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Use of NOD Mice to Understand Human Type 1 Diabetes

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Synopsis

In 1922, Leonard Thompson received the first injections of insulin prepared from the pancreas of canine test subjects. From pancreatectomized dogs to the more recent development of animal models that spontaneously develop autoimmune syndromes, animal models have played a meaningful role in furthering diabetes research. Of these animals the non-obese diabetic (NOD) mouse is the most widely used for research in Type 1 Diabetes (T1D) as the NOD shares a number of genetic and immunologic traits with the human form of the disease. In this chapter, we review both similarities and differences in NOD and human T1D and discuss the potential role of NOD mice in future pre-clinical studies aiming to provide a better understanding of the genetic and immune defects that lead to T1D.

Keywords

NOD Mouse; Genetics; Immunology; Type 1 Diabetes

Introduction

The use of animal models to study disease is fundamental to the advancement of our understanding of basic biological mechanisms, disease-specific dysfunctions, and the development and testing of therapeutics. When specifically considering diabetes, animal models have been used throughout the past century and a half for major advances in patient care, such as the discovery of insulin. More recently, mouse models, specifically the autoimmune diabetes prone non-obese diabetic (NOD) mouse have played an increasing role in discovery of disease mechanisms, identification of autoantigens, and the development of a better understanding of the genetic pathogenesis of T1D. In the post genomic era, the NOD model continues to serve essential roles in defining disease-associated alleles and identifying potential therapeutic interventions.

Initial descriptions of the Diabetes Prone BioBreeding rat (BB-DP) (1,2), and the NOD mouse (3) were published approximately 40 years ago. However, continued technological advances in genetic manipulation, transgenic development, knock-out and knock-in vectors, and conditional knockout and expression technologies for the mouse genome have led to the wider use of the NOD mouse in T1D research. In addition, pathogenic (Table 1) and genetic (Table 2) similarities to the human condition theoretically make the NOD a more useful tool

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to study the etiology, pathology, and progression of disease. While the NOD model is not without fault (4–6), this model is particularly useful in its ability to isolate, study, and manipulate specific genes, polymorphisms, and other genetic factors to identify not only how a specific gene may function deleteriously but also to understand how specific combinations of normal alleles result in immune dysregulation and autoimmune disease.

Immunology and Pathology of T1D: comparing mice and men

Trying to understand the pathology of diabetes using human samples is complex. Critical information has been derived through the study of organs procured from deceased human patients with T1D. The insulitic infiltrates of cadaveric pancreata demonstrate the presence of $CD8^+$ cytotoxic T lymphocytes (CTL), macrophages (MΦ), B cells, and $CD4^+$ helper T cells (7). In recent onset cases where insulitis was present, infiltrates affect insulin positive islets as opposed to insulin deficient endocrine clusters (8). Analysis of β and α cells shows only significant decreases of β cells, with persisting insulitis and increased expression of MHC I and Fas (9). These data support the hypothesis that specific immune reactivity to β cell antigens is central to diabetes progression. However, even with newer programs such as the Network for Pancreatic Organ Donors with Diabetes (nPOD) human samples have been scarce; therefore much of the knowledge delineating the pathogenesis of T1D has been extrapolated from studies using NOD mice.

In the NOD mouse, diabetes develops following infiltration of leukocytes into the pancreatic insulin producing β cells. At around 3 weeks of age in the NOD lymphocytic infiltration in the islet can be seen (10,11). The infiltration in NOD islets initiates with dendritic cells (DC) and MΦ followed by both $CD4^+$ and $CD8^+$ T cells as well as B cells. The leukocytes present in the infiltrate mediate β cell killing in the NOD via direct cytotoxicity (using Fas and perforin/granzyme) and indirect mediators (proinflammatory cytokines and free radical production) (reviewed in (12)). Several cell types have also been implicated in playing critical roles in the targeting and destruction of β cells, including MΦ, DC, T cell subsets, and B cells. Therefore, the pathology demonstrated in the NOD is similar to that observed in the human disease.

