The Impact of lncRNAs in Diabetes Mellitus: A Systematic Review and In Silico Analyses

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Long non-coding RNAs (lncRNAs) are non-coding transcripts that have emerged as one of the largest and diverse RNA families that regulate gene expression. Accumulating evidence has suggested a number of lncRNAs are involved in diabetes mellitus (DM) pathogenesis. However, results about lncRNA expressions in DM patients are still inconclusive. Thus, we performed a systematic review of the literature on the subject followed by bioinformatics analyses to better understand which lncRNAs are dysregulated in DM and in which pathways they act. Pubmed, Embase, and Gene Expression Omnibus (GEO) repositories were searched to identify studies that investigated lncRNA expression in cases with DM and non-diabetic controls. LncRNAs consistently dysregulated in DM patients were submitted to bioinformatics analysis to retrieve their target genes and identify potentially affected signaling pathways under their regulation. Fifty-three eligible articles were included in this review after the application of the inclusion and exclusion criteria. Six hundred and thirty-eight lncRNAs were differentially expressed between cases and controls in at least one study. Among them, six lncRNAs were consistently dysregulated in patients with DM (Anril, Hotair, Malat1, Miat, Kcnq1ot1, and Meg3) compared to controls. Moreover, these six lncRNAs participate in several metabolism-related pathways, evidencing their importance in DM. This systematic review suggests six lncRNAs are dysregulated in DM, constituting potential biomarkers of this disease.

Keywords: lncRNAs (long non-coding RNAs), type 1 diabetes mellitus (DM1), type 2 diabetes mellitus (T2DM), systematic review, target prediction

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders that have in common the chronic hyperglycemia, which results from defects in insulin secretion, insulin action, or both (1). Accordingly to the International Diabetes Federation Atlas 2019, an estimated 463 million adults are currently living with DM (9.3% of the world population), and this number is projected to reach 700 million by 2045 (2). Thus, DM has achieved epidemic proportions worldwide, being associated
with increased morbidity and mortality rates due to its specific micro- and macrovascular complications (1, 2).

Type 1 DM (T1DM) accounts for 5–10% of all DM cases and usually appears in people younger than 30 years (1, 2). T1DM is an autoimmune disease caused by the progressive destruction of pancreatic beta-cells by macrophages and T lymphocytes, making patients insulin-dependent for life (1, 3). Type 2 DM (T2DM) comprises 90–95% of worldwide diabetic cases and generally arises in subjects older than 40 years and with obesity. Hyperglycemia in T2DM patients is caused by insulin resistance associated with different degrees of a relative beta-cell failure (1, 2). It is well known that susceptibility for both T1DM and T2DM is triggered by a multifaceted interaction among several environmental, genetic, and epigenetic factors (4–8).

Epigenetic factors regulate the complex crosstalk between genes and environmental factors without altering the DNA sequence and include DNA methylation, histone posttranslational modifications, and non-coding RNAs (ncRNAs) (7, 8). NcRNAs are regulatory RNAs that typically lack protein-coding capacity and play key roles in both physiological and pathological processes (9, 10). According to their length and functions, ncRNAs can be classified into different subtypes, including the long ncRNAs (lncRNAs), which are those ncRNAs with >200 nucleotides in length (10, 11).

LncRNAs can be located in the nucleus or cytoplasm and exhibit more specific expression profiles than mRNAs, being expressed in cell/tissue-, developmental stage-, or disease state-specific manners (10, 12, 13). A number of studies have suggested lncRNAs participate in several molecular processes involved in gene regulation, including epigenetic, transcriptional, and post-transcriptional regulation, through interaction with chromatin-remodeling complexes, binding to transcription factors or regulation of mRNA-binding proteins and microRNAs (another class of ncRNAs) (10, 14–16).

