

Review Article

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Promising Epigenetic Approaches Targeting TH17 in Autoimmune Diabetes among Chronic Hepatitis C Infection

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ABSTRACT

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The revolution of Epigenetics mechanisms including mi-RNA, DNA methylation and histone modification has drawn our attention to target Th17 cell regulatory cytokines and transcription factors which in turn will inhibit the production of interleukin 17 (IL17)- as it's the key pro-inflammatory cytokine secreted by TH17 cells. The importance of targeting TH17 pathways in autoimmune diabetes come with the deeply ingrained idea of the great role of TH17 in immune pathogenesis of autoimmune diseases. Hepatitis C virus is one of the most common environmental factors which could trigger autoimmune diabetes by inducing local inflammation with cytokine and chemokine secretion (also called "bystander mechanism").

Introduction

Diabetes mellitus and hepatitis C virus infection are two important public health problems associated with high morbidity and mortality (Antonelli *et al.*, 2014).

Globally, Approximately 200 million people become infected with HCV and 350,000 people per year die from the disease (Abdel-Hameed *et al.*, 2016; Hetta, 2014; Hetta *et al.*, 2015; Mehta *et al.*, 2016; Shata *et al.*, 2013).

It has been reported that patients with chronic hepatitis C virus infection are more liable for diabetes mellitus than other liver diseases including hepatitis B virus infection (Hammerstad *et al.*, 2015).

Even though HCV is a hepatotropic pathogen, the antigen and viral sequences have been detected in pancreases of HCV infected patients which suggested that the infected pancreas might act as a reservoir for HCV and may play a role in persistence of infection and in turn triggering islet autoimmunity (Hetta *et al.*, 2016; Hieronimus *et al.*, 1997).

Also it is possible that it can promote autoimmunity by inducing local inflammation with cytokine and chemokine secretion (also called "bystander mechanism") (Hammerstad *et al.*, 2015; Helal F. Hetta and Tohamy A. Tohamy, 2017; Yan *et al.*, 2000).

The American Diabetes association classification, which is based on the etiological criteria has defined three types of diabetes type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and the third type is Latent autoimmune diabetes of the adult (LADA), sometimes called Type 1.5 diabetes as it is considered as a subtype of Type 1 diabetes, is an autoimmune diabetes defined by adult-onset, presence of diabetes associated autoantibodies, and no insulin treatment requirement for a period after diagnosis (Laugesen *et al.*, 2015). In general it is the most prevalent type of autoimmune diabetes.

Among HCV infection Type 2 diabetes may go undiagnosed for autoimmune β cell alterations and as misdiagnosed as type 2 diabetes mellitus.

The diagnosis of LADA in HCV infected patients based on their age and time of diagnosis (Antonelli *et al.*, 2014; Gale, 2005).

Lack of understanding LADA or slow-onset type 1 diabetes mellitus

Phenotypically, LADA is usually misdiagnosed as type 2 diabetes, actually LADA share genetic features with type 1 and type 2 diabetes. Also LADA has worse HbA1c levels than type 2 diabetes.

Immunologically, GAD, glutamic acid decarboxylase autoantibodies are the most common marker in adult-onset diabetes.

Also, islet cells (ICA), insulin-associated antigen (IA2A), or insulin (IAA) and ZnT8 antibodies can be detected in LADA.

Clinically, LADA patients tend to have a lower mean age at diabetes onset, lower body mass index and more frequent need for insulin treatment than patients with type 2 diabetes.

As it is known that Type 1 diabetes mellitus is caused by T-cell mediated destruction of insulin-producing cells. The role of Th17 cells in autoimmune diseases is thought to be associated with their ability to promote inflammatory cytokines and chemokines production by macrophages and other phagocytes which is usually mediated by its key pro-inflammatory cytokine IL17a (Helal F. Hetta, 2017; Ryba-Stanisławowska *et al.*, 2013). Targeting TH17 cells has received intense attention of researchers and clinicians alike with documented effects in inflammation and autoimmune diseases. Herein we will discuss in brief the different new epigenetic mechanism of targeting TH17 pathways which is suggested to be helpful for eradication of autoimmune diabetes among HCV infected patients.

TH17 and autoimmune diabetes

Nowadays, the discovery of TH17 cells and its important role in immune pathogenesis of several autoimmune diseases have changed the concept of the implication of TH1 cells in immune pathogenesis of autoimmune diseases (Zambrano-Zaragoza *et al.*, 2014).

TH17 are usually associated with the transcription factor ROR γ t and secretion of the pro-inflammatory cytokines IL-17 (IL-17A) and IL-17F (Emamaullee *et al.*, 2009).

Because Th17 subsets are increasingly considered to be a key mediator of all autoimmune disease, all the great efforts now focusing on the new therapeutic strategies designed to inhibit these cells are likely to be applicable in type 1 diabetes or type 1.5 diabetes.