The immunological characterization of T1D has been conflicting and challenging. The majority of human lymphocyte studies have derived from peripheral blood, while those using the NOD mouse have been more extensive and invasive. Antibodies specific for pancreatic islet antigens are present in both species, yet, the presence of autoantibodies in mouse appears to be far less predictive of the development of T1D in man. In some, β cell autoantibodies are observed in several mouse strains that do not develop T1D (13,14). While antibodies likely do not play a role in T1D development in the NOD mouse, complement-fixing antibodies are present in patients with T1D and these antibodies are cytolytic to human β cells (15). Work in the NOD mouse demonstrating a of lack antibodies in T1D pathogenesis as well as adoptive transfer studies demonstrating the important role of T cells in murine T1D has likely been a major force in pushing the field towards the belief that T cells are the main effectors of β cell destruction in T1D. Both patients and NOD mice exhibit autoreactivity of $CD4^+$ and $CD8^+$ T cell subsets, as well as altered function of regulatory T cells. However, as there is little evidence to support the specific mechanism of destruction or the cell types that participate in β cell death during progression of human T1D, data collected from studies with the NOD mouse remain the basis for much of the current dogma.

Genetically modified and transgenic NOD mice have provided models to establish the role of different cell types in the pathogenesis of T1D. Innate immune cells, including DC and MΦ, cells are critical for initiating the process of β cell death during T1D. DC and MΦ are

found in early insulitic infiltrates and are implicated in driving early autoreactive immune responses (16,17). Depletion of macrophages protects NOD mice from T1D and insulitis (18). T cells from a macrophage-deficient environment lack diabetogenic potential, yet islet reactivity is restored when macrophages are replenished (19). Antigen-presenting cells play an essential role in CTL activation (20). DC are also critical in the initiation of T cell responses or induction of tolerance, depending on the DC subset and T cell requirement (21–23). These data demonstrate the importance of innate immune cells to activate adaptive immunity, promoting pathogenic or tolerogenic responses, and are therefore potential targets for therapies aimed at preventing T1D. It has been proposed that T1D in the mouse and human develops due to a break in or lack of tolerance resulting from poor APC function, clinical trials are currently underway to investigate the safety and potential of DC therapy to promote tolerance or enhanced regulation of self-reactive T cells in human cohorts (24).

Adaptive immune cells, specifically T lymphocytes, are implicated as the final effectors driving β cell death resulting in overt diabetes, based on work in human samples and NOD mouse. Autoreactive responses of $CD4^+$ and $CD8^+$ T cells to islet antigen have been implicated in the pathogenesis of diabetes in humans and NOD mice (Table 1). Using the NOD model, adoptive transfer experiments using $CD4^+$ and $CD8^+$ T cells demonstrated the necessity of both T cell subsets for T1D induction (25). T cells recognize specific peptide antigens when presented in the context of Major Histocompatibility Complex [MHC] molecules, also known as Human Leukocyte Antigens (HLA). This recognition is mediated by the T cell receptor [TCR]. During the maturation of T cells in the thymus, TCR, MHC, and antigen all play essential roles. Defects in T cell development are proposed to provide significant contributions to T1D susceptibility and pathogenesis. Likewise, polymorphisms in MHC are strongly associated with susceptibility in human and murine autoimmunity and, as MHC molecules are important for T cell development and activation, these molecules greatly influence selection as well as tolerance in the periphery.

The recognition of autoantigens in the context of MHC is fundamental to initiating an autoimmune response in human and NOD diabetes. There are striking similarities in the autoantigens that are responded to in both species. T cell responses and/or circulating antibodies have been measured in T1D patients and at risk individuals to over 15 different antigens, while in the NOD mouse immune responses have been measured against 8 antigens, listed in Table 1. Of those found in the NOD, Dystrophia Myotonica-Protein Kinase [DMPK] and Chromogranin A have not yet been identified as autoantigens in man, and many of the antigens in man have surprisingly, not yet been tested for in NOD mice, demonstrating a need to further characterize potential autoreactive targets in mouse and man. Therefore, the T1D-prone mouse has lost tolerance to many of the same antigens T1D patients exhibit autoantigenic responses against. In conclusion, NOD mice have histological and immune similarities with the human disease and, as described below, have similar genetic susceptibilities as man.