In this context, growing evidence has shown lncRNAs play key roles in regulating beta-cell function, apoptosis, insulin secretion, glucose metabolism, and insulin resistance (10, 17–22). Accordingly, a number of studies have reported changes in lncRNA expressions in patients with DM or in murine models of T1DM or T2DM (10, 23–29). Thus, lncRNAs are likely to be novel potential biomarkers for early diagnosis and prognosis of T1DM or T2DM (10, 29). For example, Carter et al. showed GAS5 might be a prognostic biomarker for T2DM since this lncRNA was decreased in serum of patients with DM from a US (controls). Studies that did not have an appropriate control group were excluded. Two researchers (CD and NL) independently reviewed titles and abstracts of all articles to evaluate if they were eligible for inclusion in this systematic review.

Results were independently collected by two investigators (CD and NL) using a standardized abstraction form (31). Discrepancies between investigators were solved by discussion between them and, when necessary, a third reviewer (DC) was consulted. The following information was collected from each study included in this review: 1) characteristics of studies and samples; 2) information regarding lncRNA expressions, quantification method, analyzed tissue, and number of lncRNAs investigated; and 3) lncRNA expression profile in case and control groups.

Evaluation of IncRNA Putative Target Genes and Functional Enrichment Analysis
Potential target genes for the consistently dysregulated lncRNAs in DM were searched using lncRNA2Target v2.0 (32) and starBase (33). The criteria for selecting the consistently dysregulated lncRNAs were: 1) lncRNAs with concordant results in ≥75% of the studies in which they were analyzed; and 2) lncRNAs analyzed in at least three studies. Statistical significances were reported after Benjamini–Hochberg (q-value) corrections for multiple comparisons (34). To better understand the biological relevance of lncRNA target genes, a network analysis was executed using PathDIP (accessed 23rd April 2020) (35). The nomenclature of mRNAs and lncRNAs were unified based on HUGO gene nomenclature committee (HGNC) and LNCipedia v5.2, respectively.

MATERIALS AND METHODS
Search Strategy, Eligibility of Studies, and Data Extraction
This systematic review was designed and described in accordance with current guidelines (30, 31), and its protocol was registered at PROSPERO (http://www.crd.york.ac.uk/PROSPERO), under the identification: CRD42019124368. PubMed and EMBASE repositories were searched to retrieve all articles that investigated lncRNA expressions in T1DM or T2DM patients compared to non-diabetic controls. The research question was constructed based on the PICOS strategy (31), as follows: P (Population): patients with T1DM or T2DM; I (Intervention): lncRNA expression; C (Comparators): healthy control groups; O (Outcomes): DM; S (Study designs): case–control study, cross-sectional or cohort. The following medical subject headings (MeSH) were used: (“diabetes mellitus” OR “diabetes mellitus, type 1” OR “diabetes mellitus, type 2”) AND (“RNA, long noncoding” OR “untranslated RNA”). The search was restricted to English, Spanish, or Portuguese language papers and was finished on April 2020. Reference lists from all included articles were also manually reviewed in order to identify other relevant citations. Moreover, studies were also searched in the GEO database (https://www.ncbi.nlm.nih.gov/geo/).

We included original articles that analyzed lncRNA expressions in patients with T1DM or T2DM (cases) and subjects without DM (controls). Studies that did not have an appropriate control group were excluded. Two researchers (CD and NL) independently reviewed titles and abstracts of all articles to evaluate if they were eligible for inclusion in this systematic review.

In this context, growing evidence has shown lncRNAs play key roles in regulating beta-cell function, apoptosis, insulin secretion, glucose metabolism, and insulin resistance (10, 17–22). Accordingly, a number of studies have reported changes in lncRNA expressions in patients with DM or in murine models of T1DM or T2DM (10, 23–29). Thus, lncRNAs are likely to be novel potential biomarkers for early diagnosis and prognosis of T1DM or T2DM (10, 29). For example, Carter et al. showed GAS5 might be a prognostic biomarker for T2DM since this lncRNA was decreased in serum of patients with DM from a US military veterans cohort (23). Individuals with lower GAS5 expression were almost 12× more likely to have T2DM (23). Li et al. reported ENST00000550337.1 upregulation in blood had high diagnostic value for identifying pre-DM and T2DM in patients from a Chinese cohort (25).

