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Mouse Models for Type 1 Diabetes

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Abstract

Our understanding of the genetics, aetiology and pathogenesis of Type 1 Diabetes (T1D) was propelled by the discovery of animal models of T1D in the late 1970s and early 1980s, particularly the non-obese diabetic (NOD) mouse. Since then, transgenic and gene-targeting technologies allowed the generation of many models with reduced genetic and pathogenic complexity. These models allowed researchers to zoom in on specific aspects of this complex disease. In this review, we provide an overview of currently available mouse models for T1D.

Introduction

Type I diabetes mellitus, also called juvenile diabetes or insulin-dependent diabetes, is a chronic autoimmune disorder that precipitates in genetically susceptible individuals by environmental factors. The body's own immune system attacks the β -cells in the islets of Langerhans of the pancreas, destroying or damaging them sufficiently to reduce and eventually eliminate insulin production. When >80–90% of the β -cells have been destroyed, the production of glucagon by the neighboring α -cells is de-repressed. The metabolic consequences of insulin insufficiency and glucagon excess are hyperglycemia and ketoacidosis. Type 1 diabetes is distinguished from type 2 (non-insulin-dependent) diabetes by the presence of autoantibodies, the genetic link, the insulin dependence and by insulinitis, which is characterized by activated T lymphocytes.

Pathogen-induced models

A widely used virus-induced diabetes model is the LCMV infection of RIP-GP or R/HIP-NP on the C57Bl/6, Balb/c, or NOD background. RIP-GP mice are transgenic mice expressing the lymphocytic choriomeningitis virus glycoprotein (LCMV-GP) under control of the rat insulin promoter (RIP), resulting in expression of LCMV-GP in pancreatic β -cells [1,2]. There are two strains of RIP-GP mice: the RIP-GP Berlin mice express the LCMV-GP from LCMV strain WE [1], and the RIP-GP Arm mice express the LCMV-GP from LCMV strain Armstrong [2]. Naïve RIP-GP mice do not develop diabetes. However, after infection with LCMV, LCMV-specific T cells recognize virus-infected cells as well as GP expressed by pancreatic β -cells. The immune attack leads to destruction of these cells resulting in a very rapid development of T1D (within 1–2 weeks) [1,3]. The advantages of using this RIP-GP system is that the whole autoantigen (LCMV-GP/NP) as well as the CD4 and CD8 epitopes are defined, and that TCR transgenic mice specific for the (neo)autoantigen are available.

Our lab has set up a non-viral version of this model that harnesses both the innate and the adaptive components of the immune system and reliably induces T1D in RIP-GP mice

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within 2 weeks. The injections schedules for transfer of P14 cells, gp-peptide, CpG and poly(I:C) is described in detail elsewhere [4].

Spontaneous models

NOD model

The similarities with human autoimmune diabetes have led to the use of the NOD mouse as the mainstay of preclinical diabetes research [5]. The timeline of diabetes development starts at 5 weeks of age with an initial insulinitis that manifests by means of leukocytic aggregates at the perimeter of the islets and a lymphocytic infiltration into the pancreatic islets. The dominant initial population consists of CD4⁺ T cells followed by infiltration of CD8⁺ T cells, macrophages and B cells in smaller numbers [6]. The majority of female NOD mice develop diabetes by 40 weeks, but incidence in males is dramatically lower [7]. The specific diabetes incidence of any colony also critically depends on the “cleanliness” status of the colony [8].

T cells isolated from the pancreatic islets of NOD mice are insulin reactive after stimulation ex vivo [9], but other specificities have been found [10]. Islet reactive T cell clones have been established from NOD spleen, pancreatic islets and lymph nodes for both CD4⁺ [11,12] and CD8⁺ T cells [13,14]. Diabetes induction is possible with many of these clones in the absence of B cell help or other T cell lines. Transgenic SCID or RAG-knockout mice expressing such TCRs develop diabetes. It has recently been demonstrated that there is a progressive decrease in the ratio of Treg cell:Teff cell in inflamed islets, but not in the pancreatic lymph nodes [15]. This is probably due to increased apoptosis of the regulatory T cells, as administration of low doses of IL-2 promotes regulatory T cell survival and protects NOD mice from diabetes.

