

Review

# Regulatory MicroRNAs in T2DM and Breast Cancer

Ilhaam Ayaz Durrani , Attya Bhatti \*  and Peter John

Department of Healthcare Biotechnology, Atta-ur-Rehman School of Applied Biosciences (ASAB), National University of Sciences and Technology (NUST), H-12, Islamabad 44000, Pakistan; ilhaam.ayaz.durrani@gmail.com (I.A.D.); pjohn@asab.nust.edu.pk (P.J.)

\* Correspondence: attyabhatti@gmail.com

**Abstract:** MicroRNAs orchestrate the tight regulation of numerous cellular processes and the deregulation in their activities has been implicated in many diseases, including diabetes and cancer. There is an increasing amount of epidemiological evidence associating diabetes, particularly type 2 diabetes mellitus, to an elevated risk of various cancer types, including breast cancer. However, little is yet known about the underlying molecular mechanisms and even less about the role miRNAs play in driving the tumorigenic potential of the cell signaling underlying diabetes pathogenesis. This article reviews the role of miRNA in bridging the diabetes–breast cancer association by discussing specific miRNAs that are implicated in diabetes and breast cancer and highlighting the overlap between the disease-specific regulatory miRNA networks to identify a 20-miRNA signature that is common to both diseases. Potential therapeutic targeting of these molecular players may help to alleviate the socioeconomic burden on public health that is imposed by the type 2 diabetes mellitus (T2DM)–breast cancer association.

**Keywords:** microRNA; miRNA; T2DM; breast cancer; diabetes–breast cancer association



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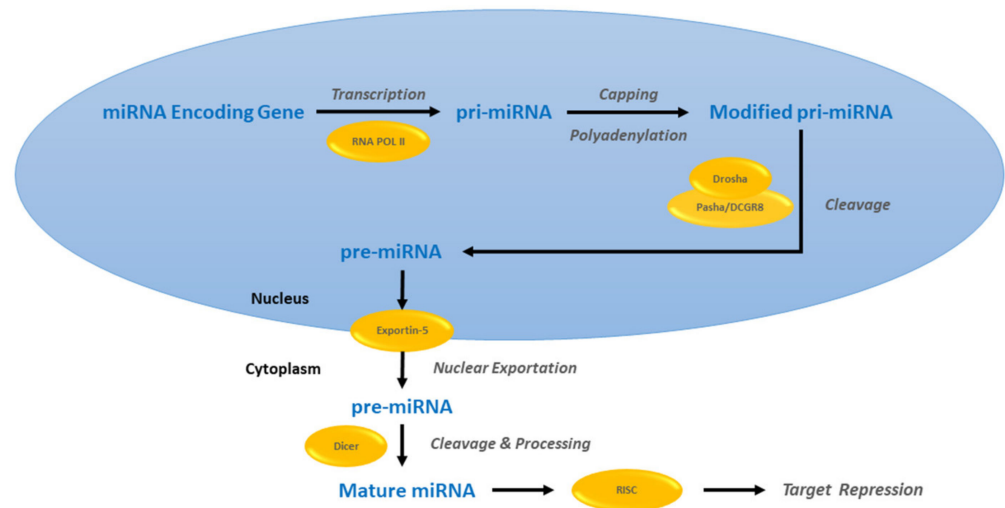
## 1. Introduction

MicroRNAs, being integral to the central dogma of life as we know it at the molecular level, orchestrate the tight regulation of cellular mechanisms, such as gene transcription, translation, RNA interference, DNA repair, and even cell–cell communication [1–3]. Also known as miRNA, these short strands of RNA, about 19–25 nucleotides long, are a subclass of endogenous small noncoding RNA molecules [4]. Unlike the coding RNA, which transcribes hereditary information from DNA and translates it into a protein, a miRNA is not translated into an amino acid primary sequence; instead, its functional significance is identified by the regulatory niche it serves for various cellular and biological functions.

miRNAs exist as antisense single strands to target genes, negatively regulating their expression post transcription. Genes encoding miRNA are transcribed into primary transcripts (pri-miRNA), which are several kilobases in length, by the enzymatic activity of RNA polymerase II within the nucleus, and which are then subjected to capping and polyadenylation, as depicted in Figure 1 [5,6]. These pri-miRNAs are shortened to form precursor miRNA molecules (pre-miRNA) by the action of Drosha, an enzyme belonging to the RNA polymerase III family, in a complex with DCGR8/Pasha and then exported to cytoplasm via exportin-5. Further cleavage by Dicer, another RNA polymerase III enzyme, and degradation of the complementary strand generates shorter single-stranded RNA molecules, referred to as mature miRNA [7]. The final form, as part of the RNA-induced gene silencing complex (RISC), binds to its complementary mRNA sequence and targets it for degradation or negative regulation at the protein translation level [8]. Hence, miRNAs serve as a critical component for transcriptional gene silencing.

