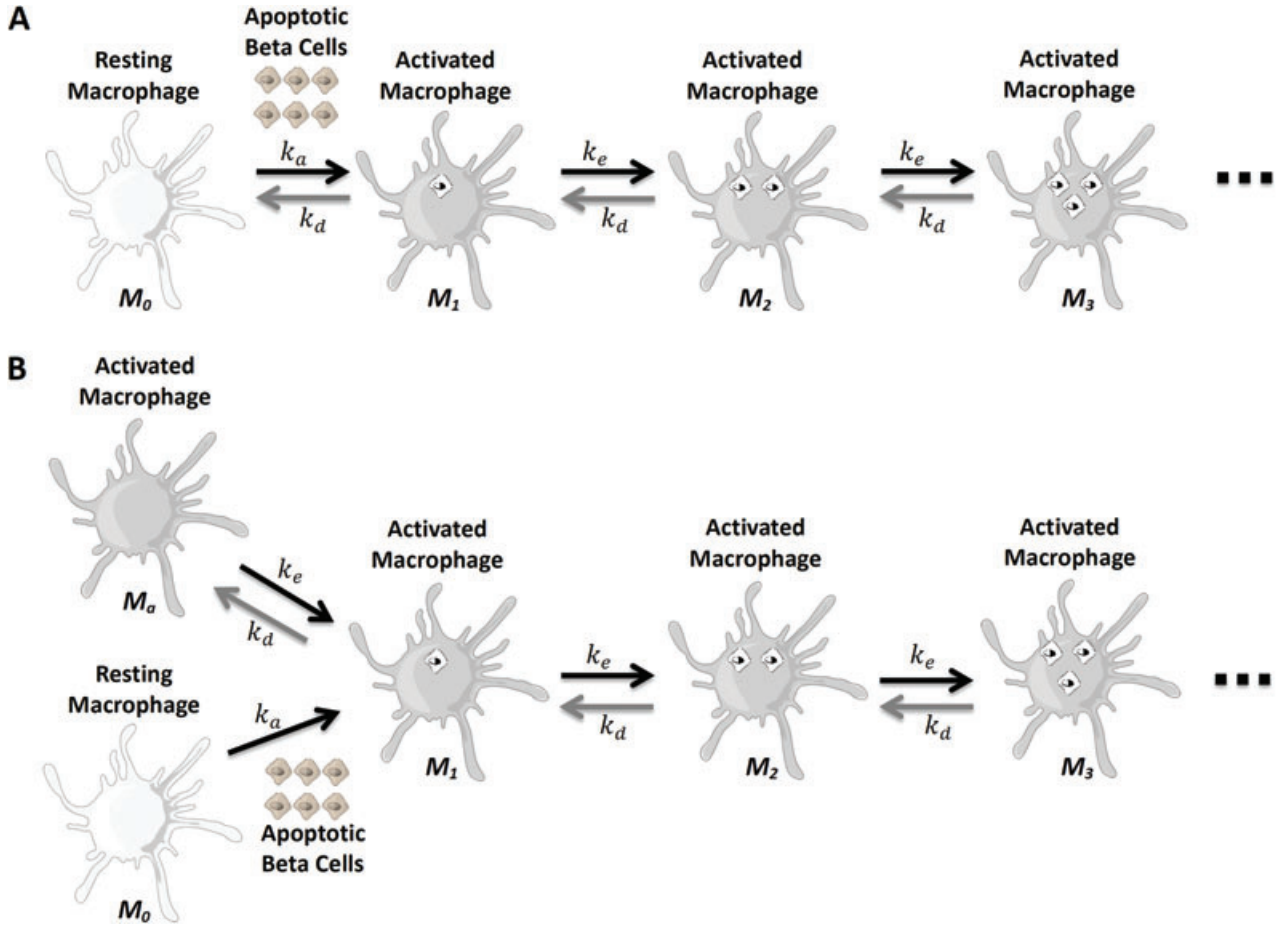

Fig. 2. Two possible Markov models describing the dynamics of phagocytosis in macrophages. Macrophages may have up to N undigested apoptotic cells inside them. Both models require an activation step of naïve macrophages with an activation rate constant k_a. The forward transitions (excluding the first step), representing the engulfment of new apoptotic cells, occur with a rate constant k_e, whereas the backward transitions, representing digestion, occur with a rate constant k_d. (A) The activation step is assumed reversible. (B) The activation step is assumed irreversible.

