
Research Article

Genes Expression in Type 1 Diabetes: An Update

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Abstract: Type 1 Diabetes (T1D) is autoimmune disease with a sturdy genetic component, which, through interactions with particular environmental factors, causes disease onset. T1D usually reveals in early to mid-childhood through the autoimmune destruction of pancreatic cells resulting in a lack of insulin production. Traditionally, prior to genome-wide association studies (GWAS), six loci in the genome were fully established to be associated with T1D. The originations of genetic factors involved in T1D through GWAS present the first step in a long process leading to cure. Genes uncovered using this approach is indeed necessary to disease biology and will define the key molecular pathways leading to cure of T1D. However, such genome wide scans can lack coverage in certain regions where it is difficult to , thus, it is possible that other loci with practical effect sizes remain to be uncovered through whole genome sequencing approaches. In this review, we address recent expansions in the genetics of T1D and provide an update on the latest predisposition loci added to the list of genes involved in the of T1D.

Keywords: Type 1 Diabetes (T1D), genome-wide association studies (GWAS), pancreatic β -cells, multifactorial disease, gene expression.

1. Introduction

The aetiology of Type 1 diabetes (T1D), like most common chronic diseases, is complex and results from the interaction of genetic and environmental factors. That interplay takes place in a sequence that is true for all autoimmune diseases, and encompasses genetic susceptibility, tissue inflammation, and clinical disease [1]. This sequence is characterised by a diminished risk of progression at each transition, with more subjects having genetic risk (roughly 20%) than have inflammation (roughly 14%), and more having inflammation than have any autoimmune disease (roughly 7%). Genetic and non-genetic factors likely operate at all stages of this process. Such a structure is seen in T1D. The general features of this genetic and non-genetic interaction in T1D risk are discussed below, as that is the purpose of this broad review. The value of understanding the genetic origins of any disease is to delineate what is not genetic and therefore potentially reversible.

2. The Perception

With the exception of one or two early attempts to modulate the disease, the field of immunotherapy for type 1 diabetes did not have a significant boost until the 1980s, during which a series of studies were initiated that made use of a drug (cyclosporine) that had by then, revolutionized immunological suppression in the context of organ transplantation. Some 20 years on from those early successes, in 2007 we reviewed the status of intervention and prevention trials for type 1 diabetes [2]. The moment of our comment was significant; the first

major advance since the emergence of cyclosporine, especially with the publication of two studies using monoclonal antibodies (mAbs) directed to CD3 and designed to have a binding limited to Fc binding, both of which demonstrated clinically relevant efficacy with manageable toxicity [3, 4]. At that level, we discussed the fact that these medicines (which later emerged as teplizumab and ielotixizumab) were the main agents of a clinical line of immunodulator. These included many medicines that came from the areas of transplant immunology and other autoimmune and inflammatory diseases as well as specific medicines for diseases based on antigens. In a related post-review document, we highlight the capabilities and difficulties in combining these agents. [5], including a proposed 'designer combo' of anti-inflammatory + immune modulator + antigen. Apart from this, for the convenience of pipelines, during this period, the critical infrastructure was emerging as a diagnostic testing network, within which diagnostic studies could be conducted for consensus and standardized design and protocol.

3. Pathophysiology

The type 1 DM is the culmination of the lymphocytic intrusion of lingers heels of islets in the pancreas and the destruction of insulin-secreting beta cells. Unless the beta-cell mass decreases, the secretion of insulin is reduced until the available insulin is enough to maintain normal blood sugar level. After 80-90% of beta cells are destroyed, hyperglycemia develops and diabetes can be diagnosed. Patients need exogenous insulin to reverse this catabolic condition, to

prevent chitosis, reduces hypergluculinemia and normalize lipid and protein metabolism.

At present, autoimmunity is considered a major factor in the pathophysiology of type 1 DM. In a genetically susceptible person, viral infection can stimulate the production of antibodies against a viral protein, which triggers autoimmune response against antigenic similar beta cell molecules.

In approximately 85% of type 1 DM patients, the islet cell antibodies are circulated, and most also have detectable anti-insulin antibodies before receiving insulin therapy. The most commonly found islet cell antibodies are directed against glutamic acid decarboxylase (GAD), which is an enzyme found within pancreatic beta cells.

The prevalence of type 1 DM increases in other autoimmune patients, such as Graves' disease, Hashimoto thyroiditis and Addison disease. High blood circulation of islet cell antibody (IA2) and anti-GAD antibody was detected in patients with autoimmune thyroiditis in Palia et al. [6]

A study by Philippe et al used computed tomography (CT) scans, glucagon stimulation test results, and fecal elastase-1 measurements to confirm reduced pancreatic volume in individuals with DM. [7] This finding, which was equally present in both type 1 and type 2 DM, may also explain the associated exocrine dysfunction that occurs in DM.

