Immunology and Cell Biology (2013) 91, 333–334

www.nature.com/icb

NEWS AND COMMENTARY

Autoimmunity treatment using pMHC-NP-based therapy

Designing nanoparticle treatment of autoimmunity with quantitative biology

Santiago Schnell and Massimo Pietropaolo

Immunology and Cell Biology (2013) **91,** 333–334; doi:10.1038/icb.2013.20; published online 23 April 2013

Quantitative biology offers enormous potential in the biomedical sciences through the use of mathematical models. These models are indispensable for understanding nonlinear systems, which are characterized by feedbacks that produce outputs that are not proportional to their inputs.[1] In this issue of *Immunology & Cell Biology*, Sugarman *et al.*[2] present a mathematical model of a peptide-major histocompatibility complex (pMHC)-nanoparticle (NP)-based therapy for Type 1 diabetes (T1D) to understand and optimize treatment conditions in the non-obese diabetic (NOD) mice. This model exemplifies both the surprising behavior of nonlinear systems and the power of quantitative biology in medicine.

Defects in memory autoregulatory $CD8^+$ T-cell homeostasis, peripheral activation and function play a role in the chain of events leading to islet autoimmunity in T1D. The ability to actively suppress a beta cell-specific autoimmune response makes autoregulatory $CD8^+$ T cell an attractive therapeutic alternative for treating T1D. Autoregulatory $CD8^+$ T cells originate from naive low-avidity T-cell precursors and can be expanded using NPs coated with specific pMHC Class I complexes.[2]

The mathematical model of Sugarman *et al.*[2] describes the effects of the therapeutic efficacy of NP treatment on three populations of $CD8^+$ T cells: reactive memory autoregulatory T-cells, reactive high-avidity effector T-cells and effector islet-specific autoreactive T-cells. A population of antigen-presenting cells (APCs) expressing $IGRP_{206\text{-}214}$-MHC is also included to reflect their deletion by autoregulatory T-cells. They relied on one factor to investigate the therapeutic efficacy of NP treatment: the dose of NPs coated with specific pMHC Class I complexes. After estimating the parameters that describe the rates of change of the APC and three T-cell populations in the average mouse, Sugarman *et al.*[2] performed a systematic analysis of the model.

Sugarman *et al.*[2] discovered that the mathematical average mouse model can exhibit two equilibrium states, which depend on the pMHC-NP concentration (Figure 1). The first is a healthy state, in which the total effector T-cell population is extinct. The second is an autoimmune state, in which the total effector autoreactive T-cell population is elevated. This result is in agreement with previous models by Khadra *et al.*[3,4] and the presence of healthy and diabetic individuals in the NOD mice model population following boosting of memory-like autoregulatory T cells.[5] The surprising model result comes from increasing the pMHC valency (expression level of pMHC) in the NPs. There is a valency threshold ($>42.5\,\mu g$) that abruptly and discontinuously destroys the autoimmune equilibrium state, creating only one equilibrium state in the population: a healthy state (Figure 1). Immunologically this result suggests that there is a threshold value of pMHC-NP optimal dose in NP-dependent expansion rate of autoregulatory T-cell population leading to a significant increase in the treatment efficacy. This abrupt change in the model behavior is 'the last straw that breaks the camel's back', something typically observed in nonlinear systems.[1] The model analysis shows that the effectiveness of the p-MHC-NP therapy relies on two important factors: (i) the expansion of $CD8+$ memory autoregulatory T-cells that are reactive to the pMHC complex coated onto the NPs, and (ii) the ability of this pool of autoregulatory T-cells to delete APCs expressing the same pMHC. Both factors are responsible for the nonlinear behavior reported in Sugarman *et al.*[2]

