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REVIEW

Role of islet microRNAs in diabetes: which model for which question?

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Abstract MicroRNAs are important regulators of gene expression. The vast majority of the cells in our body rely on hundreds of these tiny non-coding RNA molecules to precisely adjust their protein repertoire and faithfully accomplish their tasks. Indeed, alterations in the microRNA profile can lead to cellular dysfunction that favours the appearance of several diseases. A specific set of microRNAs plays a crucial role in pancreatic beta cell differentiation and is essential for the fine-tuning of insulin secretion and for compensatory beta cell mass expansion in response to insulin resistance. Recently, several independent studies reported alterations in microRNA levels in the islets of animal models of diabetes and in islets isolated from diabetic patients. Surprisingly, many of the changes in microRNA expression observed in animal models of diabetes were not detected in the islets of diabetic patients and vice versa. These findings are unlikely to merely reflect species differences because microRNAs are highly conserved in mammals. These puzzling results are most probably explained by fundamental differences in the experimental approaches which selectively highlight the microRNAs directly contributing to diabetes development, the microRNAs predisposing individuals to the disease or the microRNAs displaying expression changes subsequent to the development of diabetes. In this review we will highlight the suitability of the different models for addressing each of these questions and propose future strategies that should allow us to obtain a better understanding of the contribution of microRNAs to the development of diabetes mellitus in humans.

Keywords Animal models of Diabetes · Diabetes · Human islet donors · Insulin · Islets of Langerhans · MicroRNAs · Pancreatic beta cells · Review

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MicroRNAs as regulators of beta cell differentiation and function

Type 2 diabetes is a chronic metabolic disorder characterised by major alterations in gene expression, which affects several organs, including the islets of Langerhans. A growing number of studies demonstrate that these changes are not only caused by deregulation of key transcription factors such as v-maf musculoaponeurotic fibrosarcoma oncogene family, protein A (avian) (MafA) or pancreatic and duodenal homeobox 1 (PDX1) but are also driven by modifications in the level of another group of molecules regulating gene expression, the microRNAs [1–4]. MicroRNAs are small non-coding RNAs (typically 21–23 nucleotides long) that pair to the 3′ untranslated region of target mRNAs leading to translational repression and/or a decrease in messenger stability [5].

The importance of the microRNA regulatory network for proper differentiation and function of beta cells is highlighted by the phenotypic traits of mice lacking Dicer1, an enzyme essential for the generation of most microRNAs [5]. Deletion of *Dicer1* at different stages of pancreas development or of the pancreatic endocrine lineage results in a dramatic loss of microRNAs, accompanied by severe defects in pancreas morphology, islet organisation, beta cell formation and insulin biosynthesis [6–8]. The precise role of microRNAs in insulin-secreting cells has been investigated by deleting *Dicer1* specifically in beta cells. RIP-Cre-*Dicer1*$^{flox/flox}$ mice exhibit normal beta cell formation during fetal and neonatal life, but become progressively hyperglycaemic and finally develop overt diabetes in adulthood. These mice display defects in islet number, size and architecture, in beta-cell mass, and in insulin biosynthesis and secretion [9, 10]. Loss of *Dicer1* in the adult does not affect total beta cell mass, but results in insufficient insulin biosynthesis and release in response to glucose, causing hyperglycaemia in both fed and fasted states [11]. Taken together, these observations point to an essential role of the microRNA network in beta cell differentiation and function.

Pancreatic beta cells express a specific set of microRNAs that are present in the cells at very different levels. miR-7, miR-375 and let-7 family members are among the most abundant microRNAs expressed in human and rodent islets, and miR-7, miR-184 and miR-375 are highly enriched in islets compared with other tissues [12–15]. The specific role of each of these microRNAs in the regulation of beta cell activities has been investigated in different in vivo and in vitro models. Deletion of *MiR-375* in mice alters the cellular composition of the pancreatic islets such that they contain fewer beta cells and more alpha cells than in wild type animals [16]. These mice display hyperglycaemia and hyperglucagonaemia and, if crossed with *ob*/*ob* mice, a model of obesity and insulin resistance, they develop a severe diabetic state because of the inability of beta cells to expand and compensate for the increased insulin needs. These, together with other studies [16–19], highlight the central role played by miR-375 in endocrine pancreas development and in the regulation of insulin gene expression and release.

