Review Article

New Genes and Emerging Mechanisms of Type 1 Diabetes

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Abstract

Type 1 diabetes susceptibility depends upon the complex interaction between numerous genetic as well as environmental factors. 50% of the familial clustering of T1D is explained by HLA locus alleles. Other multiple loci contribute the rest of susceptibility, in which very little were known since last few years. Four novel loci were found from the results of stage-I, genome-wide association (GWA) studies which were carried out with high-density genotyping arrays. As the stage-II of the Genome Wide Association studies completed, hopefully, most of the genetic reasons of Type 1 Diabetes will be identified.

Key words: Type 1 diabetes, Autoimmune diseases, HLA class II

Introduction

The self destruction of the pancreatic β cells by immune system leads to produce insulin at low level as a result cause Type 1 diabetes (T1D) (Devendra *et al*. 2004). Multiple genetic as well as environmental factors are one of the reasons in the onset of Type 1 Diabetes (Knip *et al*. 2005). With the entry of dendritic cells, T lymphocytes (both CD8+ and CD4+) and macrophages, destruction of insulin producing beta cells takes place, without damaging somatic cells as well as glucagon. Young individuals are mostly affected by this disease, usually most of the cases are diagnosed before age of 18 years.

Overview of T1D genetics

About half of T1D familial clusters are related to HLA region on chromosome 6p21 (Cucca *et al*. 2001; Noble *et al*. 1996; Kelly *et al*. 2003; Devendra and Eisenbarth 2003). Insulin gene (INS) located on chromosome 11p15 (Bennett *et al*. 1995; Undlien *et al*. 1995), PTPN22 located on chromosome 1p13 (Bottini *et al*. 2004; Smyth *et al*. 2004; Qu *et al*. 2005; Ladner *et al*. 2005), CTLA4 located on chromosome 2q31 (Ueda 2003), the receptor of interleukin-2 (CD25, encoded by IL2RA) that is located on chromosome 10p15 (Vella *et al*. 2005; Lowe *et al*. 2007; Qu *et al*. 2007), IFIH1 (also called MDA5) located on chromosome 2q24 (Todd *et al*. 2007; Smyth *et al*. 2006) in recent times, CLEC16A (KIAA0350) located on chromosome 16p13 (Todd *et al*. 2007; Hakonarson *et al*. 2007), PTPN2 is mapped on chromosome 18p11 and CYP27B1 located on chromosome 12q13 are crucial regions which are associated with Type 1 Diabetes (Table 1) having less effects as compared to HLA region.

The main mechanisms and the development of T1D are revealed by the study of these susceptibility genes, focusing diagnostic, therapeutic and prophetic implications. The genetic map of type 1 susceptibility genes presented by Genome Wide Association studies might enable us to distinguish between immune-dysregulation phenotypes and homogenous phenotype which react in a different way to diverse precautionary intervention. Figure 1 represents the action sites of type 1 diabetes susceptibility genes.

HLA Class II

The DQ and DR genes of the Human Leukocyte Antigen class II region contribute strongly to T1D susceptibility. DR3-DQ2 and DR4-DQ8 are most important combinations of HLA genes (haplotypes), present in 90% of Type 1 diabetic patient. However, DR15-DQ6 has found to be involved in the protection of T1D, and is found only in less then 1% patient while in general population 20% found (Devendra *et al*. 2004; Devendra and Eisenbarth 2003). Although due to linkage disequilibrium all the T1D linkage to HLA is not explained by DR-DQ, but determination of other weaker component is not easy. Minor effects from the class I HLA molecules A and B have been identified by the regression analysis recently. All nucleated cells express class I HLA genes and act as antigen presenting cells for CD8+ T cells, which are involved in autoimmune process (Nejentsev *et al*. 2007).

INS Gene:

Second most susceptible genetic locus of T1D is the VNTR mapped at 596 bp upstream of the insulin gene (INS) that is located on chromosome 11p at position 15.5. INS gene consists of 14-15 bp tandem repeat sequences (Bennett *et al.* 1995; Undlien *et al*. 1995). Short class I VNTR alleles (26 to 63 repeats) are responsible for predisposition of T1D while class III alleles (140 to 210 repeats) may exhibit protective activity. These VNTR mapped 596 bp upstream of INS regulates cis transcription of INS gene. The class III alleles are highly associated in thymus whereas show less association in INS mRNA in pancreas as compare to class I alleles (Vafiadis *et al*. 1997; Pugliese *et al*. 1997).