While it is accepted that T1D in NOD is primarily T cell-mediated, NOD mice also develop autoantibodies to insulin first detectable at 6 weeks of age and peaking between 8 and 16 weeks. These antibodies themselves do not cause diabetes, but they contribute significantly to the rate of disease progression [16,17].

Double-Tg models: RIP-Ag and Ag-specific TCR Tg

The double transgenic models are characterized by the transgenic expression of an antigen X on the pancreatic β -cells via an insulin promoter (RIP/HIP/MIP, see above) in combination with a transgenic TCR specific for that antigen X. Current double-Tg models are based on the model antigen OVA, influenza haemagglutinin (HA), or LCMV glycoprotein (GP).

In the DO11.10 TCR-Tg $\times$ RIP-mOVA model [18], Ovalbumin is expressed as a self-Ag in the pancreas. Co-expression of the DO11.10 TCR permits development of autoreactive OVA-specific CD4⁺ T cells. These mice develop diabetes by age 10 weeks, with 100% penetrance by week 20. The advantages of this autoreactive CD4⁺ T cell model are its shorter time frame (compared to NOD), the singularity of the T cell under study, and the availability of an antibody to detect the specific T cells.

Viral antigen-based models are useful for the study of “autoreactive” CD8⁺ T cell responses. The P14/RIP-GP model combines expression of LCMV-GP under the control of RIP on pancreatic β -islet cells, with LCMV-gp(33–41)-specific CD8⁺ T cells [1]. In this model, LCMV-GP-specific CD8⁺ T cells are not tolerized, but remain immunologically unaware of the presence of their antigen. When stimulated under the appropriate conditions, e.g. LCMV infection, P14 are fully capable of responding to LCMV-GP, either in virus-infected cells or on GP-expressing β -cell. This model was used to examine how gp33-induced tolerance can be switched to autoimmunity [19]. A similar setup is the TCR-HA/Ins-HA mouse, H-2^d

mice expressing both the influenza virus HA as a transgene-encoded protein on β -cells (Ins-HA) [20], as well as the Clone 4 CD8⁺ T cell, specific for the dominant H-2K^d-restricted HA epitope. These mice develop spontaneous autoimmune diabetes and die within 2 weeks of age [21].

BDC2.5/B6^{g7}

The BDC2.5 line allows one to bypass events involved in the generation and expansion of the repertoire of autoimmune T cells, which are preformed in the Tg mice, and to focus on the later steps of diabetes development. Gonzalez et al. compared BDC2.5/NOD and BDC2.5/B6^{g7} to study the genetic control of diabetes progression [22]. The BDC2.5/B6^{g7} was generated by crossing the BDC2.5 to the MHC-congenic line B6.H2^{g7}, which carries the g7 haplotype of the MHC but has all other genes from the B6 strain. As such, the final strain contains BDC2.5 TCR transgenes together with selecting H2^{g7} MHC alleles but different alleles at all other loci [23]. One advantage of the model is that the background is C57Bl/6. Also, the diabetes incidence in this strain reaches a stable 60% at 10 weeks, allowing both increased or decreased diabetes incidence and time of onset to be studied within a reasonable amount of time.

Transfer models of autoimmune diabetes

Transfer into immunodeficient mice

Transfer of splenocytes from diabetic NOD females induces diabetes in NOD.CB17-Prkdc^{scid} (NOD-scid) which are immunodeficient. Using this transfer approach, Miller and Wicker [24] first demonstrated that both CD4⁺ and CD8⁺ cells were required for diabetes onset, which was later confirmed using β 2-microglobulin knockout (CD8 deficient), or MHCII knockout [25] and CIITA-deficient (CD4 paucity) [26]. Also, islet-infiltrating lymphocytes from prediabetic NOD mice rapidly transfer diabetes to NOD-scid mice [27]. By comparing diabetes incidence after cotransfers of combinations of gene-KO/WT CD4 and CD8, this transfer system allows determination of the defective T cell subset in gene-KO NOD mice that are resistant to diabetes (e.g. [26]). Insufficient purity of the subsets being co-transferred can hamper unambiguous interpretation of the results.

