Review article

Epigenetic and Diabetes Mellitus Type 1

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Abstract:
Type 1 diabetes mellitus (T1D) is one of the commonest chronic autoimmune diseases. It's characterized by formation of islet specific T cells and autoantibodies leading to chronic inflammation in the islelets, i.e. inflammatory destruction of the β cells resulting in an insulin deficiency.

T1D resulting from the interplay of genetic, epigenetic, and environmental factors. Worldwide, the T1D epidemic represents an increasing global public health burden, Egypt ranked 8th highest in the world. The incidence of T1D among the children has been rising. There has been an overall increase in the incidence of T1D of 3% to 5% per year. Suggested the interaction between genetic predisposition and environmental factors. The low disease concordance rate in adult-onset T1D (<20%) suggests that environmental and epigenetic changes may play a predominant role.

Circulating miRNA is now a biomarker for example miRNA 375. miRNA 375 control cellular growth, proliferation and cellular function, and it released when β cell destruction and so it can be used as a novel T1D marker .it early detected in plasma**,** while T1D is usually diagnosed when >80 % of pancreatic β cells are destroyed. miRNA 375 easily detectable can detected blood, can found in serum, plasma and urine. Also miRNA 375 is stable even against boiling low or high pH, multiple freeze throw cycle.

Diane Mathis, Benoist and co-worker at Harvard medical school and GlaxoSmithKline reported that an epigenetic drug called BET151 can effectively prevent T1D in mouse model for these diseases. This is by neutralizing the cytokines, blocking the interaction of T cells and antigen presenting cell and regeneration of β cells.

A novel epigenetic drugs for treatment of T1D by transdifferantiation of human dermal fibroblasts into insulin cell producing cells by inducing the expression of insulin through increasing acetylation and decrease methylation by two epigenetic modified compounds romidepsin a histone deacetylase inhibitor and Azacytidine that cant methylated.

Introduction:

Diabetes mellitus is a chronic metabolic disease due to an insufficient insulin response to elevated blood glucose levels ***(van Belle et al., 2011)***. It is associated with increased risk for a number of

co-morbidities including heart disease, kidney failure, blindness, and limb amputation, which culminate in a decreased life expectancy ***(Bluestone et al., 2010).*** Diabetes is divided into two major categories: T1D and type 2 diabetes (T2D). T1D, also known as insulin-dependent diabetes, occurs at all ages, particularly in children and adolescents. T1D can easily cause incapacity or even death in young patients, in contrast to T2D ***(Gang et al., 2016)***, it has been estimated that the average life span of individuals with diabetes is about 10 years shorter than diabetic general population ***(Nanees et al., 2008).***

While T2D is associated with aging, early development of insulin resistance, and a deteriorating β - cell function ***(Dirice and Kulkarn, 2011).***

T1D is a complex disease resulting from the interplay of genetic, epigenetic and environmental factors ***(Hakonarson and Gran, 2011)***. Over the last few decades, there has been an overall increase in the incidence of T1D of 3% to 5% per year ***(Karmen et al., 2013).***

The Prevalence of T1D in some eastern Mediterranean countries is among the highest in the world. The highest rates are reported in Egypt, Kuwait, Lebanon, Oman and Qatar ***(Nanees et al., 2008)***.

A role for non-genetic factors was suggested by studies of migrant populations, the recent rise in T1D prevalence and twin-cohorts. For example, a monozygotic (MZ) twin of a T1D–affected co-twin will not always develop the disease; only 50% do so, even though MZ twins are genetically identical.