PTPN22:

Recently a third T1D susceptibility gene PTPN22 mapped on chromosome 1p13 has been identified (Bottini *et al*. 2004; Smyth *et al*. 2004; Qu *et al*. 2005; Ladner *et al*. 2005) which is directly associated with T cell activation. PTPN22 encodes protein lymphoid tyrosine phosphatase which is also called as 'Lyp'. This protein dephosphorylate the three kinases which are important for TCR signaling

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Table 1. T1D-susceptibility loci

Locus	Gene	Odds ratio		Predisposing allele frequency	Postulated mechanism	Refs
		Het	Hom			
6p21	*HLA DR-DQ*	0.02–11.4	0.02–49.2	~20% of Europeans carry at least one predisposing allele and ~15% a strongly protective one	Present exogenous antigen processed by APCs, with some antigen specificity. Predisposing alleles might bind autoantigens poorly, compromising adaptive self-tolerance.	[9–13,31–34,70]
6P21	*HLA-A*	0.29–1.23		Multiple alleles	Present endogenously synthesize antigen (e.g. viral) by all cells. Mechanism might be similar to DQ-DR.	[30]
6p21	*HLA-B*	0.73–3.6		Multiple alleles		[30]
11p15	*INS*	2.68	3.27	0.71	Modulation of thymic expression and central tolerance to insulin.	[14–16,35–38,41,42]
1p13	*PTPN22*	1.95	4.16	0.94	Moderates TCR signaling by dephosphorylation. Gain of function might inhibit proper development of tolerance.	[17–21,43–50,71]
2q31	*CTLA4*	1.14	1.5	0.55	Moderates T-cell activation. Functional effect of locus to be determined.	[22,23, 51–55]
10P15	*IL2RA*	1.87	3.89	0.90	Modulation of the effect of IL2 on regulatory and/or effector T lymphocytes.	[24–26]
2q24	*IFIH1*	1.18	1.37	0.61	Triggers interferon response upon recognition of viral RNA. Might be involved in infectious etiology of T1D.	[50–53]
16p13	*CLEC16A*	1.29	1.42	0.68	Function unknown. Contains C-lectin and ITAM domains.	[12–14]
18q11	*PTPN2*	1.33	1.61	1.7	Phosphotyrosine phosphatase. Role likely similar to *PTPN22*.	[13,14]
12q24		1.24	1.74	0.48	Not mapped to specific gene.	[13,14]
12q13		1.31	1.58	0.35		[13,14]

hence inhibiting its signal transduction activity (Hill *et al*. 2002; Gregersen and Behrens 2006). Lyp also interact with kinases suppressor called Csk: C-terminal Src tyrosine kinase which results in the downregulaton of T cell activation (Gregersen and Behrens 2006; Cohen *et al*. 1999). T1D associated SNP at position 1858 from Cytosine to Thymine results in the substitution of arginine to tryptophan at location 620 of lymphoid tyrosine phosphatase protein. As tyrosine phosphatases protein play a significant role in T cell receptor signaling, hence PTPN22 is considered a good candidate gene for T1D susceptibility. PEST domain-enriched tyrosine phosphatase commonly called Pep, which is the murine homolog of Lyp, when specifically disrupted cause increased number of memory T cells that emphasize autoimmunity (Hasegawa 2004). When Lyp interacts with tyrosine kinase Csk its function of inhibiting T cell receptors transduction is greatly improved (Cloutier and Veillette 1999).

CTLA4

CTLA4 (CYTOTOXIC T-LYMPHOCYTE-ASSOCIATED ANTIGEN 4) mapped on chromosome 2q33 is also know to be a good candidate gene for type 1 diabetes as it negatively regulate T cell activation. In one of the largest genomic studies up till now (Ueda 2003), effect of flanking region of 3' end of the SNP was mapped, however, 5' effect of gene cannot be excluded. In one of the 5' effect substitution of A to G at residue 49 occur in first exon, resulting in the replacement of Ala for Thr, while C318T substitution occure in promoter region. (Anjos *et al*. 2004; Anjos and Polychronakos 2004; Teft *et al*. 2006). Primary amino acid sequence of CTLA4 is altered by A49G substitution only. Unexpected glycosylation of CTLA4 mutant in endoplasmic reticulum, as observed by A49G CTLA4 in vitro studies, cause reduction in its cell-surface expression (Anjos *et al*. 2002). On the other hand increased level of CTLA4 expression (Wang *et al*. 2002; Anjos and Polychronakos 2004) is observed in C318T polymorphism due to higher promoter activity, leading to decrease activation level of T cell. Therefore C318T polymorphism play a defensive role for autoimmune disease.