Producing an opposite effect to the absence of miR-375, the knockout of *MiR-184* in insulin-positive cells results in an increase in beta cell proliferation and greater numbers of beta cells. This is associated with improved insulin release in response to a glucose challenge [20]. The proliferative effect elicited by the downregulation of miR-184 has also been observed in dispersed islet cells in an independent in vitro study [21]. Moreover, blockade of this microRNA in rat and human islets protected the beta cells against apoptosis elicited by chronic exposure to proinflammatory cytokines or fatty acids (conditions typically associated with the diabetic state) [21]. Therefore, a reduction in miR-184 levels favours the replication and survival of insulin-secreting cells and expansion of the beta cell mass.

The role of miR-7 in beta cells has also been the focus of numerous studies. The expression of this microRNA was positively correlated with pancreatic development and beta cell differentiation in human fetus [22]. Downregulation of miR-7 in mouse embryos results in a reduction in the number of beta cells and diminished insulin production, leading to glucose intolerance in the postnatal period [23]. Inhibition of miR-7 using antisense oligonucleotides in isolated adult mouse islet cells was found to activate the mechanistic target of rapamycin (mTOR) pathway and promote beta cell proliferation [24]. However, beta cell-specific *MiR-7* knockout mice did not show significant differences in beta cell survival or proliferation, but displayed enhanced insulin release as a result of increased expression of key components of the exocytotic machinery, permitting an improved response to a glucose challenge [25].

Let-7 was the first microRNA discovered in *Caenorhabditis elegans* [26] and includes a family of 12 closely related microRNAs sharing a common seed region (a sequence spanning from nucleotides 2 to 8 that is important for target recognition). The members of this family are key regulators of embryonic development and important tumour suppressors in adult cells [27]. The role of let-7 family members in the regulation of glucose homeostasis has been investigated in an in vivo study using strategies to overexpress or block these microRNAs [28]. Overexpression of let-7 either in all tissues or restricted to beta cells resulted in impaired glucose tolerance and attenuation of glucose-induced insulin release. Moreover, general downregulation of let-7 in adult mice through injection of antisense oligonucleotides prevented impaired glucose tolerance in mice fed a high-fat diet [28].

Overall, these and many other studies (reviewed extensively elsewhere [1–3]) have identified microRNAs as essential players in beta cell development and function and in the regulation of whole body glucose homeostasis.

Inappropriate islet microRNA expression as a potential cause of type 2 diabetes

Several research teams have used comparative profiling to identify changes in microRNA expression that precede or coincide with the manifestation of diabetes and could thus potentially contribute to the development of the disease. Different rodent models of type 2 diabetes (summarised in Table 1) covering various aspects of this complex and multifactorial metabolic disease were analysed. A list of the microRNAs identified by these studies is provided in Table 2. Interestingly, a group of microRNAs including miR-34a, miR-132, miR-184, miR-199a-5p, miR-210, miR-212, miR-338-3p and miR-383 was found to be deregulated in different animal models of type 2 diabetes by independent research groups, and changes in their expression were confirmed by real-time PCR quantification [20, 21, 29–31]. The functional role of some of these microRNAs in the regulation of beta cell function has been investigated in detail. For this purpose, the expression changes observed in pre-diabetic or diabetic animals were mimicked in normal beta cells. This revealed that changes in miR-34a, miR-210 and miR-383 expression promote apoptosis of beta cells and/or inhibit glucose-induced insulin secretion [21, 32], indicating a potential involvement of these microRNAs in beta cell dysfunction and in the development of diabetes. However, not all the changes in microRNA levels detected in the islets of diabetic animals have deleterious effects on beta cell activities. Indeed, reduction of miR-184 and miR-338-3p or a rise of miR-132 was found to trigger beta cell proliferation and improve survival and/or insulin release [20, 21, 31, 33]. This suggests that these changes contribute to physiological processes that attempt to compensate for insulin resistance rather than to pathological events causing the appearance of diabetes.