Transfer of BDC2.5 TCR Tg CD4 T cells in NOD neonates

The BDC2.5 TCR transgenic line carries the rearranged TCR genes from a CD4⁺ T cell clone that is specific for an (unknown) pancreatic islet β -cell antigen, is restricted by the A^{g7}, and is diabetogenic [28]. Using transfer of Th1 or Th2 BDC2.5 CD4⁺ T cells to NOD neonates (age <11 days), Katz et al. showed that both Th1 and Th2 induce insulinitis, but only Th1 induce diabetes in the recipient mice within 2 weeks [29,30]. Cotransfer of regulatory T cells, natural or induced, can be employed to determine suppressive capacity of cell types on the islet-directed CD4⁺ T cell response. This model allows tracking T cells by tetramers, distributed by NIH [31], or by the inbreeding of an allelic marker (Thy1, or Ly5).

Transfer of P14/Smarta LCMV-specific CD8 or CD4 into RIP-GP

The LCMV-induced models of T1D (see above) allow monitoring of virus/neoantigen-specific responses by means of tetramer staining and/or *in vitro* LCMV-peptide restimulation for cytokine production. However, it does not allow tracing of a population that was manipulated before, or transgenically altered. This is solved by transfer of P14 cells (CD8⁺ T cells specific for LCMV gp33–41 on H-2Db, [32]) or the SMARTA cells (CD4⁺ T cells specific for the LCMV gp61–80 on I-A^b, [33]) a day before LCMV infection of the RIP-GP mice. These cells will respond to LCMV and subsequently migrate to the pancreas where the LCMV-glycoprotein is expressed on β -cells. Breeding in an allelic marker (CD45.1/2, CD90.1/2) or fluorochromes (GFP, DsRed), or labeling with fluorescent dyes

(e.g. CFSE, SNARF, PKH) provide means to trace the P14 or SMARTA cells accurately during their response, even in immunohistochemistry or 2-photon microscopy studies. A similar system can be set up using TCR-HA [34] into RIP-HA mice [35].

Humanized mouse models

The need for experimental studies on human haematopoietic and immune systems has propelled the development of appropriate and effective animal models that do not put individuals at risk. NOD-scid mice have been the "gold standard" for studies of human haematolymphoid engraftment in small animal models over the last 10 years. Now, immunodeficient mice bearing a targeted mutation in the IL-2 receptor common gamma chain (NOD-scid/IL-2R $\gamma^{-/-}$ mice) allow superior engraftment and function of human haematolymphoid cells as compared with NOD-scid mice and are very useful for studying human lymphocytes in vivo. NOD-scid/IL-2R $\gamma^{-/-}$ mice are also used in studies on human haematopoiesis, innate and adaptive immunity, autoimmunity, infectious diseases, cancer biology, and regenerative medicine, as reviewed elsewhere [36].

Pharmacological

Alloxan and streptozotocin (STZ) are toxic glucose analogues that preferentially accumulate in pancreatic β -cells via the GLUT2 glucose transporter [37]. Alloxan and high doses of STZ selectively kill the insulin-producing β -cells, whereas multiple low doses of STZ (MLD-STZ: 5 daily i.p. doses of 40mg/kg/day) generate H₂O₂ and induces expression of glutamic acid decarboxylase (GAD) autoantigens. GAD is a strong trigger of β -cell-specific autoimmunity, both in humans and in experimental models of diabetes, and has been shown to require a Th1-dependent inflammatory reaction. This model offers an opportunity to study the effects of compounds on synchronized groups of rodent animals within 20–30 days.

Temporary and reversible β -cell ablation can be achieved in the PANIC-ATTAC (pancreatic islet beta-cell apoptosis through targeted activation of caspase-8) mouse model [38]. This model can be used for the identification of β -cell precursors, evaluation of glucotoxicity effects in diabetes, and examination of pharmacological interventions.

Conclusion and future directions

Given the complexity of T1D, a single inbred animal model of diabetes is unlikely to unravel everything there is to know about (all forms of) autoimmune diabetes (that might exist) in the human population. These animal models can however help in the identification of many of the genetic, signalling and immune pathways involved in diabetes. Differing models have differing strengths and weaknesses, and before embarking on a clinical trial, several experimental animal models need to be consulted. The therapeutic target should direct the choice of model(s) in the experimental design that should include complimentary and/or confirming approaches. In our opinion, confirmation of those findings in NOD mice is not a strict requirement for the validity of the results. However, it is conceivable that translational potential to a complex disease as T1D increases with the broader applicability of a therapy or phenomenon in multiple model systems, each with their own emphasis and angle.