Genetics

Type 1 diabetes is a polygenic disease. To date over 50 genetic linkages have been associated with this autoimmune disease. However, the linkage to HLA Class II [termed *Insulin-Dependent Diabetes Mellitus 1 (IDDM1)*] is by far the dominant susceptibility locus (26). DQB alleles with Ser, Ala, or Val at amino acid residue 57 are associated with T1D susceptibility, while those alleles containing an Asp residue are considered protective. It is believed that the non-Asp containing alleles causes a local rearrangement within the peptide-binding site that alters the peptide-binding specificity (27), resulting in altered T cell recognition and thymic selection (28). Likewise, susceptibility has also been linked to specific HLA-A and HLA-B Class I alleles (29), however little is known about the role of

the disease-associated variants in T1D. However, it should be noted that when HLA-B*39 is combined in a HLA haplotype with DRB1*0404-DQB1*0302, patients are at significantly heightened risk (30). This is a demonstration of gene-gene interaction or epistasis, controlling T1D onset.

While HLA is by far the most highly associated *IDDM* locus several non-HLA linkages have been identified. Of the >50 other linkages mapped in genome wide association studies (GWAS) INS [*IDDM2*], PTPN22 [*IDDM5*], and Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) [*IDDM12*] have repeatedly been associated with T1D (26). The insulin gene contains a variable number of tandem repeats (VNTR) in the 5′-flanking region. The VNTR class I alleles with 26 to 63 repeats are associated with recessive susceptibility, while the dominantly protective class III alleles have significantly more repeats (140 to more than 200 repeats). The allelic effects on insulin gene transcription can be measured both in vitro and in vivo. Specifically it is believed that the Class III alleles induce higher thymic expression and potentially enhanced deletion of insulin reactive T cells (31). At this time it is unknown how the risk alleles of *PTPN22* and *CTLA4* contribute to T1D in humans, however, as discussed below, efforts using the NOD mouse are making progress in identifying mechanisms.

While the above-mentioned linkages, and many others, have been identified using population based genome wide scans or association studies, candidate gene testing has continued for the past twenty years. The majority of the candidate testing projects have failed to bear fruit (32–37). That said, polymorphisms of von Willebrand factor A domain containing 2 [Vwa2 or AMACO (*IDDM17*)] have been associated with dominant protection against T1D (38). Even so, a potential mechanism for the protection provided by Amaco has yet to be published. These studies have provided details on linkages with potentially profound significance to human T1D. A promoter polymorphism in *SLC11A1* [*NRAMP1* (*IDDM7*)] was identified and later confirmed as contributing to T1D (39,40). NRAMP1 (natural resistance-associated macrophage protein one) regulates the activation of macrophages and therefore the proliferation of intracellular pathogens. The T1D resistance allele of *SCL11A1* is associated with lower levels of expression (41). Another gene that was identified is *mt-ND2* (NADH Dehydrogenase Subunit 2), a mitochondrially encoded subunit of Complex I of the electron transport chain (42). These latter two genes have also been identified as contributing to T1D in mouse models (43,44). Therefore, genetic studies have identified regions that both predispose to and protect against T1D and there is overlap in the regions/genes comparing man to mouse.

In the late 1980s, the first genome wide screens of the NOD mouse strain were executed with the goal to identify disease susceptibility/resistance loci or *Idd (insulin dependent diabetes)* (45,46). In the mouse over 30 linkages have been mapped (Table 2), however only a few of the genes responsible have been identified. Similar to the human condition, the most significant associations are with the Major Histocompatibility Complex (MHC) alleles (45–48). The NOD MHC class II molecule, I-A^{g7} (*H2-Aa*^{g7}) as well as absence of H2-Ea expression are critical for T1D development (49,50). The $H2^{g7}$ MHC haplotype of NOD allele shares homology with the human T1D susceptibility HLA-DQB1 locus. DQB alleles with Ser, Ala, or Val at position 57 are associated with T1D susceptibility and the NOD I-A^{g7} also contains a non-aspartic residue at position 57 (51–53). Congenic mice have been a major asset for determining the genes and loci in T1D. Congenic mice are those that have been bred to be genotypically different at a particular locus. NOD mice congenic for the MHC have been used to investigate the diabetogenic potential of MHC haplotypes associated with T1D susceptibility or resistance. Congenic replacement of the NOD MHC haplotype $H2^{g7}$ with MHC haplotype from strains that do not spontaneously develop T1D, for example the $H2^{b}$ of C57BL/6 (B6), prevents NOD insulitis and overt diabetes