A molecular-based model, also in the form of ODEs, describing the processing of β-cell specific proteins in APCs, particularly macrophages, was also developed to examine why certain proteins, such as islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP), take on a dominant autoantigenic role, whereas many others do not (71). This model was based on the defective ribosomal product (DRiP) hypothesis (72), suggesting that significant fraction (over 30%) of proteins are degraded by proteasomes shortly after their synthesis, presumably due in large part to their inability to achieve a functional state. The model analyzed and quantified the interplay between antigenic stability and pMHC class I production efficiency in determining pathogenic potential of autoantigenic proteins, including IGRP, in the context of autoimmune T1D. The model examined proteins allocated to rapidly degraded vs. stable functional pools, both contributing (with relative efficiency η) to pMHC presentation on a β-cell, as well as to cross-presentation on an APC. By applying local stability analysis on the model, the study concluded that autoantigenicity (the ability to elicit T-cell activation) and pathogenicity (the ability to cause β-cell lysis) are not equivalent, and that pathogenicity peaks at low-to-moderate levels of autoantigenicity. The intriguing outcomes of this study, considered to be the first to explore the link of the DRiP hypothesis to autoimmunity, remain untested experimentally.

Modeling T-cell dynamics during T1D progression

Over the last few years, several mathematical models of T1D progression have been also developed in the form of ODEs. The two main goals in conducting these quantitative studies were to explore possible mechanisms underlying the role of $CD4^+$ and $CD8^+$ effector and (auto-) regulatory T-cells in diabetogenesis, as well as to analyze and optimize the effect of certain interventional therapies to T1D.

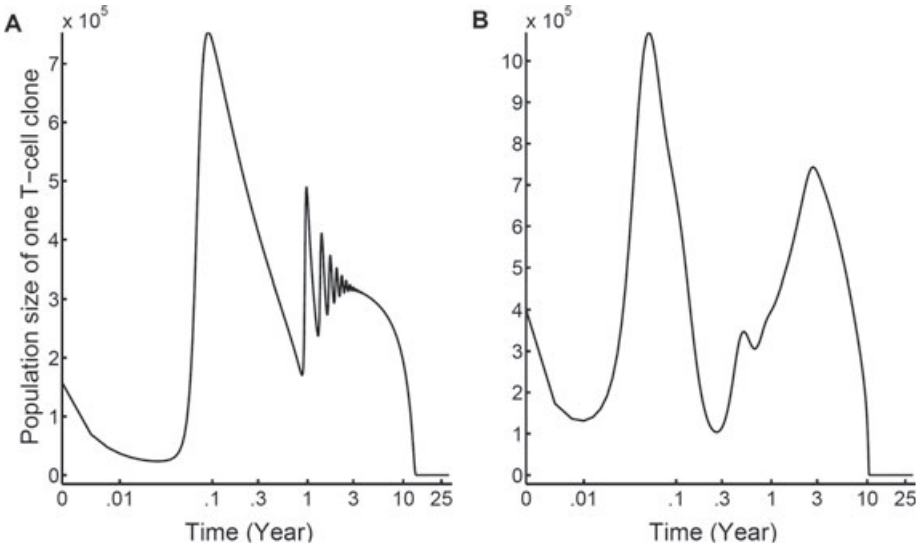

Fig. 3. Cyclic fluctuations in the pool size of effector T-cells with a given autoantigenic specificity, as predicted by the model (see reference (80)). (A) Periodic damped oscillations with high frequency. (B) Low-frequency cyclic waves with few peaks that correlate with the number of clones considered in the model.