So far, research of human T1D has been limited to blood draws of diabetic versus healthy or genetically susceptible individuals, in a cross-sectional or sometimes longitudinal study. However, the study of the diabetic (or unaffected) pancreas is mostly restricted to the use of cadaveric donors. An ethical use of living humans in research is possible through noninvasive β -cell imaging to quantify the remaining functional β -cell mass in diagnosed T1D patients or in autoantibody positive individuals, but also prove important as follow-up

tool after therapy. Modern diagnostic equipment can provide very high sensitivity, e.g. positron emission tomography (PET), single photon computed tomography (SPECT), but also spatial resolution, e.g. magnetic resonance imaging (MRI), or a combination of both by PET/CT. These imaging techniques rely on a specific molecular marker to enable differentiation between scattered islets or single β -cells, or surrounding tissue. Currently, IC2 seems to be the only useful marker for noninvasive functional imaging of native β -cells and thus in vivo β -cell mass quantification [38]. Vesicular monoamine transporter 2 (VMAT2) is present on β -cells, but was also found on pancreatic polypeptide cells [39]. Obviously, experimental animal models might benefit from these noninvasive techniques as well.

Apart from anti-CD3 therapy [40], translation of promising preclinical therapies has not demonstrated reliable predictability and/or efficacy towards patient treatments. This is most likely because of the inherent differences between the two species that make identical responses to all immunological situations impossible. Recent years have seen a boom in the application of informatics techniques to immunological data and the creation of in silico models based on this data. To aid the transition from successful mouse therapy to successful human therapy, the biotech company Entelos has created a virtual NOD mouse platform. This platform enables in silico investigation of critical pathways that regulate autoimmunity and/or β cell destruction. *In silico* animal models have the advantage of quickly and quantitatively linking observed animal behaviors with predicted human response and Entelos hopes researchers will be able to combine their own work with the benefits of in silico research. Cellular models of diabetes progression, T cell function and immunoregulation have also been created. This will allow hypothesis-driven research at the cellular level without the actual labor-intensive and expensive cell and animal work. Most importantly, these in silico platforms allow the testing of multiple parameters over large numbers of virtual immunological situations which, when performed in conjunction with traditional immunology experimentation, can help answer questions that current methodologies are not yet capable of alone. The virtual NOD mouse represents yet another valuable tool in the diabetes researcher's arsenal and the impact of this platform will increase as their sophistication - and thus predictive power - improve, both as stand-alone in silico models and as an integrated part of type 1 diabetes research.

References

1. Ohashi PS, et al. Ablation of "tolerance" and induction of diabetes by virus infection in viral antigen transgenic mice. *Cell* 1991;65(2):305–317. [PubMed: 1901764]
2. Oldstone MB, et al. Virus infection triggers insulin-dependent diabetes mellitus in a transgenic model: role of anti-self (virus) immune response. *Cell* 1991;65(2):319–331. [PubMed: 1901765]
3. von Herrath MG, et al. How virus induces a rapid or slow onset insulin-dependent diabetes mellitus in a transgenic model. *Immunity* 1994;1(3):231–242. [PubMed: 7889411]
4. Martinic MM, von Herrath MG. Real-time imaging of the pancreas during development of diabetes. *Immunol Rev* 2008;221:200–213. [PubMed: 18275484]
5. Shoda LK, et al. A comprehensive review of interventions in the NOD mouse and implications for translation. *Immunity* 2005;23(2):115–126. [PubMed: 16111631]
6. Zhang L, et al. Insulin as an autoantigen in NOD/human diabetes. *Curr Opin Immunol* 2008;20(1):111–118. [PubMed: 18178393]
7. Makino S, et al. Genetic analysis for insulinitis in NOD mice. *Jikken Dobutsu* 1985;34(4):425–431. [PubMed: 3910444]
8. Ohsugi T, Kurosawa T. Increased incidence of diabetes mellitus in specific pathogen-eliminated offspring produced by embryo transfer in NOD mice with low incidence of the disease. *Lab Anim Sci* 1994;44(4):386–388. [PubMed: 7983856]
9. Wegmann DR, Eisenbarth GS. It's insulin. *J Autoimmun* 2000;15(3):286–291. [PubMed: 11040069]