development (50). These data demonstrate that alleles encoded within the $H2^{g7}$ haplotype are critical for T1D. However, introduction of $H2^{g7}$ on a B6 background does not induce T1D. Therefore, MHC alone is not sufficient to cause disease (50). The situation is the same in man where only a minority of individuals with risk-associated HLA alleles develops diabetes. Transgenic mice have also been instrumental in demonstrating the diabetogenic potential of human HLA genes (54). NOD mice transgenically expressing human risk HLA alleles, such as HLA-DR3 or DQ8, develop T1D. Susceptibility, however, was modulated with the co-expression of HLA-DR4 or DQ6 protective alleles, correlating with human epidemiological data (55,56) and confirming the effect of HLA alleles on T1D susceptibility. Work to understand the diabetogenic role of HLA Class I has also utilized the NOD mouse. NOD mice expressing HLA-A*0201 and a deletion of the murine MHC class I genes (NOD.HHD) have been produced and have an accelerated form of T1D (57,58). These studies highlight the importance of the NOD mice in defining the role of MHC in T1D.

Similarly, Class I alleles have also been associated with T1D in the mouse. A polymorphism found in the ALR strain as well as the diabetes resistant cataract Shionogi (CTS) strain creates a unique allele $H2\text{-}D^{dx}$. Introducing this allele to the NOD background significantly reduces T1D (59). Likewise, introduction of the MHC class I allele $H\text{-}2K^{wm7}$ to the NOD background confers protection (60) (Table 2). Analysis of the $H\text{-}2K^{wm7}$ MHC molecule defined a single peptide specificity (61). This suggests that protection is afforded based on the lack of β cell antigen presented over other nondiabetogenic antigens with a higher affinity for a particular MHC allele. Similarly in the HLA linkage analysis, certain alleles provided either susceptibility or protection. Conversely, not all genes providing genetic risk are shared between the species. For example, on mouse Chromosome 1 a linkage mapped to the gene *eta 2 microglobulin* (*B2m*) and later confirmed using transgenic rescue (62), however *B2M* has not been identified as a candidate gene in humans. *B2m* is a component of MHC class I molecules. It has been conclusively demonstrated that the NOD allele provides dominant susceptibility (62). However, as *B2m* is an important component of the HLA/MHC this non-orthologous linkage demonstrates that even when exact synteny, or co-localization of loci, is not achieved, T1D associated genes mapped in the NOD may point to important pathways that are affected in patients with T1D. Therefore, the study of homologous murine alleles along with human alleles expressed in transgenic mice affords researchers the model to evaluate and define autoantigen vs nondiabetogenic antigen expression.

Obviously, in situations where a mutation associated with or even proven to play a role in T1D is shared between mouse and man, the NOD systems can be used to better understand the function of the mutation and the role it plays in T1D onset. The Class II HLA/MHC is one example of a shared mutation; another is the single nucleotide polymorphism in *mt-ND2* and *mt-Nd2*. In both the human and mouse there is a C to A nucleotide substitution resulting in a leucine to methionine amino acid substitution (42,63). To determine how this mutation modifies mitochondrial function the mouse was employed to ensure genetic homogeneity at all loci save *mt-Nd2*, therefore the genetic element was isolated. Ensuing studies were able to determine that the protective allele suppressed mitochondrial reactive oxygen species (ROS) production (64,65). This reduction in mitochondrial ROS has been highly correlated with an enhanced protection against β cell apoptosis (66,67). The mouse enabled these studies to be performed in a “clean” genetic environment at a much faster rate than if only using human samples. A second example would be that of Nramp1. While the polymorphism in the mouse is not identical to that in the human, the result of the sequence variation is the same: reduced expression and function of the enzyme. Using NOD models, including a novel RNA interference transgenic NOD for Nramp1, it was demonstrated that

knockdown of Nramp1 was protective from T1D (43), and that the role of this enzyme in T1D was altered processing and presentation of pancreatic islet antigens (68).

With the technology to genetically manipulate mouse models and the development of "humanized" models, the role of T1D-linked genes can be isolated and tested. Increased thymic expression of insulin mRNA was linked with individuals with INS protective alleles (69,70). Using genetically manipulated NOD mice insulin expression in the thymus has been both increased and deleted, resulting in altered T cell insulin autoreactivity, demonstrating that the natural levels of thymic insulin expression are important for T1D and deletion of insulin specific autoreactive T cells (71–73). Specific knock out of insulin expression in the thymus induced diabetes in NOD background as early as 3 weeks of age, demonstrating a critical loss of tolerance resulting from a lack of negative selection (74). PTPN22, a negative regulator of T cell activation (75,76), is associated with T1D (77,78), as well as other autoimmune diseases (78,79). Studies using NOD congenics for PTPN22 orthoglogue, *Ptpn8*, showed modified incidence of T1D, demonstrating a role for PTPN22 in human and murine T1D (80). Through further examination of NOD congenic and murine models the role of LYP and pathways involved in T1D susceptibility can be examined and applied to human disease.