Modeling studies of T1D progression initially started with the analysis of why soluble peptides, such as the protein fragment $IGRP_{206-214}$ intended to induce peptide-specific T-cell tolerance (73–75), mostly failed to blunt poly-specific autoimmune responses. For example, it was shown that despite effectively deleting the $IGRP_{206-214}$-reactive $CD8^+$ pool, the administration of a mimotope of $IGRP_{206-214}$ to NOD mice does not protect them from T1D (20, 73). A model consisting of (two) competing clones of T-cells, with various levels of avidities, showed that the success or failure of this treatment depends on how dose and peptide affinity alter T-cell activation, proliferation, and differentiation (76). More specifically, the model revealed that peptide treatment can lead to either an increase in the imbalance between competing $IGRP_{206-214}$-reactive T-cell clones, favoring rapid takeover of high-avidity clones, or the deletion of all $IGRP_{206-214}$-reactive clones, thereby creating a vacuum that promotes the recruitment of pathogenic subdominant specificities (also called the switch phenomenon). In the case of successful treatment, the model predicted that the imbalance between the competing clones of $IGRP_{206-214}$-reactive T-cells fosters the expansion and recruitment of low-avidity (non-pathogenic) clones instead.

This study was later extended to examine why $IGRP_{206-214}$-reactive $CD8^+$ T-cells in NOD mice eventually develop diabetes exhibit cyclic fluctuations in their proportion relative to other $CD8^+$ T-cells (77). This phenomenon was investigated quantitatively and phenomenologically by using a population model of T-cells, consisting of active, memory and effector cells, as well as β-cells (78). The study showed that these limited number of cycles (that exhibited an increase in period, nadir and amplitude at each cycle) occur when the activation of effector T-cells is assumed to increase and the production of memory cells to decline with the autoantigen level induced by a reduction in the clearance of apoptotic debris (67). Although the study was very insightful in providing a plausible mechanism for these oscillations, there were two major drawbacks; namely, the severe sensitivity of the oscillations produced by the model to small perturbations in the initial number of T-cells at the start of the autoimmune attack, and the inability of the model to reproduce the increase in the nadir at each cycle. Given that the presence of these oscillations is consistent with the relapsing-remitting nature of T1D (79), our recent analysis revealed that interclonal and intraclonal T-cell competition (possessing various levels of avidity and autoantigen specificity) are the driving force for generating such transient fluctuations (Fig. 3). Using a model that is structurally similar to another previously reported (78), we discovered that, in the presence of four competing subclones with two antigenic specificities and four ascending levels of avidity, robust fluctuations in the number of T-cells, consistent with the observed experimental behavior, are produced as either dampened periodic cycles with relatively short periods (panel A), or transient (two) waves with long periods (panel B). Details of this study are available in (80).

Recent studies by Santamaria et al. (5, 25, 26, 81) demonstrated that low-avidity autoreactive $CD8^+$ T-cells spontaneously differentiate during T1D progression into non-pathogenic memory autoregulatory T-cells specific for particular Islet Antigens. It was suggested that the expansion of this population to therapeutic levels can blunt T1D in NOD

mice. This could be performed using nanoparticles (NP) coated with pMHC class I complexes that selectively induce the expansion, in an antigen-specific manner, of low-avidity memory autoregulatory $CD8^+$ T-cells (25, 26). These $CD8^+$ T-cells suppress diabetogenic, islet-specific effector T-cells in the pancreatic lymph nodes. As a result, treatment with NP could both prevent T1D and restore normoglycemia.