IL2RA

From recently conducted genome wide association studies a novel type 1 diabetes locus IL2RA has been identified, mapped on chromosome 10p15. 1 (Vella *et al*. 2005; Lowe *et al*. 2007; Qu *et al*. 2007). Three α chains of IL-2 receptor complex, which is also called CD25, are encoded by the eight exons of IL2RA gene. IL2RA is an essential component of immune regulation as it modulate immunity. For the suppression of autoimmune disease and T cell mediated immune response, expression of IL2RA on regulatory T cell is very essential. (Salomon *et al*. 2000; Malek and Bayer 2004; Viglietta *et al*. 2004). Due to these functions IL2RA gene is considered as an appealing candidate for Type 1 diabetes, which plays an important role in its pathogenesis, involving regulatory T cells.

IFIH1

Innate immunity regulating RNA helicase, against viral infection as well as various autoimmune conditions, is encoded by interferon-induced helicase (IFIH1) mapped on chromosome 2q24 (Kato *et al*. 2006). As a result of major association study of candidate SNPs, IFIH1 which is also called Helicard, gene and MDA-5 (melanoma differentiation-associated 5) (Smyth *et al*. 2006) is identified as a new locus for Type 1 Diabetes. Even with the presence of other genes in LD block, interferon-induced helicase (IFIH1) is consider as the best candidate for type 1 Diabetes as it is only gene with some common known nonsynonymous polymorphism. Role of interferon-induced helicase (IFIH1) in the protection of host from infection that is caused by virus by recognizing nucleic acid of virus and activating apoptotic and cellular antiviral response is thought to be one of its major aspect. (Yoneyama *et al*. 2005; Meylan *et al*. 2006). As it is suggested by many studied that there is a correlation between T1D and infection caused by virus (Knip *et al*.

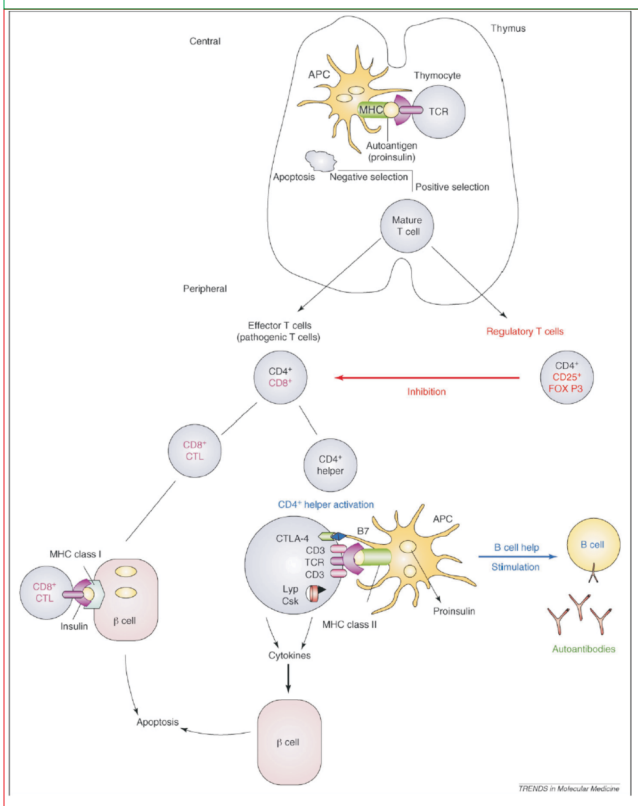

Fig. 1. Peripheral and Central tolerance to self peptides. The thymocyte maturation and its selection taking place in thymus results in central tolerance. The process engages MHC proteins and APC's interaction, the self peptide (proinsulin) and the TCR on thymocyte. Negative selection of strongly self reactive thymocytes take place (98%) and thymocytes with low affinity are positively selected (2%).

2005), hence the importance of interferon-induced helicase (IFIH1) gene as a good functional candidate of T1D is well considered. The SNP rs1990760 is supposed to be the most associated marker of IFIH1, and encode Alanine to threonine substitution at codon 946 (Smyth *et al*. 2006). As a result of these findings related to IFIH1 gene, type of pathogens which are potentially involved in triggering type 1 diabetes are somewhat narrowed down.

CYP27B1

Vitamin D 1-α-hydroxylase, which plays an important role in the synthesis of active vitamin D is encoded by CYP27B1: subfamily 27, cytochrome p450 and polypeptide 1. There are two single nucleotide polymorphisms in perfect LD (–1260C > A and +2838T > C) were establish to be related with Type 1 Diabetes (Bailey *et al*. 2007). As there is no splicing variant or common amino acid polymorphism, hence it is suggested that it probably affects the transcription mechanism. Various epidemiological evidences supporting the idea that vitamin D supplementation might be used to prevent Type 1 Diabetes has proved its significant importantance (EURODIAB 1999; Hyppo¨nen *et al*. 2001).