Polymorphisms of the class II human leukocyte antigen (HLA) genes that encode DR and DQ are the major genetic determinants of type 1 DM. Approximately 95% of patients with type 1 DM have either HLA-DR3 or HLA-DR4. Heterozygotes for those haplotypes are at significantly greater risk for DM than homozygotes. HLA-DQs are also considered specific markers of type 1 DM susceptibility. In contrast, some haplotypes (eg, HLA-DR2) confer strong protection against type 1 DM. [8]

3.1. Sensory and autonomic neuropathy

Sensory and autonomic neuropathy in people with diabetes are caused by axonal degeneration and segmental demyelination. Many factors are involved, including the accumulation of sorbitol in peripheral sensory nerves from sustained hyperglycemia. Motor neuropathy and cranial mononeuropathy result from vascular disease in blood vessels supplying nerves.

3.2. Angiopathy

Using nailfold video capillaroscopy, Barchetta et al detected a high prevalence of capillary changes in patients with diabetes, particularly those with retinal damage. This reflects a generalized microvessel involvement in both type 1 and type 2 DM. [9]

4. Etiology

Type 1A DM results from autoimmune destruction of the beta cells of the pancreas and involves both genetic predisposition and an environmental component.

4.1. Genetic factors

Although the genetic aspect of type 1 DM is complex, with

multiple genes involved, there is a high sibling relative risk. [10] Whereas dizygotic twins have a 5-6% concordance rate for type 1 DM, [11] monozygotic twins will share the diagnosis more than 50% of the time by the age of 40 years. [12]

For the child of a parent with type 1 DM, the risk varies according to whether the mother or the father has diabetes. Children whose mother has type 1 DM have a 2-3% risk of developing the disease, whereas those whose father has the disease have a 5-6% risk. When both parents are diabetic, the risk rises to almost 30%. In addition, the risk for children of parents with type 1 DM is slightly higher if onset of the disease occurred before age 11 years and slightly lower if the onset occurred after the parent's 11th birthday.

The genetic contribution to type 1 DM is also reflected in the significant variance in the frequency of the disease among different ethnic populations. Type 1 DM is most prevalent in European populations, with people from northern Europe more often affected than those from Mediterranean regions. [13] The disease is least prevalent in East Asians. [14]

Genome-wide association studies have identified several loci that are associated with type 1 DM, but few causal relations have been established. The genomic region most strongly associated with other autoimmune diseases, the major histocompatibility complex (MHC), is the location of several susceptibility loci for type 1 DM—in particular, class II HLA DR and DQ haplotypes. [15–17]

4.2. Environmental factors

Extragenetic factors also may contribute. Potential triggers for immunologically mediated destruction of the beta cells include viruses (eg, enterovirus, [18] mumps, rubella, and coxsackievirus B4), toxic chemicals, exposure to cow's milk in infancy, [19] and cytotoxins.

Combinations of factors may be involved. Lempainen et al found that signs of an enterovirus infection by 12 months of age were associated with the appearance of type 1 DM-related autoimmunity among children who were exposed to cow's milk before 3 months of age. These results suggest an interaction between the 2 factors and provide a possible explanation for the contradictory findings obtained in studies that examined these factors in isolation. [20]

One meta-analysis found a weak but significant linear increase in the risk of childhood type 1 DM with increasing maternal age. [21] However, little evidence supports any substantial increase in childhood type 1 DM risk after pregnancy complicated by preeclampsia. [22]

A study by Simpson et al found that neither vitamin D intake nor 25-hydroxyvitamin D levels throughout childhood were associated with islet autoimmunity or progression to type 1 DM. [23] This study was based in Denver, Colorado, and has been following children at increased risk of diabetes since 1993.

Early upper respiratory infection may also be a risk factor for type 1 diabetes. In an analysis of data on 148 children considered genetically at risk for diabetes, upper respiratory infections in the first year of life were associated with an

increased risk for type 1 diabetes. [24, 25] All children in the study who developed islet autoimmunity had at least 2 upper respiratory infections in the first year of life and at least 1 infection within 6 months before islet autoantibody seroconversion.

Children with respiratory infections in the first 6 months of life had the greatest increased hazard ratio (HR) for islet autoantibody seroconversion (HR = 2.27), and the risk was also increased in those with respiratory infections at ages 6 to almost 12 months (HR = 1.32). [24, 25] The rate of islet autoantibody seroconversion was highest among children with more than 5 respiratory infections in the first year of year of life. Respiratory infections in the second year of life were not related to increased risk. [24, 25]