Within the mature miRNA's structure, the 5' end constituting the “miRNA seed” displays evolutionary conservation in its sequence and has been studied for miRNA target recognition [9]. It is also crucial for mature miRNA's stability, as well as its recruitment

within the miRNA–RISC (miRISC) complex [10–14]. With the seed sequence being only six nucleotides long, each miRNA is believed to regulate multiple genes [15]. The entire biogenesis process is regulated in a spatiotemporal manner, following which, miRNAs are found to be present in all main cellular compartments and bodily fluids, implying the diversity in their biological role.



**Figure 1.** MicroRNA (miRNA) biogenesis and target gene repression. A miRNA encoding gene is transcribed into a primary miRNA (pri-miRNA), which undergoes subsequent post-transcriptional modification and then cleavage to generate a precursor miRNA (pre-miRNA). These pre-miRNA molecules are exported out of the nucleus and further cleaved and processed to their final form, mature miRNAs.

Hence, specific miRNA dysregulations may impose detrimental consequences on gene regulation and subsequent disease development [16]. The role of miRNA in various complex pathological conditions, such as diabetes, cardiovascular conditions, autoimmune disorders, and human cancers, including breast cancer, has been well established [17–21]. Diabetes and cancer, which are two polygenic and multifactorial diseases, exercise a significant overlap in cell signaling pathways and their dysregulations [22–24]. This lays a solid molecular base for a diabetes–cancer association, which is a subject of focus for numerous studies to date, as diabetes-induced carcinogenesis becomes an increasingly common phenomenon [25,26].

There is an increasing amount of epidemiological evidence associating diabetes, particularly type 2 diabetes mellitus (T2DM), which is the most prevalent type of diabetes, to an elevated risk of cancers of various tissue origins. However, not all cancers associate equally. Diabetic patients have shown a greater increased risk for liver, pancreatic, and endometrium cancers as compared to cancers of the breast, colon-rectum, and bladder, all of which reportedly associate positively with T2DM [27–32]. Furthermore, prostate cancer has shown a negative association and lung cancer has depicted no association with T2DM [33,34]. With diabetes and cancer already emerging as two leading causes of death, an association between the two only aggravates the socioeconomic burden on global public health, and hence, needs to be addressed [35].

Unfortunately, beyond the epidemiological basis, the underlying molecular mechanisms mediating the diabetes–cancer association are not fully understood. So far, hyperglycemia, hyperinsulinemia, insulin resistance, oxidative stress, inflammation, and hormonal imbalances, which are all characteristic of T2DM, have been employed as potential molecular bases underlying this association [36–38]; however, the role of miRNA-mediated dysregulations in modulating these features and their tumorigenesis-driving potential in diabetic patients is still underexplored.

In this context, miRNAs are crucial cellular regulatory factors; as such, this review focuses on highlighting their significance in mediating the diabetes–breast cancer crosstalk that leads to breast-cancer-induced T2DM onset and specifically T2DM-induced breast cancer. By discussing the roles of specific miRNAs in both T2DM and breast cancer individually and then interpreting the overlap between disease-specific regulatory miRNA networks, this paper identifies a conserved miRNA signature that is common to both diseases. Further molecular studies investigating these miRNAs may potentiate their role as biomarkers with diagnostic, prognostic, and therapeutic significance for diabetes and breast cancer patients.

## 2. Article Selection for the Literature Review

For this literature review, the online database PubMed was searched through using the keywords “T2DM” (OR “diabetes”) AND “breast cancer” (OR “cancer”) AND “microRNA” (OR “miRNA”) and “T2DM” (OR “diabetes”) OR “breast cancer” (OR “cancer”) AND “microRNA” (OR “miRNA”) in the given combinations and separately. Original articles published on both in vitro and in vivo experimental results were retrieved. Review articles were also studied to extract second references for original articles that were relevant to the research topic. A total of 301 articles were extracted for T2DM and over 6000 for breast cancer for the period 2011–2021. In view of the extensive literature available, further shortlisting was done to include studies based on miRNA’s implication in either disease, yet targeting a pathway common to both diabetes and breast cancer. Hence, around 170 articles were summarized in this review and utilized for Venn diagram analysis.

