MICRO*RNA*S WITH SPECIFIC ROLES IN DIABETES AND PSYCHIATRIC DISEASES

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Abstract

Diabetes mellitus is one of the most cited non communicable diseases and the most common metabolic disorder. Epigenetics represents the field of study of heritable changes in gene expression which are not directly related to DNA. Epigenetics is concerned, alongside histone modifications, short interfering RNAs etc., with microRNAs (miRNAs) as well. These are small noncoding RNAs, 21 to 23 nucleotides in length, which either inhibit translation or affect mRNA stability and degradation. At present, there are dozens of miRNAs which have been proven to be involved in the animal and human pathology of diabetes (type 1 or 2). This review focuses on the miRNAs which have been identified as playing a role in both psychiatric diseases and diabetes.

Keywords: diabetes mellitus, microRNA.

Introduction

Diabetes mellitus is one of the most common metabolic disorders. Epigenetics represents the field of study of heritable changes in gene expression which are not directly related to DNA and it studies: histone modifications, short interfering RNAs etc., microRNAs (miRNAs). These are small noncoding RNAs, 21 to 23 nucleotides in length, which either inhibit translation or affect mRNA stability and degradation. There are miRNAs involved in the animal and human diabetes mellitus (type 1 or 2). We review the miRNAs with a dual role in psychiatric diseases and in diabetes.

MicroRNA-9

MicroRNA-9 (mir-9) has been correlated with modifications in glucose-stimulated insulin release (GSIS). Plaisance et al. demonstrated, in the rat B-cell line INS-1E, that higher levels of mir-9 decrease the expression of the OneCut-2 (OC2) gene which determines an increase in granuphilin, exerting a negative control on insulin exocytosis. The authors have stipulated that, although mir-9 expression is higher in neurons than in B-cells, the lack of granuphilin expression in the former allows neurons to support these higher concentrations [1]. More recently, Ramachandran et al. showed, in vivo, on B-cells from Adult Swiss male mice, that "mir-9 levels increase during the fall-

ing phase of insulin secretion" [2].

The same group has also shown that mir-9 negatively regulates SIRT1 by targeting its 3'UTR region thus affecting GSIS in B-islets [2,3]. SIRT1 represents a mammalian class-III protein deacetylase that has also been linked to senescence and to cognitive functioning in an analysis of the Leiden 85-plus study [4,5]. It has also been shown that SIRT1 is correlated with depression in two Japanese human studies, one including patients with major depressive disorder or bipolar disorder, but not correlated to the therapeutic response to selective serotonine reuptake inhibitors (SSRIs) [6,7]. As such, mir-9, through its effects on OC2 and especially SIRT1 plays important roles both in insulin release and in depression, with much still to be learned about the molecular pathways through which these effects are obtained.

MicroRNA-16

Advanced glycation end products (AGEs) represent important molecules in the pathology of diabetes that act through the receptor for advanced glycation end products (RAGE) to induce cyclooxygenase-2 (COX-2), an inflammatory gene [8]. S100B is a ligand of RAGE that can increase COX-2 in different tissues, including pancreatic islets [9,10]. Physiologically, microRNA-16 (mir-16) can promote a rapid degradation of Cox-2 mRNA but this process is blocked, in vitro, by S100b which inhibits mir-16 expression [11].

A recent study by Baudry et al. on mice showed that chronic treatment with fluoxetine (a SSRI) increased

mir-16 levels in serotonergic raphe nuclei thus reducing the levels of the serotonin transporter (SERT), whilst the raphe released the molecule S100B, previously shown to be implicated in diabetic complications. S100B decreased mir-16 levels, promoting the expression of the serotonergic functions in noradrenergic neurons. The study also proved the implication of the Wnt receptor and of the connection between the locus coeruleus and the raphe in the treatment of depression with fluoxetine. This study is the first to prove the role of microRNAs in the treatment of depression [12,13] and it might explain the delayed onset of action of SSRIs in treating depression, at least in part [14].

While S100B is believed to have only a paracrine/autocrine function [15], it has already been demonstrated that this protein, through the immune reactions towards it, might represent a factor in Parkinson's disease and the impaired insulin response that occurs in this disease [16]. S100B has already been associated with depression, as shown previously, with a recent study demonstrating this association in patients with end-stage renal disease as well [17]. S100B has also been shown to be involved in mental stress [15], neurodegenerative disorders [16,18, 19], brain injury [20,21], head injury [22], and schizophrenia [23]. As such, S100B is already of interest as a treatment for several neurological and psychiatric diseases [15,21].