5. Susceptibility Determinants of Type 1 Diabetes

Susceptibility to type 1 diabetes is influenced by both genetic and environmental factors. The importance of inherited risk determinants is demonstrated by the clustering of the disease within families. The life time risk of diabetes among first degree relatives of diabetic individuals is 5–6%, compared with approximately 0.4% in the general white population. [26] Furthermore, the concordance rate for the disease is much higher among monozygotic twins (30–40%) than dizygotic twins (6%). [27, 28] Although this observation is indicative of a large genetic contribution to disease risk, the relatively low concordance rate among identical twins suggests that the susceptibility genes have low penetrance; that is, not all individuals who are genetically “at risk” of type 1 diabetes will develop the disease. Discordance between identical twins may reflect the generation of disparate immunological repertoires, through random rearrangement of the genes encoding T cell receptors and B cell receptors, stochastic events, or somatic mutations. Alternatively, it may indicate an important non-genetic (environmental) input to disease susceptibility. The importance of environmental determinants of disease risk is further supported by the seasonal variation in the incidence of diabetes, with most new cases occurring in autumn and winter, [29] and the geographical variation in disease incidence. For example, the incidence of type 1 diabetes among French and Jewish children living in Canada has been reported to be higher than among their counterparts living in France or Israel. [29] Overall, environmental factors are thought to account for up to two thirds of disease susceptibility.

6. The future pipeline

We would like to argue that animal models, when employed correctly, can be extremely useful for testing and optimizing new interventions for human type 1 diabetes. In addition, the new knowledge being accrued must be assimilated. We suggest the following strategic guidelines for pipeline development.

6.1. Defining the optimal dose for an antigen or biologic.

Treating with the correct dose is of paramount importance, for ASI treatment with incorrect doses may result in loss of

efficacy or may even be accelerating. For biologics, treating at an incorrect dose may not only mean loss of effect, but also increased side effects, if too much drug is given. Assumptions may be made that, for example, a monoclonal antibody targeting T cells will be effective as long as there is target molecule internalization; however, studies in mice show that there may be an approximate log-fold difference in dose between internalization and full efficacy. Thus, careful dosing studies in models, coupled with appropriate biomarkers, will be critical in attaining good efficacy in humans.

6.2. Preclinical testing of combinations.

Despite the logic of this approach, it is becoming clear that not all combinations exhibit additive effects, let alone synergies. Thus, careful optimization of combinations prior to clinical trials is needed. As a case in point, for example, not all antigens synergize with anti-CD3 therapy [30]. To accelerate translation in this arena, the Immune Tolerance Network has established a combination therapy testing consortium, in which four independent laboratories evaluate combinations of biologics and antigens in recent-onset diabetes in NOD mice. Such studies have so far demonstrated limited additive effects when examining potentially new combinations of biologics and antigens in recent-onset diabetes. Clearly, it will be important to establish which combinations work, and how.

6.3. Assessing patient heterogeneity.

Is all type 1 diabetes the same? Our knowledge to date indicates that this is unlikely to be the case, and this should caution us to anticipate subgroup effects. For example, the rate of β cell loss varies between individuals, being most rapid in younger individuals aged 20 or less [31]. The fact that Diapep277 only had its effects in older patients and in those with lower-risk major histocompatibility complex (MHC) illustrates this [32]. To date, we are not certain whether the underlying immune pathology varies between different forms of type 1 diabetes.

6.4. Defining the optimal disease stage for a given therapy.

One paradigm that may emerge from ongoing diabetes trials is that the more aggressive the immune CD8 reactivity to islets, the more advanced β cell loss is, the less likely it is that any treatment will be effective. Monoclonal anti-CD3 antibodies do not appear to preserve C-peptide in patients with advanced β cell loss.

6.5. Managing expectations.

Taking the above issues at face value, not overinterpreting the data from animal models or being excessively optimistic and refraining from conducting trials simply because drugs are available and effective in other immune disorders is an important message set to help avoidance of disappointments with future diabetes trials.

7. Conclusions

T1D, like other autoimmune diseases, is a composite of genetic and non-genetic effects, leading to the destruction of insulin-secreting cells. However, the variability in presentation

of the disease and the presence of distinct immunogenotypes points to heterogeneity reflected in a heterogeneity of the underlying genetic susceptibilities. This heterogeneity is particularly noted in the age at onset of T1D, in which the HLA load is greater with an earlier disease onset.

If genetic and epigenetic analyses are to have clinical utility, it will likely be in disease prediction, prediction of disease outcome, and prediction of best therapeutic approaches; and in this, autoimmune T1D is no different from Type 2 diabetes. Much of what we have discussed relates to disease prediction, given that the combination of genetic risk plus diabetes-associated autoantibodies is a powerful predictor of clinical disease. Less certain, and not discussed, is the potential for genes to predict the macrovascular and microvascular consequences of the disease. However, the genetic risk factors are likely to be shared with T2D, just as are the complications of diabetes. Since T1D and T2D are genetically distinct, the genetic susceptibility to these complications is unlikely to reside within genes associated with the disease risk. The same may not be true for the management of the disease, as the genetic evidence points towards disease heterogeneity, and by implication different approaches may be required to prevent or limit the progression of T1D based on the variable genetic predisposition described here.

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