Therefore, to further investigate which lncRNAs may be involved in DM pathogenesis and used as potential biomarkers of this disease, we performed a systematic review of the literature on the subject. Moreover, bioinformatics analyses were performed to investigate the regulatory and functional roles of dysregulated lncRNAs in DM pathogenesis.
RESULTS

Literature Search and Characteristics of Eligible Studies

Figure 1 shows the flowchart illustrating the strategy used to identify and select articles for inclusion in this systematic review. Following the search criteria, a total of 3,314 publications were retrieved from databases; however, after careful full text analysis, only 53 articles fulfilled the eligibility criteria and were included in the present review. The main characteristics of these studies are shown in Table 1 and the Supplementary Table 1.

The number of IncRNAs differentially expressed between case and control groups from the different included studies varied from 1 (23, 39, 41, 43, 46–49, 52, 57, 60, 64, 68, 69, 73–75, 77) to 97,286 (58), and the sample sizes ranged from 4 (66) to 370 (73). Among the 53 studies included in this systematic review, 74% of them analyzed T2DM patients, while 26% did not report which DM type patients had. The tissues most analyzed were serum, plasma, and peripheral blood mononuclear cells (PBMCs).

Differentially Expressed IncRNAs in DM

As shown in the Supplementary Table 2, 623 IncRNAs were reported as being dysregulated in patients with DM from one study (17, 21, 24–28, 41, 42, 44, 47, 54, 55, 57–60, 64, 73, 75), while only seven were dysregulated in cases in two studies (ENST00000550337.1, Pluto, LncRNAp3134, n335556, n336109, n342533, and Pvt1) (17, 19, 21, 25, 28, 63, 66, 67). Eight IncRNAs were dysregulated in patients from three or more studies, being chosen for further evaluation (Supplementary Table 2 and Table 2). Among these eight IncRNAs, those showing concordant results in more than 75% of the studies were considered consistently dysregulated in DM. Thus, as shown in Table 2, six IncRNAs were consistently dysregulated in patients with DM (upregulated: Anril, Hotair, Malat1, Miat, and Kcnq1ot1; downregulated: Meg3) compared to controls. GAS5 and H19 were upregulated in patients from some studies and downregulated in others, which could be explained by differences in the tissue types analyzed (serum, pancreatic islets, liver, plasma, and PBMCs) (Table 2).

Putative Target Genes and Enrichment Pathway Analysis of the Six Differentially Expressed IncRNAs in Human Samples

Bioinformatics analyses were carried out to find putative targets and biological pathways regulated by the six IncRNAs (Anril, Hotair, Malat1, Miat, Kcnq1ot1, and Meg3) consistently dysregulated in samples of DM patients. These six IncRNAs regulate together the expression of 1,860 unique target genes (Supplementary Table 3). Malat1 has the largest number of target genes (1,671), followed by Kcnq1ot1 (91), Miat (65), and Hotair (59), while Meg3 and Anril have the lowest number of targets (32 and 20, respectively) (Figure 2A and Supplementary Table 3). Among the 1,860 target genes, 1,307 were protein coding genes, 287 were pseudogenes, 100 were small nuclear RNAs (snRNAs), and 225 were other type of ncRNAs, including microRNAs, tRNA, rRNA, and mitochondrial RNA (mtRNA) (Supplementary Table 3).