Table 1 Main characteristics of common rodent models of type 2 diabetes

Species	Models	Main characteristics	Ref.
Rat	Goto–Kakizaki	• Spontaneously develop T2D unrelated to obesity. • Animals are insulin resistant, moderately hyperglycaemic and have impaired insulin secretion in response to glucose. Limitations: The precise cause of the development of T2D remains unclear. Poorly representative of most human T2D populations.	[40]
Mouse	Diet-induced obesity	• Mice are fed a high-fat diet to induce obesity and insulin resistance. • Model of pre-diabetes or early phases of T2D. Limitations: Large inter-individual differences. Most of the animals become glucose intolerant but never develop overt T2D.	[41]
	db/*db*	• Leptin receptor deficiency leading to T2D. • Animals are severely obese, insulin resistant, hyperglycaemic and hyperinsulinaemic. Limitations: Model of extreme obesity that is poorly representative of most human T2D populations.	[37]
	ob/*ob*	• Leptin deficiency. • Severely obese, insulin resistant and hyperinsulinaemic. • Beta cell hyperplasia and compensation for insulin resistance. Limitations: Model poorly representative of human obesity. The animals do not develop T2D.	[36]
	B6 strain	• Resistant to obesity-induced diabetes. • B6-*ob*/*ob* are hyperinsulinaemic and transiently hyperglycaemic. • Beta cell hyperplasia and increase in insulin secretion. Limitations: Need to be crossed with *ob*/*ob* mice to obtain a phenotype. Not well characterised.	[30, 42]
	BTBR strain	• Susceptible to obesity-induced diabetes. • BTBR-*ob*/*ob* display severe hyperglycaemia. • Failure of beta cells to proliferate and to increase insulin secretion. Limitations: Need to be crossed with *ob*/*ob* mice to obtain a phenotype. Not well characterised.	[30, 42]

T2D, type 2 diabetes

Can findings obtained from animal models of diabetes be extrapolated to humans?

Several groups have now compared microRNA levels in islets obtained from healthy donors with those in islets from type 2 diabetic donors, a type of analysis that is expected to become more popular in the coming years. Surprisingly, only a minor fraction of the microRNAs differentially expressed in animal models were also found to be modified in samples collected from type 2 diabetic patients. Conversely, several microRNA changes revealed by the screening of human islets were not previously highlighted by the systematic analysis of islets isolated from animal models of diabetes. Indeed, the islets of type 2 diabetic donors were found to express higher levels of miR-187, miR-187*, miR-224 and miR-589 and decreased levels of miR-7, miR-369, miR-487a, miR-655 and miR-656 (see Table 3) [13]. Similar changes in the expression of miR-187 and miR-7a were confirmed by independent research groups [25, 34]. These data will need to be reproduced in additional laboratories, but if confirmed, what value will the experiments carried out in rodents have? Should they be abandoned in favour of experimental approaches focusing exclusively on the analysis of human samples? If not, would it be possible to design experiments in animal models and human islets to reconcile these apparently discrepant findings? In the following paragraphs we will attempt to answer these important questions by scrutinising the advantages and limitations of the experimental models currently available to study the involvement of islet microRNAs in the development of diabetes.

There are several factors that should be considered when looking to explain the differences between the results obtained in human and rodent samples. Human and rodent islets are known to display genetic, morphological and functional specificities, but differences between species are unlikely to be the major cause of the discrepant findings. Indeed, the sequence, genomic organisation and signals regulating the expression of almost all microRNAs are highly conserved between mammals. Several experiments on rodent islets have been performed with microarray or quantitative PCR approaches. The use of these highly sensitive techniques may have allowed the detection of differences in microRNAs expressed at a very low level in the cells that may not be functionally relevant. However, the use of different profiling methodologies cannot explain the observed discrepancies. In fact, at least part of the rodent studies were performed with the same approaches applied for the analysis of the microRNAs in human samples. Moreover, differential microRNA expression in rat islet samples determined by small RNA sequencing and with the Agilent microarray platform yielded highly concordant results (C. Jacovetti, S. Matkovich and R. Regazzi unpublished observation).