Modeling these aspects of the autoimmune response and optimizing the therapeutic effects of NPs have become a fascinating new direction in the field of modeling autoimmune T1D. More specifically, the protective role of the low-avidity autoregulatory memory $CD8^+$ T-cells was investigated by developing a series of differential equation models for (i) the interactions of low-avidity autoregulatory and high-avidity effector $IGRP_{206-214}$-reactive T-cells, (ii) the effect of APCs in T-cell activation, and (iii) the positive feedback from killed β-cells (82). The models were used to test two independent hypotheses supported by *in vivo* and *in vitro* experimental data. The first hypothesis suggested that the memory T-cell pool crowds islets and outcompetes effector high-avidity $CD8^+$ T-cells, whereas the second hypothesis suggested that APCs get deleted by this memory T-cell pool (26). The results showed that the steady-state level of β-cells in the former case increases much more rapidly (see Fig. 4), an outcome incompatible with data, strongly suggesting that the latter hypothesis is more likely. These models were then used to examine the influence of various treatment strategies based on NPs coated with β-cell-specific pMHC and targeted towards expanding autoregulatory T-cells, on the progression of the disease. The model revealed that progressive accumulation of memory T-cells during disease progression makes treatments aimed at expanding these protective T-cell types more effective close to or at the onset of clinical disease.

This study was then expanded to a protocol, based on a data fitting method called the genetic algorithm, which was devised for providing parameters for the model using *in vivo* experimental data obtained from NOD mice (83, 84). Heterogeneity along with the type and paucity of data made, and continue to make, this a challenge. The models developed in these studies included a class of subdominant non-$IGRP_{206-214}$-reactive T-cells in addition to those clones considered (82). These models were used to understand the dynamics of competition between T-cell pools and their role in inducing the switch phenomenon (Fig. 5), to predict the outcome of pMHC-NP therapy, and as a guide to optimize treatment frequency, dose and pMHC-NP valency (the expression level of pMHC on NPs). It was shown, e.g., that increasing the frequency of injection is therapeutically more effective than increasing the dose (83) and that a moderate

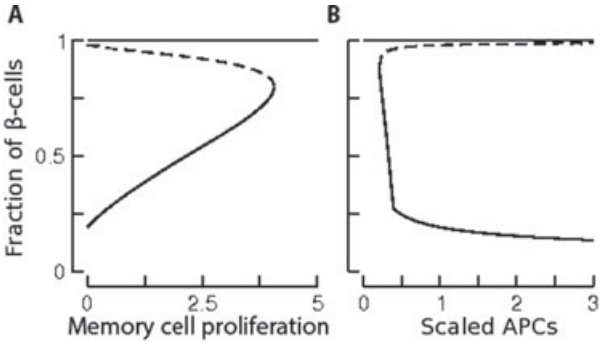

Fig. 4. The steady-state level of the fraction of surviving β-cells (β_{ss}) predicted by the model (see reference (82)) based on two independent hypotheses: (A) memory autoregulatory T-cells crowd the islets and block effector T-cells from reaching β-cells; and (B) memory autoregulatory T-cells kill antigen presenting cells (APCs). Solid lines represent the physiologically attainable steady states, whereas dashed lines represent the physiologically unattainable steady states. The horizontal solid lines in both panels represent the healthy and unaltered $\beta_{ss} = 1$, in the absence of autoimmunity, whereas the other solid lines represent $\beta_{ss} < 1$ in the presence of autoimmunity. Notice that increasing the proliferation rate of memory autoregulatory T-cells in (A) causes a rapid rise in β_{ss} in the autoimmune case, whereas decreasing the scaled pool size of APCs induces a slow increase, suggesting that the latter is more physiological.

increase (≥1.6-fold) in the NP-dependent expansion rate of autoregulatory T-cells leads to a significant increase in the efficacy and the area corresponding to the effective treatment regimen provided that NP dose is ≥8 μg (84). By taking into account the underlying hypothesis that the expansion of autoregulatory T-cells and deletion of autoantigen-loaded APCs by these T-cells are biphasic (increases at low NP doses and decreases at high NP doses) (84), resonance-like behavior was observed in these models, and ranges in pMHC-NP valency, exhibiting no autoimmunity, were also identified. The importance of the models presented in both of these studies arise from the fact that they could be generalized to other autoimmune disorders and could eventually serve as computational tools to understand and optimize pMHC-NP-based therapies in these diseases.