Next, to further explore the functional consequences of the dysregulation of the six IncRNAs of interest, we performed functional enrichment analysis of their protein-encoding target genes...
| Author, year [Reference] | Sample size Case/Control | Tissue | Method | Total number of studied lncRNAs | Statistically significant lncRNAs |
|--------------------------|--------------------------|--------|--------|---------------------------------|-----------------------------------|
| Akerman et al. 2017 (17) | 10 T2DM patients/50 controls | Pancreatic islets | RNA-seq and qPCR | 2,373 | 0 16 |
| Alikhah et al. 2018 (36) | 18 T2DM patients/18 controls | PBMCs | qPCR | 1 | 0 0 |
| Carter et al. 2015 (23) | 5 T2DM patients/5 controls | Serum | Microarray and qPCR | 84 | 0 1 |
| Chen et al. 2019 (37) | 25 DM patients/20 controls | Serum | qPCR | 1 | 0 0 |
| Chen et al. 2018 (39) | 27 DM patients/17 controls | Serum | qPCR | 1 | 0 0 |
| Cheng et al. 2019 (39) | 30 DM patients/30 controls | Peripheral blood | qPCR | 1 | 1 0 |
| Dai et al. 2020 (40) | 60 T2DM patients/60 controls | Plasma | qPCR | 1 | 0 0 |
| Das et al. 2018 (41) | 5 T2DM patients/5 controls | CD14+ monocytes | qPCR | 1 | 1 0 |
| De Gonzalez-Calvo et al. 2016 (42) | 48 T2DM patients/12 controls | Serum | qPCR | 12 | 1 3 |
| Erfanian Omidvar et al. 2019 (24) | 100 T2DM patients/100 controls | PBMCs | qPCR | 2 | 0 2 |
| Esguerra et al. 2020 (43) | 9 T2DM patients/10 controls | Pancreatic islets | qPCR | 1 | 1 0 |
| Facista et al. 2014 (44) | 12 T2DM patients/51 controls | Pancreatic islets | qPCR | 493 | NA NA |
| Fawzy et al. 2020 (45) | 53 T2DM patients/110 controls | Plasma | qPCR | 2 | 1 1 |
| Gao et al. 2014 (46) | 5 T2DM patients/4 controls | Lateral quadriceps muscle biopsy | qPCR | 1 | 0 1 |
| Jiao et al. 2019 (47) | 43 DM patients/48 controls | Serum | qPCR | 1 | 1 0 |
| Morcan et al. 2012 (57) | 10 T2DM patients/10 controls | Liver biopsy | qPCR | 1 | 1 0 |
| Li et al. 2019 (50) | 56 T2DM patients/40 controls | Serum | qPCR | 1 | 0 0 |
| Li et al. 2018 (51) | 63 DM patients/56 controls | Plasma | qPCR | 1 | 0 0 |
| Li et al. 2018 (25) | 6 T2DM patients/6 controls | Peripheral blood | Microarray and qPCR | 41,000 | 14 3 |
| Liu et al. 2019 (52) | 90 T2DM patients/30 controls | Serum | qPCR | 1 | 1 0 |
| Luo et al. 2018 (53) | 6 T2DM patients/6 controls | PBMCs | Microarray and qPCR | NA | 316 126 |
| Ma et al. 2020 (54) | 5 T2DM patients/5 controls | PBMCs | Array and qPCR | 41,000 | 44 24 |
| Mansoori et al. 2018 (26) | 100 T2DM patients/100 controls | PBMCs | qPCR | 2 | 0 2 |
| Mohamadi et al. 2019 (55) | 100 T2DM patients/100 controls | PBMCs | qPCR | 2 | 0 0 |
| Moran et al. 2012 (56) | 16 T2DM patients/19 controls | Pancreatic islets | qPCR | 13 | 1 1 |
| Motterle et al. 2017 (57) | 10 T2DM patients/10 controls | Pancreatic islets | qPCR | 1 | 0 1 |
| Pengyu et al. 2020 (58) | 4 T2DM patients/4 controls | Serum | RNAseq and qPCR | NA | 68783 28523 |
| Prades-Junie et al. 2020 (59) | 4 T2DM patients/4 controls | Liver | RNAseq | 13,805 | 126 384 |
| Reddy et al. 2014 (60) | 4 T2DM patients/4 controls | Monocytes | qPCR | 1 | 1 0 |
| Ren et al. 2019 (61) | 178 T2DM patients/44 controls | Plasma | qPCR | 1 | 0 0 |
| Ruan et al. 2018 (19) | 3 T2DM patients/3 controls | Blood | Microarray and qPCR | 40,914 | 2269 |
| Saeidi et al. 2018 (27) | 30 T2DM patients/30 controls | Exosome serum/exosome-free serum | qPCR | 1 | 1 0 |
| Sathishkumar et al. 2018 (21) | 100 T2DM patients/100 controls | PBMCs | qPCR | 2 | 0 2 |
| Shaker et al. 2019 (62) | 30 T2DM patients/32 controls | PBMCs | qPCR | 17 | 13 2 |
| Torah et al. 2019 (63) | 55 T2DM patients/106 controls | Plasma | qPCR | 2 | 2 0 |
| Wan et al. 2020 (64) | 32 T2DM patients/32 controls | Serum | qPCR | 4 | 4 0 |
| Wang et al. 2018 (65) | 296 T2DM patients/56 controls | Serum | qPCR | 1 | 1 0 |
| Wang et al. 2018 (66)* | 2 T2DM patients/2 controls | Blood | Microarray and qPCR | NA | NA NA |
| Wang et al. 2017 (28) | 6 T2DM patients/6 controls | Peripheral blood | Microarray and qPCR | NA | 39 16 |