Genome-wide association studies (GWAS) are another tool that has provided additional information on regions of the genome where T1D susceptibility is linked. Depending on the initial analysis, the genetic region containing the responsible gene may be quite large. In these cases a subphenotype may be used to more quickly identify genes that may contribute to the gross phenotype of T1D. For example, *Ctla4*, a candidate gene for T1D (Table 2), is involved in controlling the function of regulatory T cells (81,82). By evaluating the subphenotype a genetic region can be identified. Databases can then be used to identify a small number of candidate genes associated with this subphenotype and T1D. This process may also speed the discovery of the gene in the interval. The process of subphenotpyic analysis in many cases is preferable to positional cloning as creating a congenic mouse to identify only a single gene is a demanding, protracted, and therefore a costly process. Subphenotypic analysis has been successfully performed to determine *Slc11a1* (Nramp1) was a contributing gene for T1D in the NOD mouse (43) and confirmation of the T1D-associated polymorphisms in patients with T1D (40).

This process can also be beneficial to identify the role of a single locus or multiple loci with epistatic.interactions. When the *Idd5* locus was initially detailed, it became apparent that there were at least four genes within this region contributing to T1D. However, the effect for each of these four regions is different, with the NOD allele at *Idd5.1* demonstrating the majority of the susceptibility. Congenic mice harboring this segment had a markedly reduced risk for T1D [50% compared to 85% in NOD mice (83)]. However, the NOD-*Idd5.2* had exactly the same T1D incidence as NOD mice. An epistatic interaction between these two regions was realized in NOD mice with both regions [NOD.*Idd5.1/5.2*]. These NOD-*Idd5.1/5.2* mice had a T1D incidence of about 10% demonstrating that when combined the protective genes in these two regions (likely *Ctla4* and *Slc11a1*) synergized for T1D protection. Moving forward, the transgenic expression or knock-in of human T1D susceptibility alleles into the NOD mouse will allow for rigorous testing of epistasis for resistance or susceptibility to T1D.

Technological advances, including sequencing of the mouse genome, genome wide maps, and databases that allow targeted searches of these data assist researchers in defining and studying susceptibility and resistant loci. Databases are integral components in research of genetic diseases and in defining *Idd* loci. NCBI and MGI are databases for genetic and mapping data from various mouse strains, providing information for the sequence of the

entire NOD genome, microsatellite markers, single nucleotide polymorphisms, and known and predicted genes. T1Dbase provides a catalogue of human *IDDM* and murine *Idd* loci and genes. These major advances in technology continue to provide the field with information that should speed discovery of mechanisms influencing T1D onset.

The development of humanized mice is another advance expected to help researchers bridge the gap in translation from mouse to man. Humanized mice are those engrafted with human cells or express human transgenes, allowing researchers to study human cells *in vivo* in the context of autoimmune animal. Immunodeficient NOD mice were found to support engraftment of human hematopoietic cells (84) and hematolymphoid tissues (85). Through the introduction of a targeted mutation in IL-2 receptor common gamma chain, mice with severe defects in innate and adaptive immune cells can be used to study and characterize human hematopoietic stem cells and the function of the multiple lineages produced (86). The ability to transplant xenogeneic islet grafts to immunodeficient mice provides researchers the ability to study human β cell function and response to killing. However, there are still problems in these models, including level of engraftment, the need for chemically-induced hyperglycemia, and islet stem cell progenitor sensitivity. Current work is underway to eliminate the need for diabetes-induction, optimizing and stabilizing engraftment to provide models to study human islets as well as the diabetogenic potential of human immune system (review in (87)). These latest models should speed discovery by allowing more invasive studies to be performed on the genetic- and immunopathology of diabetes using human effectors cells, human β cells, in the context of human susceptibility/ resistance genes.