Since 2003, the discovery of IL23 and its great role in promoting autoimmune diseases as it serves as a pivotal factor that initiate differentiation and inflammatory function of

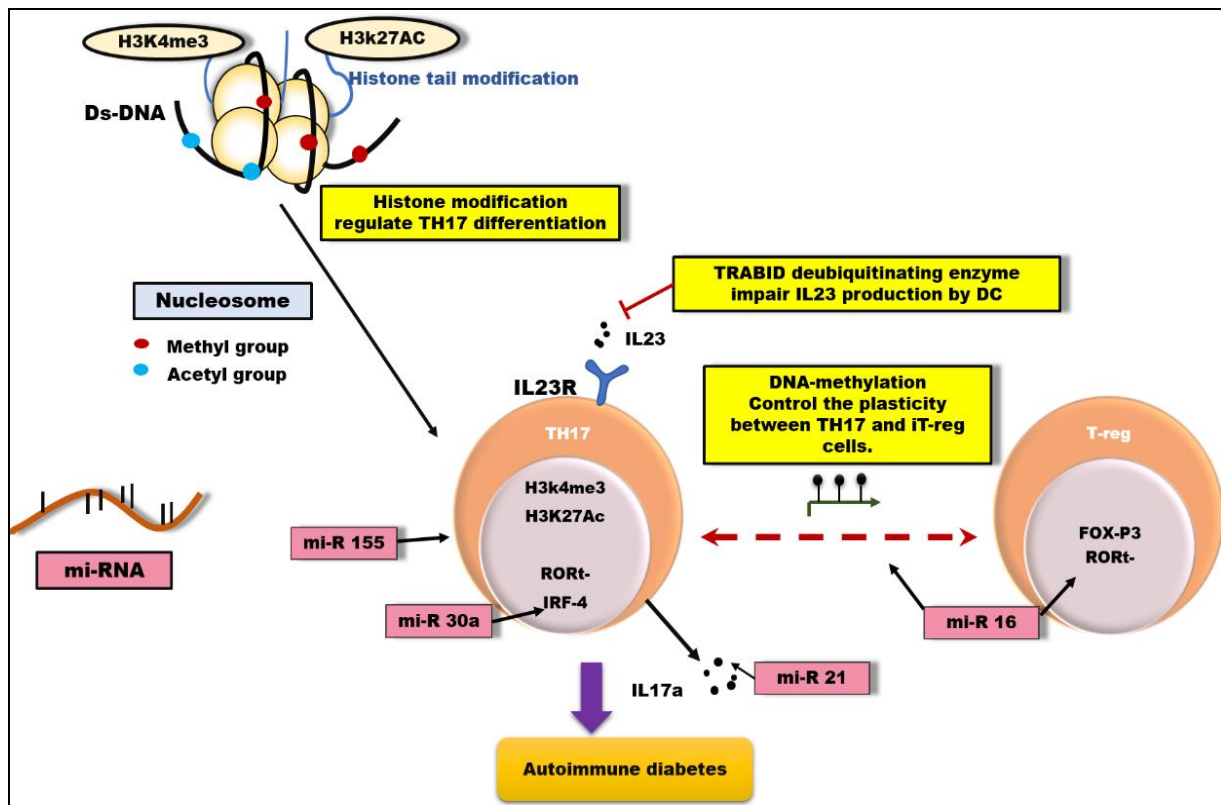
pathogenic TH17 as it is critical for expansion and survival of TH17 cells. Interaction of IL-23-producing APCs and Th17 cells has been shown to have a role in many autoimmune diseases. In support of this view, all the immunologist trials is targeting IL-23 pathway, IL-17 production or action by using IL-17R antagonist and IL-17A-blocking antibodies have been shown to attenuate autoimmune diseases(Gaffen *et al.*, 2014). A recent study has reported that the combination of inhibition of IL-23 and IL-17 is more potent in treating Th17-mediated

autoimmunity in mouse models (Mangan *et al.*, 2015).

Epigenetic regulation of TH17 cells

There are three main epigenetic modifications, including DNA methylation, histone modification, and microRNA. All of them are associated with transcriptional regulation and determination of the cellular transcriptome, thereby contributing to cell function (Lee *et al.*, 2009) as shown in figure 1.

Fig.1 Different epigenetic mechanisms that regulate TH17 differentiation. MicroRNA 21 is highly upregulated in Th17 cells and increase expression of IL17. MicroRNA 16 control the balance between iTreg and TH17 by affecting the expression of ROR γ t and FoxP3.MicrRNA 155 enhance TH17 cells differentiation and increase IL17 production. MicroRNA 30a regulates Th17 differentiation by inhibiting the translation of IRF-4 factor which in turn facilitate ROR- γ recruitment and binding to TH17 cells. Histone modification control TH17 differentiation by increase exhibition high levels of H3K27Ac and H3K4me3 which are two active regulations during Th17 cell differentiation. TRABID which is one of deubiquitinating enzymes impaired the induction of IL23 which in turn impair production of TH17. DNA methylation is also important for the generation and plasticity of Th17 and iTreg cells



mi-RNA and TH17 cells

There is no doubt that miRNA is able to regulate the expression of several (maybe even hundreds of) target genes and are involved in important processes, such as embryonic development, immune response, inflammation, and oncogenesis, as well as cellular growth and proliferation. Positive correlations in miRNA expression and IL-17 levels have been observed in different studies (Khan & Ansar Ahmed, 2015).