We believe that the explanation for the differences between the results obtained in rodents and humans lies in the

Table 2 Overview of microRNAs reported to be differently expressed in pancreatic islets of different animal models of type 2 diabetes

Animal model	Detection method	Change up/down	microRNAs changed	Ref.
Goto–Kakizaki rats	Microarray	Up	let-7i*, miR-7b, -124, -127, -130a, -132, -136*, -142-3p, -142-5p, -152, -199a*-3p, -199a-5p, -212, -335, -369-3p, -376a, -376a*, -376b-3p, -376c, -409-3p, -410, -411, -433, -434	[29]
		Down	miR-28*, -216, -217, -493, -503, -708	
Diet-induced obesity (DIO) mice	Microarray	Up	let-7d*, miR-7a-1*, -34c, -101b, -125a-3p, -130b*, -132, -152, -182, -193, -200c*, -205, -211, -216b, -221, -322, -323-3p, -337-3p, -362-5p, -380-3p, -433, -455*, -484, -485*, -494, -540-3p, -615-3p, -670, -671-5p, -680, -702, -705, -714, -770-3p, -802, -1224, -1894-5p, -1897-5p, -1904, -1906	[21]
		Down	let-7b*, miR-10a, -24-1*, -28, -29a*, -30b*, -30c-1*, -31*, -32, -33, -100, -148a*, -181d, -184, -199a-3p, -202-3p, -203, -210, -215, -218, -223, -301b, -328, -335-5p, -344b, -378, -383, -384-5p, -539-5p, -541, -543, -676, -690, -697, -700, -1187, -1198-5p, -1892	
	qPCR	Up	miR-132, -375	[20, 21, 25]
		Down	miR-7a, -184, -203, -210, -383	
db/*db* mice				
Young (6 weeks)	Microarray	Up	miR-22, -132, -139-5p, -141*, -142-3p, -146a, -146b, -150, -152, -182, -193, -212, -301b, -337-3p, -337-5p, -433, -452, -455, -455*, -483, -582-5p, -676, -721	[21]
		Down	miR-23b, -24-1*, -27b, -31*, -100, -184, -194, -201, -203, -216a, -218, -338-3p, -378, -671-5p, -762, -802	
	qPCR	Up	miR-132	[21]
		Down	miR-184, -203, -210, -383	
Adult (16–20 weeks)	Microarray	Up	miR-10a, -10b, -21, -22*, -34a, -34b-5p, -34c, -99a, -100, -126-3p, -132, -139-5p, -143, -146a, -146b, -152, -181c, -195, -199a-3p, -199a-5p, -199b*, -212, -320, -322, -337-5p, -365, -455*, -497, -676, -721, -802, -1224	[21]
		Down	miR-23b, -26a, -27b, -30e, -30e*, -30d, -31, -103, -129-3p, -129-5p, -184, -203, -204, -210, -301a, -324-3p, -324-5p, -325, -328, -331-3p, -338-3p, -341, -374, -378, -381, -383, -384-5p, -434-3p, -652, -872	
	qPCR	Up	miR-21, -34a, -132, -146, -199a-3p, -199a-5p, -802	[20, 21, 25, 31, 43]
		Down	miR-7a, -184, -203, -210, -338-3p, -383	
	in situ hybridisation	Up	let-7b	[44]
		Down	miR-30d	
ob/*ob* mice				
B6 strain	Microarray	Up	miR-132, -133a, -152, -185, -199a-5p, -199b, -206, -202, -302b, -422a	[30]
		Down	miR-184, -383	
	RNA seq	Up	miR-22, -99b, -132, -152, -181d, -183, -212, -337, -433, -455, -494, -574, -666, -671, -708, -1957, -5115	[20]
		Down	miR-1a, -23b, -27b, -92b, -99a, -100, -125b, -137, -149, -181a, -181b, -184, -203, -210, -215, -221, -222, -335, -338, -378, -383, -672	
	qPCR	Up	miR-204, -375	[16, 20, 25, 45]
		Down	miR-7a, -184	
BTBR strain	Microarray	Up	miR-34a, -34b, -132, -199a-5p, -212, -379	[30]
		Down	miR-1, -7b, -17-3p, -27b, -31, -124a, -133a, -147, -184, -187, -198, -203, -204, -207, -210, -211, -294, -302a*, -302b, -302c, -324-3p, -338, -371, -378, -383, -384, -422b	
	qPCR	Up	miR-204	[45]