CLEC16A

One locus was identified in several populations by using different techniques (Todd *et al*. 2007; Hakonarson *et al*. 2007). It is located to a 300 kb LD block on chromosome 16p at position 13.2 and it contains a single gene. This gene is known as C-type lectin domain family 16 gene A (CLEC16A), formerly called as KIAA0350). It is expressed in immune cells as well as encodes a sequence of protein that is predicted having a C-type lectin domain (Finn *et al*. 2006). It also expresses in specialized APC like Dendritic Cells and B lymphocytes as well as in Natural Killer cells. This is very fascinating as C-type lectins participate in up taking of antigen and its presentation by DCs and b cells. There is a possibility that there is no association between T1D and CLEC16A but variants are affecting other two genes that slightly overlap the related LD block. Genes that were predicted theoretically and have't been studied so far are LOC729954 and dexmethasone induced (DEXI) that is upregulated in emphysema (Tafuri *et al*. 2001). Effects on the immune system that is caused by glucocorticoids usually make DEXI as a interesting candidate, but the problem associated with it is that it is usually expressed in low levels in heart, lung, liver and brain [GNF SymAtlas (http://symatlas.gnf.org/ SymAtlas)].

PTPN2

GWA studies present a novel locus which is located on chromosome 18q11 and is known as Phosphotyrosine-protein phosphatase non-receptor (PTPN2) (Todd *et al*. 2007) PTPN2 is stands for phosphotyrosine protein phosphatase, non-receptor 2. Tyrosine phosphorylation that occur in activation of lymphocytes elucidate the importance of this gene in pathogenesis of T1D which may results in designing novel therapies and patho-physiological insights by some special types of inhibitors.

Genome Wide Association studies have revealed high level of statistical significance in only a little percentage of loci, leading to replication. It is hoped that as the replication stages completed it will augment additional groups that will improve statistical power. To reveal actual genetic basis of T1D will take some time. Molecular basis of T1D will be revealed with the help of fine mapping and functional studies that will also help in designing novel therapies.

Conclusions and Future Perspectives

T1D is a multifaceted and polygenic disease. Identification of T1D susceptibility genes is hindered by the multi-factorial character of the disease and genetic interactions that occur between loci. Up till now, HLA-DQ genes, located in HLA region are the most susceptible genes in T1D. MHC genes may modify their influence (i.e. HLA-B, -DRB1 and -DPB1). The VNTR of insulin gene also play crucial role in this disease. Genome wide screening has identified many regions of chromosomes which may contain genes that are susceptible to T1D, though its location and aetiological mutations or polymorphisms have to be identified.

More genetic study is needed in order to recognize all the T1D susceptible genes as well as to identify their role in pathogenesis of disease. This type of information will help to develop the screening approaches to identify those individuals that are higher at risk to develop T1D. This information will facilitate us to develop strategies for treatment. Thus, genetics understanding of T1D will make a significant contribution for the prevention of the disease.

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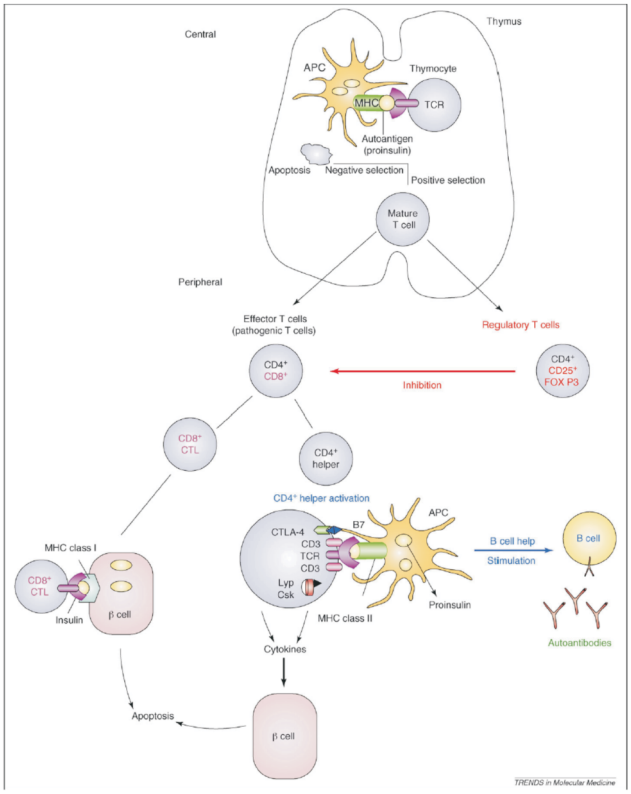

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