Pre-Clinical trials

Insulin treatment is a necessity for T1D to help maintain euglycemia, yet it is not a cure. Patients are still at risk for serious complications. The primary goals of ongoing research of T1D in the NOD mouse is to determine factors that contribute to and drive autoimmune pathogenesis, to develop ways to intervene and/or reverse the course of β cell loss and ultimately apply these therapeutics to cure and prevent human T1D. Therapies to modulate tolerance to autoanitgens such as insulin, have been tested in NOD (88–90) and human patients (91). Treatments to modulate the immune response through administration of anti-CD3 in mouse (92–95) and humans (96) as well as anti-thymocyte globulin (ATG) (97) have also been investigated. While such treatments are effective in the mouse, responses in human patients have been underwhelming, demonstrating the need to better bridge the gap in our understanding of how to apply and translate dosing and timing requirements as well as evaluation of subgroups to determine which regimens are the most successful stratified by biological markers and disease state.

Using the genetic information of homologous NOD and human T1D susceptibility [Table 2] to determine potential therapeutic targets is an important starting point. As previously discussed NOD and human T1D susceptibility has strong correlation to MHC/HLA haplotypes, which can be used to screen for risk. Of other non-MHC linked alleles, an important linkage, CTLA-4, has been described in NOD and humans. CTLA-4 is expressed on activated T cells and has been functionally characterized as a negative regulator of T cell activity (98). Binding of CTLA-4 to B7 molecules signals inhibition of effector T cells (99). Genetic analysis linked a splice variant of CTLA-4 (liCTLA4) with T1D in the NOD. It has been shown that liCTLA4 inhibits T cell reactivity and is more highly expressed in T cells from T1D resistant NOD congenics (100). NOD mice treated with CTLA-4 immunoglobulin or anti B7-2 were protected from T1D onset. However, treatment was only protective when given early, prior to disease onset, and did not reduce insulitis (101). Blocking CTLA-4 in NOD transgenic mice (102,103) and partial reduction of expression in lentivirus-transduced

RNAi mice (104) both accelerated disease onset. Also, β cells expressing a single chain anti-CTLA-4 in transgenic NOD mice were protected from T cell mediated destruction (105). These data highlight an essential role for CTLA-4 in modulating peripheral tolerance in early diabetes progression. CTLA-4 is also proposed as the candidate gene for *Idd5.1* (106) and *IDDM12* (Table 2). Therefore, CTLA-4 is a potential target for immune modulation and protecting from T cell mediated β cell destruction. Currently, a phase II clinical trial administering CTLA4-Ig to new onset T1D patients is in progress. Continued use of the NOD to determine the roles of *Idd/IDDM* on T1D is needed to determine the multi-therapeutic approaches needed to significantly intervene in autoreactivity and β cell death.

Much of the work in the NOD demonstrates that diabetes is a multigenic, multifaceted disease and there are most likely many genetic and immunological dysfunctions that, when combined with environmental factors, influence disease pathogenesis. Investigation of T cell activation demonstrates that many conditions can affect activation status. Cytokine production and mechanisms of killing involve multiple pathways with overlap and redundancy, suggesting that therapeutics targeting these products will require multi drug approaches. It is important to note that there are dozens of therapies which can prevent and a few that can reverse T1D in the NOD (reviewed in (49,91)). This leads some to criticize the usefulness of the NOD. However these failures in translation may prove useful in exposing both the similarities and differences between diabetes in mouse and man. These observations also reinforce the need to standardize disease state, assessment of biological targets, and outcome of therapies in the NOD. Timing and dosing thresholds for effective prevention or reversal are critical. Similarly, standardized definitions of biomarker positivity, such as autoantibody titer, C-peptide, and markers of immune modulation during the course of treatment are needed to assist researchers in comparing successes and failures within and between laboratories and to assist in the translation of these data to human T1D trials.

Summary

The NOD has significantly enabled our understanding of the histology, pathology, and genetics associated with autoimmunity. That said, the speed of disease onset, and relative ease of both disease prevention and reversal in this animal model emphasizes the lack of complete translatability to human T1D. As such, disease mechanisms clarified in the NOD mouse should be translated to human T1D with considerable caution. Despite its limitations, the NOD mouse may play a critical role in furthering the development of therapies for T1D. Humanized NOD models likely represent the next major technological advancement in murine models designed to study the pathophysiology of human T1D and evaluate potential therapeutic targets for immune modulation and enhanced β cell survival.

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Table 1

Similarities between Human T1D and NOD mice.