10. von Boehmer H, Sarukhan A. GAD, a single autoantigen for diabetes. *Science* 1999;284(5417): 1135–1137. [PubMed: 10366347]
11. Haskins K, et al. T-lymphocyte clone specific for pancreatic islet antigen. *Diabetes* 1988;37(10): 1444–1448. [PubMed: 2458291]
12. Verdaguer J, et al. Spontaneous autoimmune diabetes in monoclonal T cell nonobese diabetic mice. *J Exp Med* 1997;186(10):1663–1676. [PubMed: 9362527]
13. Lieberman SM, et al. Individual nonobese diabetic mice exhibit unique patterns of CD8+ T cell reactivity to three islet antigens, including the newly identified widely expressed dystrophin myotonia kinase. *J Immunol* 2004;173(11):6727–6734. [PubMed: 15557165]
14. Wong FS, et al. CD8 T cell clones from young nonobese diabetic (NOD) islets can transfer rapid onset of diabetes in NOD mice in the absence of CD4 cells. *J Exp Med* 1996;183(1):67–76. [PubMed: 8551245]
15. Tang Q, et al. Central role of defective interleukin-2 production in the triggering of islet autoimmune destruction. *Immunity* 2008;28(5):687–697. [PubMed: 18468463]
16. Greeley SA, et al. Elimination of maternally transmitted autoantibodies prevents diabetes in nonobese diabetic mice. *Nat Med* 2002;8(4):399–402. [PubMed: 11927947]
17. Kagohashi Y, et al. Maternal factors in a model of type 1 diabetes differentially affect the development of insulinitis and overt diabetes in offspring. *Diabetes* 2005;54(7):2026–2031. [PubMed: 15983203]
18. Clough LE, et al. Release from regulatory T cell-mediated suppression during the onset of tissue-specific autoimmunity is associated with elevated IL-21. *J Immunol* 2008;180(8):5393–5401. [PubMed: 18390721]
19. Garza KM, et al. Role of antigen-presenting cells in mediating tolerance and autoimmunity. *J Exp Med* 2000;191(11):2021–2027. [PubMed: 10839816]
20. Lo D, et al. Peripheral tolerance to an islet cell-specific hemagglutinin transgene affects both CD4+ and CD8+ T cells. *Eur J Immunol* 1992;22(4):1013–1022. [PubMed: 1348026]
21. Morgan DJ, et al. CD8(+) T cell-mediated spontaneous diabetes in neonatal mice. *J Immunol* 1996;157(3):978–983. [PubMed: 8757600]
22. Gonzalez A, et al. Genetic control of diabetes progression. *Immunity* 1997;7(6):873–883. [PubMed: 9430232]
23. Luhder F, et al. Major histocompatibility complex class II molecules can protect from diabetes by positively selecting T cells with additional specificities. *J Exp Med* 1998;187(3):379–387. [PubMed: 9449718]
24. Miller BJ, et al. Both the Lyt-2+ and L3T4+ T cell subsets are required for the transfer of diabetes in nonobese diabetic mice. *J Immunol* 1988;140(1):52–58. [PubMed: 3275717]
25. Slattery RM, Miller JF. Influence of T lymphocytes and major histocompatibility complex class II genes on diabetes susceptibility in the NOD mouse. *Curr Top Microbiol Immunol* 1996;206:51–66. [PubMed: 8608725]
26. Mora C, et al. Pancreatic infiltration but not diabetes occurs in the relative absence of MHC class II-restricted CD4 T cells: studies using NOD/CIITA-deficient mice. *J Immunol* 1999;162(8): 4576–4588. [PubMed: 10201997]
27. Rohane PW, et al. Islet-infiltrating lymphocytes from prediabetic NOD mice rapidly transfer diabetes to NOD-scid/scid mice. *Diabetes* 1995;44(5):550–554. [PubMed: 7729614]
28. Haskins K, McDuffie M. Acceleration of diabetes in young NOD mice with a CD4+ islet-specific T cell clone. *Science* 1990;249(4975):1433–1436. [PubMed: 2205920]
29. Katz JD, et al. T helper cell subsets in insulin-dependent diabetes. *Science* 1995;268(5214):1185–1188. [PubMed: 7761837]
30. Pakala SV, et al. T helper 2 (Th2) T cells induce acute pancreatitis and diabetes in immune-compromised nonobese diabetic (NOD) mice. *J Exp Med* 1997;186(2):299–306. [PubMed: 9221759]
31. Stratmann T, et al. Susceptible MHC alleles, not background genes, select an autoimmune T cell reactivity. *J Clin Invest* 2003;112(6):902–914. [PubMed: 12975475]