properties specific to each experimental model (the advantages and disadvantages are summarised in the text box). Animal studies offer the possibility of correlating the microRNA changes with the development of type 2 diabetes. In fact, the onset of the disease occurs at well-defined time points, allowing the focus to be on microRNA changes immediately preceding the failure of beta cells which are those most likely to contribute to the development of diabetes. The precise role of the identified microRNAs in the manifestation of the disease can then potentially be assessed by modulating the level of the microRNAs in vivo, for example, by transgenesis or by injection of oligonucleotide derivatives that mimic or sequester the microRNAs. This is an important issue because it is often difficult to determine whether microRNAs differentially expressed in the islets of overtly diabetic individuals are a direct cause of the disease or are the consequence of the chronic exposure of islet cells to the elevated levels of glucose, lipids and inflammatory mediators that typically

Table 3 Overview of microRNAs reported to be differentially expressed in pancreatic islets of human diabetic vs non-diabetic donors

Diabetes type	Detection method	Change up/down	microRNA changes	Ref.
Type 2 diabetes	Global profiling	Up	miR-187, -187*, -224, -589	[13, 34]
	+ qPCR	Down	miR-7, -369, -487a, -655, -656	
	qPCR only	Down	miR-7a, miR-184	[20, 25]

occur under diabetes conditions. As mentioned above, certain modifications in islet microRNA expression may even have a positive impact on islet function [20, 21, 31] and be part of the physiological mechanisms involved in meeting the rise in insulin requirements caused by insulin resistance in peripheral tissues of obese and ageing individuals.

Animal models of diabetes

Advantages:

- Possibility to correlate changes in microRNA levels with the development of type 2 diabetes
- Possibility to study the role of microRNAs in vivo
- Number of samples is not limiting
- Inter-individual differences can be minimised by the use of congenic strains
- Islet isolation is standardised and highly reproducible

Disadvantages:

- Potential differences between humans and rodents (microRNA levels, cell composition)
- The available animal models only partly match the phenotype of human patients
- Difficult to estimate the influence of the genetic background to diabetes susceptibility

Human islets from type 2 diabetic patients

Advantages:

- The detected differences in microRNA levels reflect the situation in human patients
- Possibility to correlate the level of islet microRNAs and genetic predisposition to diabetes

Disadvantages:

- The number of available islet preparations is limited (in particular for preparations from type 2 diabetic donors)
- microRNA levels are likely to be influenced by donor factors such as age, sex, ethnicity, treatment
- Major inter-individual differences
- Islet preparations are difficult to standardise, resulting in important variability in purity, cell viability, etc.
- Difficult to correlate the changes in microRNA levels with the development of diabetes
- Difficult to distinguish between causes and consequences of diabetes

A unique characteristic of the studies carried out in animal models is the use of congenic strains. This, combined with the possibility of standardising and precisely controlling the islet isolation procedure minimises the variability between the biological replicates and allows the generation of highly reproducible data. The reproducibility of the results allows tiny differences in microRNA expression to be detected even when a small group of individuals is compared. Measurements of islet microRNA levels in human islet preparations are usually characterised by much larger inter-individual variations. These can be attributed to a combination of islet donor factors that potentially modify the microRNA profile, including differences in age, sex, ethnicity, BMI, the duration of diabetes and treatment (or not) with different glucose-lowering drugs [35]. In view of the strong inter-individual variability, relatively small changes in microRNA expression will go undetected unless a large number of islet preparations are analysed. This is a major obstacle because, at present, the availability of human islets is a limiting factor, in particular for samples obtained from type 2 diabetic donors. It is possible that changes in microRNA expression that have so far only been observed in animal models will later be confirmed in humans when data for a larger number of diabetic individuals becomes available. One such example is the decrease in islet miR-184 expression observed in several independent animal studies [20, 21, 29, 30]. Although changes in the level of this particular non-coding RNA were not detected on global profiling of a small number of human samples [13, 34], they were readily confirmed by a study that focused specifically on miR-184 in which a large number of islet preparations were compared [20].