A limited number of models examining the role of ($CD4^+FOXP3^+CD25^+$) T_{regs} in the progression of T1D have also been developed. A mathematical model that takes into account the dynamics of functional and dysfunctional β-cells, T_{regs}, and pathogenic T-cells was presented (85) to understand the impact of altering the balance between pathogenic T cells mediating T1D and T_{regs} on autoimmunity (86). The model provided that quantitative information on how the ratios of pathogenic T-cells to T_{regs}, as well as other kinetic parameters, affect the timing of disease onset and progression. The drawback of this study was the assumption that T_{regs}, contrary to experimental evidence, secrete IL-2. Another similar study that extended the Freiesleben De Blasio model by including

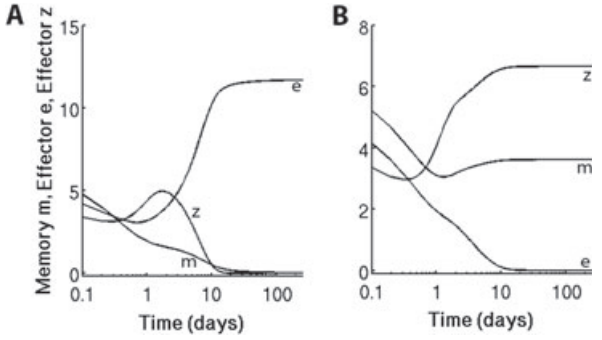

Fig. 5. Increasing the proliferation rate of memory autoregulatory T-cells (T_{aut}) (denoted by m) may lead to the switch phenomenon. (A) At a low T_{aut} proliferation rate, the level of islet-specific glucose-6-phosphatase catalytic subunit-related protein ($IGRP_{206-214}$)-reactive effector T-cells is elevated. (B) At a high T_{aut} proliferation rate, the total level of other subdominant effector T-cells is elevated.

the dynamics of T_{regs} was also conducted to address the same questions (87).

Models of islet autoantibodies

Autoimmune T1D is associated with a series of conventional and novel anti-islet autoantibodies, produced by mature B-cells that may be present for years in high-risk subjects (HRS), i.e., first degree relatives of T1D patients, prior to the onset of hyperglycemia. It has been suggested (79) that these autoantibodies accumulate sequentially and gradually during epitope spreading associated with disease progression. Recent studies revealed that novel autoantibodies, such as those against the extracellular domain of I-A2, have a success rate of 100% in predicting disease onset in HRS within 10 yr of follow up, unlike conventional autoantibodies (e.g., against GAD65) that require 15 yr of follow up for only 74% predictive rate (i.e., 74% of HRS develop the disease within 15 yr) (27, 34). The former group was labeled as fast progressors and the latter slow progressors. Using data collected over at least 13 yr from cohorts of children at risk of T1D in various countries, a new detailed study (35) revealed that T1D incidence at 10-yr follow-up after seroconversion in children with multiple islet autoantibodies is 69.7%, with a single islet autoantibody is 14.5%, and with no islet autoantibodies is 0.4% (by the age of 15 for the latter group). It was also found that T1D progression in children with multiple islet autoantibodies is age-dependent, being faster in children who seroconverted at less than 3 years of age than children who seroconverted at 3 yr or older.

The first modeling attempt in analyzing these intriguing experimental results was quantitatively performed in the T_{regs} study described in the previous section (85). In this model, the production of pathogenic T-cells was assumed to be the sum of a sequence of step functions that correlated with the sequential appearance of autoantibodies during T1D. Although the study did not consider the dynamic behavior of autoantibodies and B-cells that produce them, it provided some insights into how β-cell loss is manifested when 1–3 autoantibodies appear in circulation.