	Human	**NOD**
Age at onset	Most often diagnosed in children/young adults	3–6 months
Insulitis	CD8+ T cells, Macrophages, B cells, and CD4+ T cells. Very few NK cells	CD4+ T cells, B Cells, CD8+ T cells, Macrophages, and Dendritic cells
Ketoacidosis	Controlled with insulin	Mild until late stages
Potential Autoantigens	INS*, GAD 65, HSP60, IAPP, Slc30a8 (ZnT8), CPE, G6PC2 (IGRP), PDX-1, PTPRN (IA2), HSP90AB1, PTPRN2 (IA2β), REG3A, ICA1 (ICA69), IMO38 (MRPS31), PRPH, & SOX13	INS, GAD65, G6PC2 (IGRP), PDX-1, ICA69, IA-2, DMPK**, & Chromogranin A**
MHC linked	Alleles of Class HLA-II DR/DQ and Class I HLA-A/B	MHC Class II Ab^{g}/Ea^{null}, Class I K^{d}/D^{b}
Reported non-MHC linkages	>50	>40
Lymphopenia	No	No
T lymphoaccumulative	Yes	Yes
Role of T Regulatory Cells	No change in numbers, functional differences yet to be conclusive	No decrease in numbers, potential decrease in suppressive function
B cells required	Likely required for the majority of cases‡	Required for the majority of the Cases†
NK-cell number	No correlation found	Absent
NK-cell function	No correlations found	Poor
NKT-cell number	Deficiencies linked with susceptibility	Low
Hemolytic complement	Dysregulation linked with complications	C5 deficient

* - Insulin (INS), Heat Shock Protein 60 (HSP60), Islet Amyloid Polypeptide [IAPP], Solute Like Carrier 30A8 [Slc30a8 or ZnT8], Carboxypeptidase E [CPE], Glutamic Acid Decarboxylase 65 [GAD2 or GAD65], Glucose-6-phosphatase 2 [G6PC2 or IGRP], Pancreatic and Duodenal Homeobox 1 [PDX-1], protein tyrosine phosphatase receptor type N [PTPRN or IA2], Heat shock protein HSP 90-beta [HSP90AB1], Receptor-type tyrosine-protein phosphatase N2 [PTPRN2 or IA2β], Regenerating islet-derived protein 3 alpha [REG3A], Islet cell autoantigen 1 [ICA1 or ICA69], Peripherin [PRPH], and SRY-related HMG-box 13 [SOX13].

** - Dystrophia Myotonica-Protein Kinase [DMPK] and Chromogranin A have not yet been identified as autoantigens in the human

‡ - Case report of an individual with X-linked agammaglobulinemia developed diabetes with T cell reactivity to GAD65 and IA-2

† - While B-cell-deficient NOD mice are strongly resistant to spontaneous autoimmune diabetes, these mice are susceptible to mild insulitis and, on treatment with cyclophosphamide, develop diabetes

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Table 2

Insulin dependent diabetes (Idd)

loci mapped in mouse models of T1D.

Idd	Chr.	Position (bp)	Outcross partner	T1D incidence of congenic	Latest Publication	Gene Candidate	Homologous Human locus	Gene Candidate
Idd1	17	34,132,973–35,404,440	NON, C57BL/10, C57BL/6	0% (50)	2005(107)	*MHC*	*IDDM1*	*HLA*
Idd1.1	17					*H2-Ab1*		
Idd1.2	17					*H2-Ea*		
Idd2	9	99,810,752–99,810,847	NON	ND	1998(108)	*Znf202*	*IDDM3*	
Idd3	3	60,270,627–60,270,801	B10.H2g7, B6.PL-Thy1a	15% (106)	2009(109)	*Il2, Il21*		
Idd4	11	74,677,336–74,677,434	C57BL/6, C57BL/B10.H2g7		2007(110)			
Idd5	1	40.0 cM*	B10.H2g7	50% (111)	2009(112)		*IDDM6, IDDM7*	
Idd5.1	1	60,883,084–62,840,206		50% (43, 106)	2009(68)	*Ctla4, Icos, Als2cr19, Nrp2*	*IDDM12*	*CTLA4*
Idd5.2	1	73,984,129–75,465,013		90%(43)	2009(113)	*Slc1a1, IL8rb*	*IDDM13*	*SLC11A1, IGFBP-2.5*
Idd6	6	73.0 cM*	NON.H2g7	10% (114, 115)	2008(116)	*HIF1β*		
Idd6.1	6	146,377,508–149,517,037	C3H		2006(114)			
Idd6.2	6	137,388,269–146,377,508	C3H		2008(116)			
Idd6.3	6	146,261,958–147,388,045	C3H		2006(114)			
Idd7	7	19,998,822–19,998,946	NON.H2g7, B10.H2g7	ND	2008(117)			
Idd8	14	21,656,627–21,656,804	B10.H2g7		1993(118)			
Idd9	4	124,439,115–124,439,213	B10.H2g7, B6.PL-Thy1a, NON.H2g7	5% (59, 119)	2007(110)			
Idd9.1	4	128,365,830–131,179,223			2010(120)			
Idd9.2	4	144,968,503–149,098,840		30% (121)	2010(121)			
Idd9.3	4	149,300,308–150,522,796		60% (121)	2010(121)			
Idd10	3	48.5 cM*	B10.H2g7, B6.PL-Thy1a, NON.H2g7		2005(122)	*CD101*		
Idd11	4	64.6 cM*	C57BL/6	17–27% (123)	2006(124)	*Slc9a1*	*IDDM16*	
Idd12	14	35,170,432–35,170,533	C57BL/6		1994(125)			
Idd13	2	71.0 cM*	NOR	0% (126)	2007(110)			