A major concern regarding animal models of diabetes is that they may not faithfully recapitulate the conditions of the human disease. For example, the degree of obesity associated with many traditional models of type 2 diabetes, such as *ob*/*ob* and *db*/*db* mice, is exceedingly high and is not representative of the obesity observed in most type 2 diabetic populations [36, 37]. Diet-induced obese mice are probably more representative of human obesity. However, this model is characterised by large inter-individual differences in the response to high-fat-diet feeding and the animals become glucose intolerant but usually do not develop overt type 2

diabetes. For other popular rodent strains such as the Goto–Kakizaki rat the precise causes of the disease remain unclear [38], and the form of diabetes developed by these animals may be representative only of a very particular subgroup of type 2 diabetes cases in humans. Consequently, changes in the level of certain islet microRNAs identified in animal models may be observed in humans only if specific subpopulations of type 2 diabetic patients are selected.

Finally, an important point to consider is that the differential expression of several microRNAs detected in the islets of type 2 diabetic donors may not be the result of changes occurring during the pre-diabetic phases preceding the development of the disease but may rather reflect pre-existing characteristics that predispose the individual to the development of the disease. Indeed, most of the microRNAs that were found to be differentially expressed in the islets of type 2 diabetic donors belong to a large epigenetically controlled cluster generated from an imprinted locus on chromosome 14q32 [13]. As mentioned above, the studies carried out in animal models are usually performed in congenic individuals. Since in this case all individuals share the same genetic background, the analysis of microRNA expression in the islets isolated from these experimental models will obviously fail to identify phenotypic differences that favour the development of diabetes.

Future perspectives

As discussed above, there are fundamental differences between studies that focus on animal models of diabetes and those that involve the analysis of islets collected from human donors. These two approaches have been used to highlight either candidate microRNAs that show changes in expression coinciding with the development of diabetes or pre-existing differences between diabetic and non-diabetic microRNA that predispose to the disease. Therefore, it is not too surprising that human and rodent studies have so far led to the identification of distinct sets of microRNAs. Animal studies are more appropriate for investigating a causal link between changes in microRNA expression and the manifestation of diabetes. Thus, these experiments should continue to guide the quest to identify the microRNAs that contribute to beta cell dysfunction and failure. Confirmation of the relevance of the findings obtained in rodents to the causes of diabetes in humans will be essential and will be facilitated by a better understanding of the impact of confounding factors such as age, sex and treatment with glucose-lowering drugs on islet microRNA profile. In principle, it should not be too difficult to evaluate the effect of these variables on islet microRNA expression in animal models. In view of the increasing number of groups entering the field and the rapid dissemination of platforms offering solutions for the global assessment of microRNA expression, we are confident that this information will soon become available.

The analysis of the microRNA profile in human islets obtained from healthy and type 2 diabetic donors offers a unique opportunity to identify inter-individual characteristics that predispose individuals to the manifestation of the disease. This important information cannot be obtained with commonly used animal models and will complement our knowledge on the role of specific microRNAs acquired in rodents. To date, a major obstacle to the studies performed with human islets from cadaveric donors is the fact that it is not possible to correlate the changes over time in microRNA expression with the manifestation and progression of diabetes. An interesting approach to partially overcome this limitation would be the generation of so-called ‘humanised’ animal models. This strategy involves the elimination of endogenous beta cells by injecting the animals with streptozotocin [39]. The rodent insulin-secreting cells are then replaced with human islets that are transplanted under the renal capsule and ensure the metabolic control. By carefully selecting the recipient animal model, it would be possible to expose the transplanted human islets to diabetogenic conditions such as, for example, obesity or high-fat-diet feeding, and then analyse the impact of this on microRNA expression. This approach would permit the determination of whether human islets exposed in vivo to adverse environmental conditions display the same changes in the microRNA profile observed in the islets of the corresponding animal model.

Conclusion

The discovery of microRNAs has opened new perspectives on our understanding of the mechanisms responsible for the failure of beta cells and the development of type 2 diabetes. This has focused a lot of interest on these small non-coding RNA molecules and has promoted an exponential increase in the number of studies aiming to identify the microRNAs involved in this disease. The determination of the relevance for human diabetes of candidate microRNAs identified through experiments carried out in animal models still needs to be demonstrated and will occupy scientists in the coming years. We are only beginning to appreciate the importance of these tiny RNA molecules in islet physiology but their discovery has provided new hope to elucidate the causes of beta-cell dysfunction and of the development of diabetes. MicroRNAs have now entered the limelight and, no matter what experimental model will be used to study them, they are likely to remain at the forefront of diabetes research for some time to come.

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