A subsequent study was then performed to analyze more systematically the role of islet-specific autoantibodies in predicting disease onset in HRS (83). The main goal of the study was to test the hypothesis that heterogeneity in both TCR-binding affinity (T-cell avidity) and killing efficacy (i.e., the rate of T-cell dependent β-cell lysis) is responsible for inducing clinical differences between fast and slow progressors of T1D. A series of competition-based population models, in the form of ODEs, that accounted for T-cell, B-cell, β-cell, autoantigen, and autoantibody dynamics were presented in this study. The models revealed that low-avidity, low-efficacy T-cell clones can compete with high-avidity, high-efficacy clones to confer a degree of protection. Moreover, by assuming that T- and B-cell avidities are correlated (i.e., the binding affinity of TCRs and autoantibodies are correlated), the study showed that, on average (over a heterogeneous population of individuals, each represented by a set of parameters with physiologically reasonable values), an increase in avidity leads to faster β-cell destruction and rise in islet-autoantibodies over time, but the peak amplitude of the autoantibody titer is most pronounced at intermediate avidities (see Fig. 6). Interestingly, when both T-cell avidity and killing efficacy were assumed to be very high, and perhaps higher than their physiological limits, the autoantibody level remained undetectable throughout disease progression due to the lack of peptide accumulation necessary for T- and B-cell activation. This study was then extended by considering multiple clones of T- and B-cells to show how competition induces cyclic fluctuations in T-cells, underlying relapse-remission in T1D, and how these fluctuations regulate sequential accumulation of islet-autoantibodies (80).

Discussion and future directions

Understanding autoimmune responses in the context of T1D using experimental tools can be very daunting. With the emergence of the field of computational biology and non-linear dynamics, the complex systems regulating these responses can be analyzed theoretically. Examining various aspects of these immunological systems by developing mathematical models and designing computational tools to investigate them represents an alternative and cost-effective way to do so. These models not only provide important insights into the cellular and molecular processes occurring in these systems, but