Emerging studies indicate that miR-21 promotes inflammation and plays important roles during the pathogenesis of autoimmune disease including type 1 diabetes (T1D) (Osipova *et al.*, 2014). In an interesting study, Murugaiyan *et al.*, found that miR-21 expression is elevated in Th17 cells and that miR-21-deficient mice produce fewer Th17 cells and are resistant to EAE (Murugaiyan *et al.*, 2015). Another recent study, Dong *et al.*, have reported that miR-21 negatively regulate the TH17 differentiation in PBMCs of RA patients. (Dong *et al.*, 2014). Also Wu YH *et al.*, have found that miR-16 may be involved in Th17/Treg imbalance of RA patients by affecting the expression of ROR γ t and FoxP3 (Wu *et al.*, 2016).

Ryan O'Connell *et al.*, have shown that miR-155 plays an important role in driving chronic inflammation that is inappropriately directed at tissue-specific antigens, a destructive process that is at the heart of human autoimmune diseases as miR-155's has positive role in Th17 cell development by blocking the inhibitory impact of cytokines such as IL-4 and IFN- γ on the Th17 cell differentiation pathway (O'Connell *et al.*, 2010).

IRF-4, member of interferon regulatory factor family, is one of the pioneer factors that could facilitate ROR- γ recruitment and binding to

TH17 cells. Due to its great role in regulation of the differentiation of TH17 cells, Ming Zhao *et al.*, put all his focus in his recent study on, MS, multiple sclerosis patients to find the miRNA that could control IRF-4 regulation by using in-depth RNA-sequencing analysis. Finally, he succeeded to be the first one which reported that miR-30a regulates Th17 differentiation by inhibiting the translation of IRF-4 factor (Zhao *et al.*, 2016)

Role DNA methylation and histone modification in regulation of TH17 cells

DNA methylation and Histone modifications, which include methylation, acetylation, ubiquitination, phosphorylation, and simulation, are classified as transcriptionally active or repressive markers and one of the epigenetic maintainers (Araki & Mimura, 2017)

It has become interestingly enough that histone modifications, such as acetylation or methylation, are widely found at many Th17 cell-specific gene loci, including RORC, IL-23r, therefore playing significant roles in maintaining Th17 cell chromatin state. The ROR γ t loci is indispensable for Th17 development and exhibits high levels of H3K27Ac and H3K4me3, which are two active regulations during Th17 cell differentiation, as well proved to be marked at the IL17a and IL17f loci (Wang *et al.*, 2016), (Akimzhanov *et al.*, 2007).

Also in an interesting study highlighted an epigenetic mechanism for regulation IL12 and IL23. The deficiency of Trabad which is TRAF-binding domain (TRABID) and one of deubiquitination enzymes-in DCs and macrophages impaired the induction of IL12 and IL23 which in turn impair production of the TH1 and TH17 subsets of inflammatory T cells and this could render autoimmune encephalomyelitis as Trabad regulates histone

modifications at the IL12 and IL23 promoter by controlling the fate of the histone demethylase Jmjd2d (Jin *et al.*, 2016).

DNA methylation is also important for the generation and plasticity of Th17 and iTreg cells. The IL17a gene remains hypermethylated in naive CD4+ T cells and is only demethylated in IL17A-producing effector cells. The recent evidence indicates that the chromatin structure of the IL17a, IL17f, IFNG, and ROR γ t loci in Th17 cells alter rapidly in response to cell-extrinsic factors, thereby showing a particularly high degree of plasticity.

Th17 cells have the capacity to express IFN- γ and IL17. The differentiation of Th17 into stabilized Treg cells was usually associated with stable FoxP3 demethylation and obtain suppressive function. Interestingly, Th17-derived regulatory T cells (Tregs) were resistant to Th17 reversion, which could have important clinical implications for immunotherapy. (Singh *et al.*, 2014; Suarez-Alvarez *et al.*, 2012)

In conclusion, the recent discoveries in the field of epigenetic including the three main mechanisms mi-RNA, DNA methylation and histone modification have improved our knowledge in immunotherapy for diabetes mellitus type 1 and type 1.5 which is considered one of the most common extrahepatic endocrine manifestation. Due to its pivotal role in regulation of TH17 cells which play the major role in the pathogenesis of diabetes mellitus type 1.

Signature miRNA profile can be potentially used as novel biomarkers for Th17-mediated immune reactions. However, more in-depth and mechanistic studies are required to further define the role of miRNAs in IL-17 induction and interplay of miRNA with IL-17-related transcription factors and signaling pathways

Conflict of Interest

The authors declare that they do not have conflict of interests.

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