Another role for mir-16 seems to be in pancreas regeneration. While this organ is known for its regenerative capabilities, so far neurogenin3 (NGN3) is the only molecule that is expressed only during the pancreas' development and not during its regeneration. A recent study performed by Joglekar et al. has shown that during pancreas regeneration in mice, several microRNAs, including mir-16, activate an alternate, new pathway, which does not involve NGN3 [24], thus offering new therapeutic options for type 1 and 2 diabetes mellitus.

MicroRNA-132

In the past years, the dysfunction of circadian rhythms has been shown to play a role in major depression (MD) [25]. The first proof of microRNA-132 (mir-132) being involved in the circadian rhythms has come from Cheng et al. who have shown that mir-132 is induced by photic stimulation through several pathways [26]. In a more recent human study including 359 patients with MD and 341 controls, Saus et al. concluded that "we suggest a precise posttranscriptional regulation of circadian rhythms by miRNAs" with a role of rs76481776 SNP [single nucleotide polymorphism] in the control of sleep – awake rhythm [27].

Recently, Yang et al. have also proven that mir-132 represents an important factor in the differentiation of embryonic stem cells into dopamine neurons through a direct regulation of the expression of the nuclear receptor subfamily 4 group A member 2 (Nr4a2, also known as Nurr1) [28].

Reports regarding the function of mir-132 in dia-betes and insulin signaling are diverse: Numakawa et al. did not find insulin-like growth factor-1 (IGF-1) to have an effect in mir-132 regulation [29], while the in vivo experiments on Goto-Kakizaki (GK) rats of Esguerra et al. have shown that the expression of rno-mir-132 is upregulated by hyperglycemia, although during prolonged exposure to hyperglycemic conditions, the GK islets strived "to reset the levels of miRNAs to that of the controls" [30]. This last result is also confirmed by results obtained in isolated pancreatic islets of other mouse models [31].

An interesting finding is related to a study of gestational diabetes mellitus (GDM) in which the levels of mir-132 were significantly decreased in GDM patients in comparison with controls (p=0.042), the authors suggesting the utility of mir-132 as a "serum-based non-invasive biomarker" during early second trimester [32].

Malnutrition and over-nutrition: epigenetic mechanisms for diabetes and mental diseases

There have been numerous studies in which malnutrition of the mother during pregnancy or malnutrition of the child in the first years of life has been linked to diabetes. An Ethiopian study including 107 patients showed that diabetes was strongly associated (odds ratio= 5.5, 95% CI: 1.5-7.8) with a history of childhood malnutrition [33], while two studies of Mexican patients have suggested that early impaired nutrition in extrauterine life is correlated with insulin anomalies in young adult males [34] and that there is "a decreased activity of beta-cell function and increased insulin sensitivity in stunted children" [35]. A historical cohort study of 300.000 men exposed to the Dutch famine of 1944-1945 showed that nutritional deprivation in the first half of the pregnancy resulted in higher obesity rates (p<0.0005), while exposure in the last trimester of pregnancy and the first months of life led to lower obesity rates (p<0.005) [36].

One of the possible explanations for this association is gene methylation in utero which was demonstrated by a study done by Lillycrop et al. which shows that an "unbalanced prenatal nutrition induces persistent, gene-specific epigenetic changes that alter mRNA expression" [37]. Recent studies support the results of Ravelli et al. that both malnutrition and over-nutrition act through epigenetic mechanisms leading to an increased risk of diabetes [38,39,40,41].

Another study on the Dutch famine has shown that people conceived during the famine were at increased risk for schizophrenia and depression, possibly through inheritable epigenetic mechanisms [42]. The protein proopiomelanocortin (POMC) seems to play an important role in the presented pathology as it is involved in energy homeostasis and has been recently shown to be modulated by epigenetic changes, as shown by a recent study in patients with anorexia nervosa [43].

A recent review analyses the strong associations be-

tween prenatal famine, diabetes and schizophrenia [44], a thorough review of under-nutrition effects [45], as well as the homocysteine hypothesis of depression elaborated by Folstein et al. [46,47].

Conclusion

As it may be seen from the information presented, the field of miRNAs in the diagnosis and the pathology of psychiatric diseases, as well as in diabetes mellitus, is still new, but researchers have already identified several such molecules that are involved in both conditions.

Acknowledgement

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