32. Kyburz D, et al. T cell immunity after a viral infection versus T cell tolerance induced by soluble viral peptides. *Eur J Immunol* 1993;23(8):1956–1962. [PubMed: 8344359]
33. Oxenius A, et al. Virus-specific MHC-class II-restricted TCR-transgenic mice: effects on humoral and cellular immune responses after viral infection. *Eur J Immunol* 1998;28(1):390–400. [PubMed: 9485218]
34. Sarukhan A, et al. Changes in function of antigen-specific lymphocytes correlating with progression towards diabetes in a transgenic model. *EMBO J* 1998;17(1):71–80. [PubMed: 9427742]
35. Roman LM, et al. The expression of influenza virus hemagglutinin in the pancreatic beta cells of transgenic mice results in autoimmune diabetes. *Cell* 1990;61(3):383–396. [PubMed: 2185889]
36. Pearson T, et al. Humanized SCID mouse models for biomedical research. *Curr Top Microbiol Immunol* 2008;324:25–51. [PubMed: 18481451]
37. Lenzen S. The mechanisms of alloxan- and streptozotocin-induced diabetes. *Diabetologia* 2008;51(2):216–226. [PubMed: 18087688]
38. Saudek F, et al. Imaging the Beta-cell mass: why and how. *Rev Diabet Stud* 2008;5(1):6–12. [PubMed: 18548165]
39. Saisho Y, et al. Relationship between pancreatic vesicular monoamine transporter 2 (VMAT2) and insulin expression in human pancreas. *J Mol Histol* 2008;39(5):543–551. [PubMed: 18791800]
40. Chatenoud L, Bluestone JA. CD3-specific antibodies: a portal to the treatment of autoimmunity. *Nat Rev Immunol* 2007;7(8):622–632. [PubMed: 17641665]

Figure 1. Pathogenesis of Type I diabetes

Initial β -cell damage or death (1) releases antigens (2), including auto-antigens (in red, e.g. insulin, GAD65), which are presented by antigen-presenting cells (APC) in the lymph nodes draining the pancreas (3). Priming of auto-reactive effector T cells occurs only in susceptible individuals by an environmental triggers leading to an unbalanced immune response. Auto-aggressive T cells migrate to the pancreas (4) and start destroying the β -cells in the islets of Langerhans (5).

Table 1

Summary of mouse models for type 1 diabetes.

Pathogen-induced models	Spontaneous models	Transfer models	Pharmacological
RIP-LCMV-GP (C57Bl/6, Balb/c)	NOD mice	NOD lymphocytes into immunodeficient NOD mice	Alloxan
RIP-LCMV-NP (C57Bl/6, Balb/c)	BDC2.5/B6 ^{g7}	CD4 ⁺ BDC2.5 TCR Tg into neonates	Streptozotocin
HIP-LCMV-NP (NOD)	Double Tg-models: DO11.10 × RIP-mOVA P14 × RIP-LCMV-GP TCR-HA × Ins-HA	Smarta CD4 ⁺ into RIP-LCMV-GP P14 CD8 ⁺ into RIP-LCMV-GP	PANIC-ATTAC mice

Tg : Transgenic; RIP : Rat Insulin Promotor; HIP : Human Insulin Promotor; OVA : Ovalbumin; BDC : Barbara Davis Center; HA : Haemagglutinin; LCMV : Lymphochoriomeningitis Virus; GP : Glycoprotein; NP : Nucleoprotein; PANIC-ATTAC : pancreatic islet beta-cell apoptosis through targeted activation of caspase-8.