Waddington coined the term epigenetics to refer to "the branch of biology which studys the causal interactions between genes and their products which bring the phenotype into being" ***(Waddington, 1942)***. Now epigenetics is defined as modifications of the genome, heritable during cell division, that do not involve a change in DNA sequence ***(Haig, 2004)*** through its ability to mediate gene silencing or gene activation ***(Hamm and Costa, 2015).*** It include control of gene expression by DNA methylation and histone modification ***(Dana and Klaus, 2012)*** and microRNAs ***(Esteller, 2011).***

Epigenetic modifications can occur when individuals are exposed to environmental factors, such as infections and nutritional changes, which may predispose them to diseases such as diabetes**.**

Nucleosomes, the basic subunits of chromatin, consist of octamers of histones H2A, H2B, H3 and H4, wrapped by DNA. Histone modification (e.g., acetylation, methylation, phosphorylation, and ubiquitylation) form an epigenetic layer affects gene transcription ***(Feng et al., 2014).***

In mammalian cells, DNA methylation occurs on cytosines in the context of cytosine-phosphate-guanine (CpG) dinucleotides at the

5 position to create 5-methylcytosine, and is mediated by methyltransferase Enzymes ***(Dana and Klaus, 2012).***

Pathogenesis of T1D:

Pancreatic cells are the target of an autoimmune assault in T1D, with invasion of the islets by mononuclear cells in an inflammatory reaction termed "insulitis," leading to loss of most β cells due to epigenetic DNA hypermethylation of cluster of differntiation (CD4) T cell lead to autoreacivity ***(Richardson, 1986).***

Cell death caused by direct contact with activated macrophages, T-cells and/or exposure to soluble mediators secreted by these cells, including cytokines, nitric oxide, and oxygen free radicals. After prolonged exposure to interlukin 1-β (IL1-β), interferon gamma (IFNγ) and/or tumor necrosis factor alpha (TNFα) but not to either cytokine alone, this functional impairment evolves to β-cell death ***(Miriam, et al., 2005)***.

In T1D, epigenetic phenomena, such as DNA methylation, histone modifications and microRNA (miRNA) dysregulation, have been associated with altered gene expression ***(Dang et al., 2013).***

Micro Rnas As Disease Biomarkers:

miRNAs identified as a class of conserved 19-25 nucleotide non-coding RNA which could regulate gene expression through a post-transcriptional approach ***(Ling et al., 2013)***. The importance of miRNAs in the regulation of multiple biological processes has become evident recently ***(Ameres and Zamore, 2013).*** miRNAs regulate approximately 30% of the human protein-coding genome and miRNAs control the expression of genes involved in several biologic processes such as apoptosis, proliferation, differentiation , metastasis ***(Filipowicz et al.,2008)*** growth and development ***(Barte, 2004).***

miRNAs have been detected in biological fluids including blood which known as 'circulating miRNAs', can originate from dying cells ***(Emeline et al., 2014)*** and several studies confirm their presences in body fluids as blood, saliva, urine and serum. The stability of serum miRNAs has been investigated under harsh conditions including boiling, low/high pH, extended storage and freeze thaw cycles ***(Lotte et al., 2012).*** It can be easily detected and quantified by PCR.

T1D is associated with distinct modification in the profile of miRNAs in the blood which are sometimes detectable several years before the disease manifests, also certain miRNAs seem to be predictive of long term complication ***(Guay and Regazzi, 2013).***

T1D is initiated years before clinical onset and continues until nearly all insulin-producing cells