(Continued)
genes using pathways maps from the KEGG repository. As a result, a total of 168 unique pathways were enriched for lncRNA target genes (Supplementary Table 4). Moreover, as demonstrated in Figure 2B, only one pathway is shared among the five lncRNAs (Anril, Hotair, Malat1, Kcnq1ot1, and Meg3): Kaposi sarcoma-associated herpes virus infection. Many of the 168 pathways are well established to be involved in DM pathogenesis, such as PI3K/Akt, MAPK, apoptosis, AGE/RAGE, and FoxO (Figure 3 and Supplementary Table 4). Of note, we could not find any significant KEGG pathway for Miat.

**DISCUSSION**

Currently, several studies have reported the association between epigenetic mechanisms and DM development [reviewed in

**TABLE 1 | Continued**

| Author, year [Reference] | Sample size Case/Control | Tissue | Method | Total number of studied lncRNAs | Statistically significant lncRNAs |
|---------------------------|--------------------------|--------|--------|--------------------------------|----------------------------------|
| Wang et al. 2020 (67)     | 156 T2DM/100 controls   | Peripheral blood | qPCR | 3 | 3 0 |
| Yang et al. 2018 (68)     | 8 DM patients/8 controls | Serum | qPCR | 1 | 1 0 |
| Yang et al. 2018 (69)     | 6 DM patients/6 controls | Serum | qPCR | 1 | 1 0 |
| Yang et al. 2018 (70)     | 36 DM patients/41 controls | Serum | qPCR | 1 | 0 0 |
| Yang et al. 2017 (71)     | DM patients/controls    | Serum | Array | 30,586 | 245 680 |
| Yin et al. 2019 (72)      | 62 DM patients/48 controls | Plasma | qPCR | 1 | 0 0 |
| Zha et al. 2019 (73)      | 244 T2DM patients/126 controls | Plasma | qPCR | 1 | 0 1 |
| Zhang et al. 2018 (74)    | 28 DM patients/30 controls | Serum | qPCR | 1 | 0 1 |
| Zhang et al. 2020 (75)    | 99 T2DM patients/50 controls | Serum | qPCR | 1 | 0 1 |
| Zhang et al. 2017 (76)    | 30 DM patients/28 controls | Plasma | Microarray | NA | NA NA |
| Zhang et al. 2019 (77)    | 24 T2DM patients/26 controls | Serum | qPCR | 1 | 1 0 |
| Zhang et al. 2019 (78)    | 244 T2DM patients/102 controls | Plasma | qPCR | 1 | 0 0 |
| Zhang et al. 2019 (79)    | 60 DM patients/60 controls | Plasma | qPCR | 1 | 0 0 |

*Abstract from congress. DM, diabetes mellitus; NA, information not available; PBMCs, Peripheral blood mononuclear cells; qPCR, quantitative real time PCR; RNA seq, RNA sequencing; T2DM, type 2 diabetes mellitus.