Idd	Chr.	Position (bp)	Outcross partner	T1D incidence of congenic	Latest Publication	Gene Candidate	Homologous Human locus	Gene Candidate
Idd13.1	2		C57BL/6			*B2m*		
Idd13.2	2		C57BL/6			*Mertk*		
Idd14	13	41,008,627–41,008,790	NON.H2g7, C57BL/6-susceptible allele	+33% (127)†	2007(110)		*IDDM15*	
Idd15	5	8,797,672–8,797,875	NON.H2g7	ND	1995(48)			
Idd16	17	33,737,692–33,737,814	CTS, C57BL/6, R209, ALR		2004(128)	*Tnf*		
Idd16.1	17	18.0 cM*	C57BL/6, R209		2005(59)	*H2K*		
Idd16.a	17	19.0 cM*	ALR		2005(59)	H2-Ddx		
Idd16.b	17	17.0 cM*	ALR		2005(59)			
Idd17	3	79,484,163–87,105,657	NON.H2g7, C57BL/6J		2004(129)			
Idd18	3	53.3 cM*	NON.H2g7, C57BL/6J		2009(112)			
Idd19	6	117,439,553–128,469,043	PWK	No change (130)	2006(130)	*Tnfrsf7, Tnfrsf1a, Hrh1*		
Idd20	6	83,595,701–91,990,027	C3H/H3J		2006(130)			
Idd21	18	24.5 cM*	ABH Biozzi	35%(131)	2003(131)			
Idd21.a	18	74,588,921–84,295,862			2005(132)			
Idd21.b	18	61,299,030–74,588,997			2005(132)			
Idd21.c	18	6,108,402–21,671,921			2005(132)			
Idd22	8	90,626,802–90,626,908	ALR	ND	2008(67)	*Nod2, Klf2, Ndufa13*		
Idd23	17	8 cM*	C57BL/6		2004(128)			
Idd24	17	35,340,111–41,438,922	C57BL/6					
Idd25	4	133,341,830–133,341,946	NOR		2005(133)			
Idd26	1	19,802,051–40,319,403	NOR		2005(133)			
Idd27	7	86,521,272–127,029,671	CBcNO6/Lt		2005(134)			
mt-Nd2	mt	4738	ALR	ND	2008(66)	*mt-Nd2*	*mt-ND2*	
Susp	3		ALR	ND	2008(66)			
Rthyd1	7	60.0 cM*	B10.Br/SgSnJxNOD-H2<k>		2004(135)			
Rthyd4	14	27.5 cM*	B10.Br/SgSnJxNOD-H2<k>		2004(135)			

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Idd	Chr.	Position (bp)	Outcross partner	T1D incidence of congenic	Latest Publication	Gene Candidate	Homologous Human locus	Gene Candidate
Rthyd5	15	22.0 cM*	B10.Br/SgSnJxNOD-H2<k>		2004(135)			
Ssial3	7	58.7 cM*			2002(136)			

*centiMorgan (cM) position used when bp interval not defined

†B6 susceptibility allele increases incidence in NOD

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