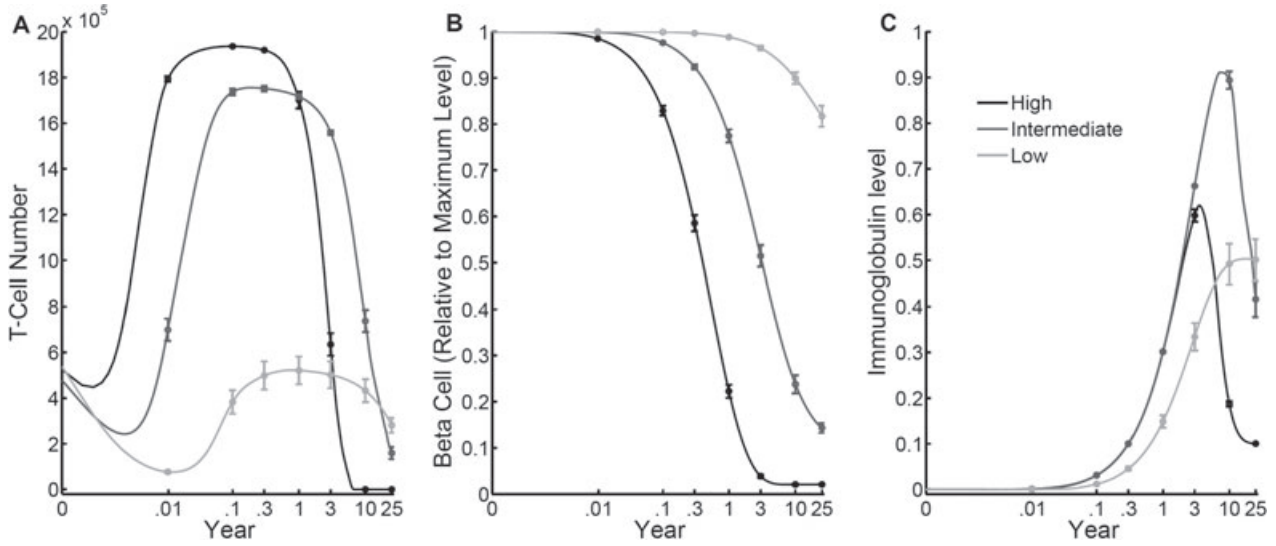

Fig. 6. Increasing T-cell avidity on average leads to a faster β-cell destruction, a faster rise in cognate autoantibodies, and a biphasic response in the peak amplitude of the autoantibody titer. Time evolution of (A) the average pool sizes of high (black), intermediate (dark gray), and low (light gray) avidity T-cells. (B) Fraction of surviving β-cells in the presence of high (black), intermediate (dark gray), and low (light gray) avidity T-cells. (C) Scaled titer level of cognate high (black), intermediate (dark gray), and low (light gray) affinity autoantibodies.

they also raise intriguing mathematical questions that are tackled numerically using computational tools or theoretically using methods of non-linear stability analysis. In this review, we presented a summary of the most recent advances and major contributions made using mathematical models to this field.

Several questions associated with T1D onset and progression were tackled, including the role of macrophages, pathogenic $CD4^+$ and $CD8^+$ autoreactive T cells, (auto)regulatory T cells, B cell, and β-cells. The models constructed and used were mostly ODE models that described the temporal dynamics of the various factors involved in the processes under investigation. Although the predictions and insightful conclusions made by these studies helped direct new experiments in the field, validating these models against experimental data collected from animal models and extending them to human-based data still remain a challenge. There are, however, several statistical methods available in the literature that can be used to probabilistically validate these models and determine their implications in understanding how these immunological systems work. Certainly, there are still many open questions in the field of autoimmunity and T1D that mathematical modeling could undertake.

The vital role of T-cell avidity in determining the course of the autoimmune response in T1D is quite evident experimentally. Typically, in these experimental studies, T-cells are divided into (sub)clones possessing different levels of avidity that is measured by their sensitivity to peptide-dependent activation (88, 89). Fluorescence-activated cell sorting (FACS) plots in most of these studies, however, show that ($CD4^+$ and $CD8^+$) T-cells exhibit a whole spectrum of reactivity to autoantigenic peptides. In other words, T-cell avidity in the physiological sense is not a discrete quantity, but more likely a continuum that covers a whole range of values. In all of the T-cell models developed so far to analyze the T1D progression, avidity was taken to be discrete, generating distinct classes of T-cell clones and ODEs to describe them dynamically. It will be interesting to extend such models to integro-differential equations by making avidity an independent variable in order to generate more physiological models that can be used to examine the polyclonal nature of T1D, determine the underlying mechanism of avidity maturation, and explore ways to manipulate the disease for therapeutic purposes.

Another important step in the study of T1D using these quantitative approaches is to combine models of disease initiation (describing macrophage involvement) with models of disease progression (describing the involvement of the adaptive immune system) to see how they influence each other and how they affect β-cell destruction and ER stress including the unfolded protein response (16). The difficulty of achieving this experimentally, especially *in vivo*, makes mathematical modeling a very attractive approach to explore the interaction between these two components of the disease at various stages. Dealing with the complexity of the model will certainly be a challenge, but the fact that the dynamics of its different components are well understood makes this step feasible.

As indicated in the review, two important factors have not been addressed so far by the modeling community; namely, the effect of various cytokines in T1D onset and progression along with the role of age in determining the timing of seroconversion and

the severity of the disease. The magnitude of β-cell destruction will depend on the velocity of the feedback circuit between APCs and the T_h-lymphocytes, i.e., the efficacy of antigen transport/presentation/recognition, on the magnitude and type of cytokine production, and on the capacity of β-cell defense mechanisms during the cytokine exposure. B-cell activation and autoantibody production during these processes will also require the involvement of certain cytokines. Developing models that explicitly describe the dynamics of cytokines would be an important step towards deciphering their function in T1D and in defining the role of age in the autoimmune response.

It should be mentioned here that there exists a large volume of modeling papers that focus on the electrophysiological properties of β-cells, and how they are affected in disease conditions. We refer the reader to a recent review on this topic by Ajmera et al. for more details (90).

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