**TABLE 2 | LncRNAs differentially expressed in at least three studies included in the systematic review.**

| LncRNA | Reference | Samples | Tissue | Change of expression |
|--------|-----------|---------|--------|----------------------|
| ANRIL  | Sathishkumar et al. (21) | T2DM patients | PBMCs | Up |
|        | Toraih et al. (63)       | T2DM patients | Plasma | Up |
|        | Zhang and Wang (77)      | T2DM patients | Serum | Up |
| GAS5   | Carter et al. (23)       | T2DM patients | Serum | Down |
|        | Esquerra et al. (43)     | T2DM patients | Pancreatic islets | Up |
|        | Sathishkumar et al. (21) | T2DM patients | PBMCs | Up |
| H19    | Cheng et al. (39)        | T2DM patients | Peripheral blood | Up |
|        | Fawzy et al. (45)        | T2DM patients | Plasma | Up |
|        | Gao et al. (46)          | T2DM patients | Muscle | Down |
| HOTAIR | Li et al. (49)           | T2DM patients | Liver | Up |
|        | Sathishkumar et al. (21) | T2DM patients | PBMCs | Up |
|        | Shaker et al. (62)       | T2DM patients | Serum | Up |
| Kcnq1ot1| Möran et al. (56)        | T2DM patients | Pancreatic islets | Up |
|        | Yang et al. (68)         | DM patients | Serum | Up |
|        | Yang et al. (69)         | DM patients | Serum | Up |
|        | Liu et al. (52)          | T2DM patients | Serum | Up |
| MALAT1 | Luo et al. (53)          | T2DM patients | Blood | Up |
|        | Sathishkumar et al. (21) | T2DM patients | PBMCs | Up |
|        | Shaker et al. (62)       | T2DM patients | Blood | Up |
|        | Toraih et al. (63)       | T2DM patients | Plasma | Up |
| MEG3   | Kameswaran et al. (48)   | T2DM patients | Pancreatic islets | Down |
|        | Luo et al. (53)          | T2DM patients | Blood | Down |
|        | Sathishkumar et al. (21) | T2DM patients | PBMCs | Up |
|        | Shaker et al. (62)       | T2DM patients | PBMCs | Up |
|        | Zhang et al. (74)        | DM patients | Serum | Down |
| MiAT   | De Gonzalo-Calvo et al. (42) | T2DM patients | Serum | Up |
|        | Sathishkumar et al. (21) | T2DM patients | PBMCs | Up |
|        | Toraih et al. (63)       | T2DM patients | Plasma | Up |

DM, diabetes mellitus; PBMCs, Peripheral blood mononuclear cells; T2DM, type 2 diabetes mellitus.
In this context, lncRNAs are a class of ncRNAs that appear to be involved in DM pathogenesis (10). Thus, here, we performed a systematic review to further investigate which lncRNAs are mainly associated with DM. Our results demonstrated six lncRNAs were consistently dysregulated in patients with DM. Anril, Hotair, Kncq1ot1, Malat1, and Miat were consistently upregulated, while Meg3 was downregulated in diabetic cases compared to controls.

Malat1 (metastasis-associated lung adenocarcinoma transcript 1, also known as Neat2) is one of the most analyzed lncRNAs in T2DM samples. Here, our qualitative analysis shows this lncRNA is upregulated in serum, plasma, and PBMCs of
T2DM patients (21, 52, 53, 62, 63). Moreover, studies performed in animal models of DM indicate that the expression of Malat1 is increased in liver, macrophages, and serum of different murine models of T2DM compared to controls (20, 27, 52). Malat1 is a highly conserved nuclear lncRNA initially identified as a predictor of lung cancer metastasis (82). Several studies have reported the involvement of this lncRNA in signaling pathways related to DM pathogenesis, such as PI3K/Akt (83), NF-κB (84), MAPK/ERK (85, 86), and Wnt/β-catenin (87). Accordingly, our in silico analysis shows Malat1 is involved in a number of pathways involved in DM and its complications that, besides PI3K/Akt, MAPK, and Wnt, include apoptosis, insulin, cell cycle, AMPK, FoxO, ErbB, HIF-1, AGE/RAGE, adipocytokines, and protein processing in endoplasmic reticulum. In agreement with Malat1 upregulation in T2DM, its expression was also increased in human umbilical vein endothelial cells (HUVECs) cultured with high-glucose (HG) and positively correlated with inflammatory cytokine (IL6 and TNF) levels (88). Additionally, this lncRNA was upregulated in mice with diabetic retinopathy (DR) compared to control animals (89).