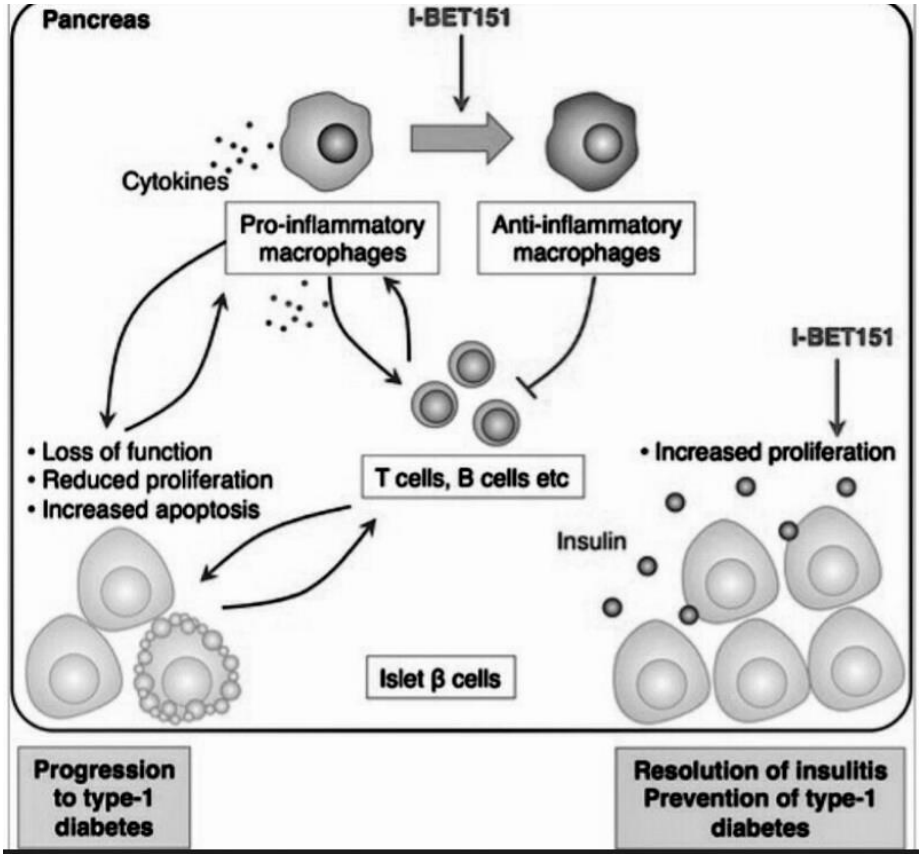
have been destroyed by autoimmune processes. ***(Jasmin et al., 2013).*** However, these antibodies appear fairly late in the course of T1D, not being ideal biomarkers of the initial destruction of β cells ***(Tais et al., 2015).***

On the other hand miRNA 375 is islet specific miRNA that can be used as an early marker of β cells death and potential predictor of the disease ***(Suheda et al., 2013).***

Is T1D can be curable?

Novel Epigenetic Drugs:

recently Diane Mathis, Christophe Benoist and co-workers at the Harvard Medical School and GlaxoSmithKline—including Wenxian Fu as first author—report that a drug called I-BET151 can effectively prevent T1D in a mouse model for this disease ***(Fu et al., 2014)***,Figure :(1)



(Yohko and Naganari, 2014)

Fu et al, reveal that I-BET151 works to resolve inflammation of the islet β cells (insulitis) mainly by two mechanisms. Firstly, it encourages macrophages in the pancreas to convert from being pro-

inflammatory (which release cytokines that promote inflammation, to being anti-inflammatory type. This inhibits the further recruitment of T cells and dampens inflammation. Secondly, I-BET151 enhances the proliferation of islet β cells and enhances insulin production ***(Yohko and Naganari, 2014)***.

Epigenetic Islet Transdifferentiation:

Transplant islets from cadaveric donors have been developed ***(Shapiro and Lakey, 2000)***, however, their use was limited mainly because of the shortage of donors ***(Lakey et al., 2006).***

Liora et al. (2013) reported successful transdifferentiation of primary human dermal fibroblasts (hDFs) to induce expression of transcription factors (TFs) and hormones characteristic of the islets of Langerhans. They showed that histones associated with the insulin gene were hyperacetylated and that insulin gene DNA was less methylated in islet cells compared to cells that didn't express insulin. Using two compounds that alter the epigenetic signature of cells, romidepsin (Romi), a histone deacetylase inhibitor, and 5-Azacytidine (5-AzC), a chemical analogue of cytidine that cannot be methylated, they reported that, hDFs exhibited a distinctive regulation of expression of TFs involved in islet development as well as of induction of insulin ***(Liora et al., 2013)***.

Recommendation:

More researches on the use of miRNA as early diagnosis of T1D instead of traditional markers are necessary for prevention and or controlling of T1D in predisposed individuals.

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