The majority of the quantitative biology models in the literature are limited to the investigation of the behavior of the average organism. To avoid this limitation, Sugarman *et al.* expanded their analysis by considering a population of 100 'model mice'. Each 'mouse model' has a set of random parameter values and initial conditions from physiologically reasonable ranges, which display heterogeneity within the mouse population. The analysis shows that around 81% of the mice are responsive to the treatment, while 19% are nonresponsive. In both the response and nonresponsive groups, the pMHC-NP treatment leads to an increase in the size of the $CD8^+$ NRP-V7 reactive memory autoregulatory T-cell population, and a decline in the size of both the $CD8^+$ NRP-V7 reactive high-avidity effector T-cell population, and $CD8^+$ effector islet-specific autoreactive T-cell population. However, there are some significant quantitative differences between the responsive and nonresponsive model mice. After analyzing such differences, Sugarman *et al.*[2] find that there is a minimum threshold in the size of memory autoregulatory T-cell population that must be in circulation for the pMHC-NP treatment to be effective at a given dose, inter-injection interval and pMHC valency. Interestingly, they also found that maximizing the expression level of pMHC on

Professor S Schnell is at Department of Molecular & Integrative Physiology, University of Michigan Medical School, Ann Arbor, MI, USA; Professor S Schnell and Professor M Pietropaolo are at Brehm Center for Diabetes Research University of Michigan Medical School, Ann Arbor, MI, USA and Professor M Pietropaolo is at Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA
E-mail: schnells@umich.edu

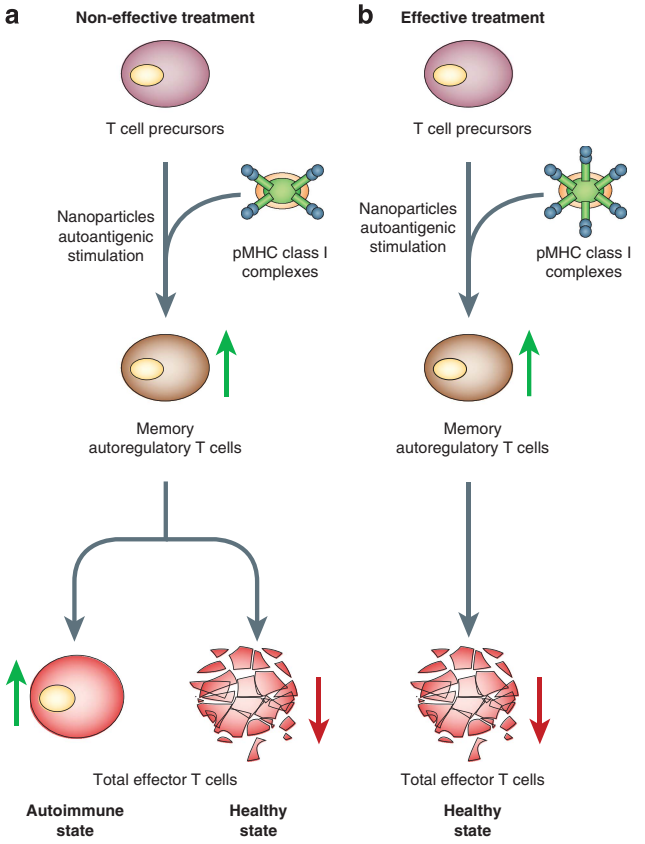

Figure 1 The reactive memory autoregulatory T-cells arise from the autoantigenic stimulation with nanoparticles coated with pMHC class I complexes. According to the model of Sugarman *et al.*,[2] this will occur with both non-effective and effective treatments. The optimal treatment is a function of nanoparticle doses, inter-injection interval and the expression level of pMHC on nanoparticles. In a non-effective treatment regime (**a**), the NOD average model mice can exhibit either an autoimmune or a healthy phenotype. In the autoimmune state, the total effector T-cell population is elevated. In the healthy phenotype, the total effector T-cell population is extinct. In contrast, the healthy state is the only possible state in an effective treatment regime (**b**).

NPs (pMHC valency) improves treatment outcomes in the NOD mice more than increasing the nanoparticule dose.