Hotair was also consistently upregulated in liver, blood, and PBMCs of patients with T2DM (21, 38, 62). Accordingly, Li et al. reported this lncRNA was upregulated in liver of two T2DM murine models (db/db and C57BL/6J mice) treated with high-fat diet (49). Hotair is located within the HOMEobox C (HOXC) gene cluster on chromosome 12q13.13 and is involved in cellular proliferation, inhibition of apoptosis, genomic instability, angiogenesis, and metastasis (90–92). Moreover, Hotair upregulation promotes hepatic insulin resistance via the Akt/GSK pathway (38), which might partially explain its association with T2DM. Our in silico analysis demonstrates the involved of Hotair in several DM-related pathways, such as apoptosis, PI3K-Akt, MAPK, HIF-1, TNF, and FoxO. This lncRNA seems also to be involved in the pathogenesis of diabetic chronic complications. Hotair was upregulated in serum of patients with different degrees of DR compared to healthy controls, and its expression was able to distinguish patients with non-proliferative DR from those with proliferative DR (62). Increased expression of Hotair was also found in kidney of patients with diabetic kidney disease (DKD) and in kidneys of db/db and STZ-induced diabetic mice (93). Accordingly, mouse podocytes cultured under HG conditions also expressed high levels of Hotair (93).

In addition to Malat1 and Hotair, the lncRNA Anril was also increased in PBMCs, plasma, or serum of patients with T2DM compared to controls (21, 63, 77). This lncRNA has been associated with several types of cancer, such as gliomas, breast, lung, liver, colon, and thyroid cancers [reviewed in (94)]. Anril seems also to be involved in DR pathogenesis, since its expression was upregulated in human retinal endothelial cells (HRECs) cultured under high-glucose (HG) and positively correlated with inflammatory cytokine (IL6 and TNF) levels (88). Additionally, this lncRNA was upregulated in mice with diabetic retinopathy (DR) compared to control animals (89).

Kcnq1ot1 is another lncRNA consistently upregulated in islets and serum of patients with T2DM (56, 68, 69). Kcnq1ot1 is an antisense lncRNA that seems to regulate the expression of both neighboring or distant genes (98), including the CDKNIC, a known regulator of beta-cell development (99). Interestingly,
a meta-analysis study, including 51,075 DM cases and 10,6134 controls, demonstrated the association between the rs231362 polymorphism in the Kcnq1ot1 gene and risk for T2DM [OR 1.10 (95% CI 1.06–1.15), P < 10−4] (100). Our in silico analysis indicates this lncRNA regulates genes from the protein processing in endoplasmic reticulum stress pathway.

Miat was also consistently upregulated in serum, plasma, or PBMCs of T2DM patients compared to controls (21, 42, 63). This lncRNA seems to act as a regulator of several signaling pathways related to cellular function, such as proliferation and apoptosis and as a competitive endogenous RNA (101). Additionally, Miat seems to be involved in diabetic complications (102). Miat was upregulated in the myocardium of diabetic rats, while its knockdown inhibited apoptosis in cardiomyocytes exposed to HG (103). In contrast, in renal tubuli of diabetic rats, Miat was downregulated compared to control rats and negatively correlated to serum creatinine levels (104). Growing evidence has also shown Miat dysregulation in a number of diseases, such as myocardial infarction, age-related cataract, different cancers, and ischemic stroke [reviewed in (101)]. Here, we were not able to find any significant KEGG pathway for Miat; therefore, how this lncRNA is involved in DM and other diseases still needs to be clarified.

Our systematic review indicates Meg3 is downregulated in islets, whole blood, and serum of patients with DM (48, 53, 74). Accordingly, this lncRNA was downregulated in islets of db/db mice (105) and in serum of diabetic patients with DR compared to controls (74). However, it was upregulated in liver or primary hepatocytes of different T2DM murine models (59, 106). In a murine beta-cell line (MIN6), Meg3 expression lead to increased apoptosis due to caspase-3 and Bax upregulation and Bcl2 downregulation (105). In addition, Meg3 seems to regulate insulin synthesis and secretion due to its blockade in murine beta-cells decreased the expression of key transcription factors involved in insulin synthesis (Pdx-1 and mafa); thus, decreasing insulin gene transcription (105). Besides apoptosis, our in silico analysis suggests this lncRNA is involved in PI3K/Akt, VEGF, and MAPK pathways.

Of note, our bioinformatics analysis also demonstrated that Anril, Hotair, Malat1, Kcnq1ot1, and Meg3 regulate genes from the Kaposi sarcoma-associated herpes virus infection (KSHV) pathway. KSHV, also known as human herpesvirus 8, is a human tumor virus associated with the pathogenesis of Kaposi’s sarcoma, primary effusion lymphoma, and Multicentric Castleman’s disease. The KSHV pathway contains genes related to IFN antiviral response, inflammatory cytokines, and cell proliferation pathways [https://www.genome.jp/kegg/kegg2.html]. Interestingly, the association between KSHV and DM was previously reported by observational studies (107, 108). Cui et al. described that patients with T2DM had an elevated risk of KSHV (107). Accordingly, Piras et al. showed 58% of T2DM patients were seropositive for KSHV vs. 27% of the healthy subjects (108). Even though the mechanisms behind this association are unknown, this virus causes metabolic changes that might lead to altered insulin uptake and accumulation of neutral lipids in cells and also induce an impairment of the immune system [review in (109)], which are mechanisms related to DM pathogenesis.

Even though this systematic review indicates a group of lncRNAs consistently associated with DM and the pathways possible regulated by them, it has few limitations. First, there is no official nomenclature for lncRNAs; thus, we cannot exclude the possibility that we have lost some information. Second, some studies, especially those using RNAseq and microarrays technologies, did not inform which were the differentially expressed lncRNAs or their expression pattern (up- or downregulation) (19, 25, 44, 53, 54, 58, 66, 71, 76). Third, studies used different techniques to quantify lncRNA expressions and usually did not provide the expression values, only the pattern of expression of the dysregulated lncRNAs; therefore, making impossible to perform a reliable quantitative analysis of the data (meta-analysis). Fourth, most of the studies investigated lncRNAs in patients with T2DM or did not inform the type of DM, evidencing the lack of studies in T1DM population. In this context, four of the dysregulated lncRNAs found in this study were analyzed only in T2DM patients (Anril, Hotair, Malat1, and Miat). Thus, our results are more representative of this type of DM. Fifth, although six lncRNAs were consistently dysregulated in patients with DM compared to controls, it was not possible to perform a stratified analysis by tissue since the number of studies that evaluated the same lncRNA in a given tissue is very small. Lastly, as commented above, Anril, Hotair, Kcnq1ot1, Malat, Meg3, and Miat lncRNAs seem to be dysregulated in patients with DR and DKD. However, most of the studies included in this systematic review did not report the percentage of patients with these diabetic chronic complications. Thus, here, it was impossible to evaluate if presence of diabetic chronic complications is impacting our results. Further studies are required to clarify this point.

In conclusion, our systematic review indicates that six lncRNAs are consistently dysregulated in DM, especially in patients with T2DM. This study also contributes to enlighten the pathways regulated by these lncRNAs and involved in the DM pathogenesis, such as PI3K/Akt, MAPK, apoptosis, AGE/RAGE, and FoxO. Although this systematic review included 53 studies which analyzed lncRNA expression in DM-related tissues, further studies are necessary to better understand the involvement of lncRNAs in the pathogenesis of this complex disease and its chronic complications. As much as lncRNAs seem to be good candidates as biomarkers and therapeutic targets for DM, further investigations on organ-specific distribution of these regulatory molecules may be useful to clarify their role in DM.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

CD designed the study, researched data, performed the analysis, and wrote the manuscript. NL researched data, performed the analysis, and reviewed the manuscript. NC researched data and...
reviewed the manuscript. TA researched data, performed the bioinformatic analyses, contributed to discussion, and reviewed the manuscript. DC designed the study, contributed to the discussion, and wrote and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING
This study was partially supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundo de Incentivo à Pesquisa e Eventos (FIPE, number 2018-0470) at Hospital de Clínicas de Porto Alegre, Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERSGS) (Editorial FAPERSG/CNPq 12/2014 PRONEX - Processo nº 16/2551 - 0000483-8), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). DC is recipient of scholarships from CNPq, while CD and TSA are recipients from scholarships from CAPES, and NL is recipient of scholarships from FAPERSGS.

SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.602597/full#supplementary-material

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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