All mathematical modeling is a simplification of one type or another. The model of Sugarman *et al.*[2] is focused on three populations of $CD8^+$ T cells, which expand or reduce in respond to stimulation to pMHC class I complexes in NPs. However, there is a sequential hierarchy of $CD8^+$ cells in reactivity to islet autoantigens in the NOD.[6] The authors are aware of this limitation and provide a discussion. For example, the elimination of autoimmune responses to insulin prevents the development of the disease in NOD mice. In contrast, transgenic overexpression of islet-specific glucose-6-phosphatase catalytic-subunit-related protein (IGRP) resulted in loss of intra-islet IGRP-specific T cells but did not protect NOD mice from insulitis or T1DM. These data provide supporting evidence that T-cell responses against IGRP are downstream of the response to proinsulin,[6] at least when applying a transgenic mouse approach.

The major challenge going forward is to prove the existence of $CD8^+$ reactive memory autoregulatory T cells in humans. Converging lines of evidence demonstrate that immunoregulatory dendritic cells (DC) exist that can promote Treg development both *in vitro* and *in vivo*.[7] It is not clear if DCs exert a similar effect on memory autoregulatory T cells. In addition, the antigen-specific expansion of memory autoregulatory T cells and other regulatory T-cell subpopulation to suppress ongoing pathogenic responses could also depend on a number of additional critical issues that may need to be addressed and introduced into future models. For example,

- Do regulatory T cells in the NOD mouse model increase the avidity of primary $CD8^+$ T-cell responses and promote memory?
- What are the mechanisms by which autoregulatory cells exert their action, for example, regulating DCs, indoleamine 2,3-dioxygenase (IDO), interleukin-34?
- Do memory autoregulatory T cells expanded by NPs coated with specific pMHC Class I complexes have a unique ability to cause a 'cascade' suppressive effect by creating a regulatory milieu that promotes development of additional memory autoregulatory T cells?
- How do specific pMHC Class I complexes block effector T-cell function?

Owing to the complexity of the autoimmune response in TD1, quantitative modeling can be used to understand complex immunological signals and system-level processes that are difficult to interrogate via experimental methods alone. The model of Sugarman *et al.*[2] is an excellent starting point. It also demonstrates that a simple model can show surprising behaviors. To understand more complex models, unaided experimental intuition is not enough: future collaborative efforts between experimental immunologists and quantitative biologists will be essential to understand the mechanisms of the immune response and improve treatment outcomes in autoimmune diseases.

1 Drazin PG. *Nonlinear Systems*. Cambridge University Press, Cambridge, UK, 2006, p 1.
2 Sugarman J, Tsai S, Santamaria P, Khadra A. Quantifying the importance of pMHC valency, total pMHC dose and frequency of nanoparticle therapeutic efficacy. *Immunol Cell Biol* 2013; **91**: 350–359.
3 Khadra A, Santamaria P, Edelstein-Keshet L. The role of low avidity T cells in the protectionagainst type 1 diabetes: a modeling investigation. *J Theor Biol* 2009; **256**: 126–141.
4 Khadra A, Tsai S, Santamaria P, Edelstein-Keshet L. On how monospecific memory-like autoregulatory CD8+ T cells can blunt diabetogenic autoimmunity: a computational approach. *J Immunol* 2010; **185**: 5962–5972.
5 Tsai S, Shameli A, Yamanouchi J, Clemente-Casares X, Wang J, Serra P *et al.* Reversal of autoimmunity by boosting memory-like autoregulatory T cells. *Immunity* 2010; **32**: 568–580.
6 Krishnamurthy B, Dudek NL, McKenzie MD, Purcell AW, Brooks AG, Gellert S *et al.* Responses against islet antigens in NOD mice are prevented by tolerance to proinsulin but not IGRP. *J Clin Invest* 2006; **116**: 3258–3265.
7 Tang Q, Bluestone JA. The Foxp3+ regulatory T cell: a jack of all trades, master of regulation. *Nat Immunol* 2008; **9**: 239–244.