## 3. The Role of miRNAs in T2DM

The functional roles of many miRNAs have been established in T2DM with numerous studies implicating miRNA dysregulation in diverse aspects of T2DM pathogenesis. These include beta-cell function, islet development, adipocyte and beta-cell differentiation, insulin production and its secretion, insulin resistance, glucose homeostasis, lipid metabolism, and diabetic treatment [39,40]. For instance, miR-148b, miR-223, miR-126, miR-19a, and miR-130a have all been identified as diagnostic biomarkers for T2DM [41,42], while miR-126, which has been shown to positively correlate with impaired glucose tolerance, has been identified as a prognostic marker for T2DM. Furthermore, miR-182-5p and potentially miR-30a-5p may be pursued as diagnostic markers for T2DM [43]. miR-375 has also been reported as a novel biomarker as its upregulated plasma levels correlate with the T2DM phenotype [44].

Additionally, Karolina et al. reported a signature of 4 miRNAs, namely, miR-142, mi-146a, miR-150, and miR-182, which could differentiate between impaired fasting glucose (IFG) and T2DM, besides the miR-29a, miR-192, and miR-320 reported previously. Other miRNAs differentially expressed for T2DM include miR-21, miR-30d, miR-148a-3p, miR-146b, miR-148a-3p, miR-147, and miR-486 (upregulated) and let-7b-5p, miR-1-3p, miR-222-3p, miR-186, miR-23a, and miR-126 (downregulated) [45–48].

Hence, a vast number of miRNAs have been implicated in diabetes pathology so far and this section classifies these miRNAs based on their functional significance in T2DM, the summary of which is listed in Table 1, along with their target genes or implicated pathways.

**Table 1.** miRNA expression and target gene regulation in type 2 diabetes mellitus (T2DM).

T2DM Characteristic	miRNA	Expression	Target mRNA/Implicated Pathway	Reference
Beta-cell function	miR-143	↑	<i>ORP8/insulin</i> –AKT pathway	[49]
	miR-144	↑	<i>IRS1</i>	[50]
	miR-30d	↑	<i>Cyclin E2, RUNX2, PI3K/insulin</i> pathway	[51–54]
	miR-126	↑	<i>IRS1</i>	[55]
	miR-146a	↑	<i>NF-κB</i>	[56]
	miR-375	↑	<i>ERK1/2, Mtpn</i>	[57,58]
	miR-21	↓	<i>PTEN/PI3K</i> –AKT pathway, <i>TGF-β1/SMAD3</i> pathway	[54,59]
	miR-24	↑	<i>MAPK, P38</i>	[60]
	miR-34a	↑	<i>VAMP2</i>	[61]
	miR-96	↑	<i>FoxO1, SOX6</i>	[62]
	miR-199a-5p	↑	<i>SIRT1</i>	[63]
	miR-125b-5p	↑	Inhibits <i>JNK</i> pathway	[64]
	miR-9	↑	<i>SYTL4</i>	[65,66]
	miR-124a	↑	<i>Mtpn, FoxA2, Rab27A</i>	[67–69]
miR-15	↑	-	[70]	
Insulin resistance	miR-27a	↑	<i>PPARγ</i>	[71]
	miR-221	↑	Impairs the <i>PI3K/AKT</i> pathway	[72]
	miR-382-3p	↑	<i>Resistin</i>	[73]
	miR-223	↑	<i>GLUT4</i>	[74]
	miR-128-3p	↑	<i>ISL1</i> -dependent <i>Wnt</i> pathway	[75]
	miR-145	↑	<i>Insulin</i> –AKT pathway	[54]
	miR-155	↓	<i>HDAC4</i>	[76]
	miR-18a	↓	<i>PTEN</i>	[77,78]
Metabolism	miR-194	↓	<i>PI3K/AKT</i> pathway	[79]
	miR-146b	↑	<i>IRS1, GLUT4</i>	[80]
	miR-182	↓	<i>FoxO1, PDK4</i>	[81]
	miR-222	↑	<i>GLUT4</i>	[54,82,83]
	miR-125a-5p	↑	<i>STAT3</i>	[84]
	miR-33a/b	↑	<i>IRS2, SIRT6, AMKPKα, CRAT, CPT1A, HADH</i>	[85]
Oxidative stress/ inflammation	miR-146a	↑	<i>NF-κB</i>	[56]
	miR-424	↑	Activates <i>KEAP1</i> and <i>NRF2</i>	[86]
	miR-181b/miR-126-5p	↓	<i>NF-κB</i>	[87]
	miR-21	↓	<i>PDCD4, Pclo</i>	[88]
	miR-223	↓	<i>KEAP1</i>	[89]
	miR-199a-5p	↑	<i>SIRT1</i>	[63]
	miR-126-3p	↓	<i>VCAM-1</i>	[90]
Clinicopathological features	miR-496	↓	<i>mTOR</i> upregulation	[91]
	miR-486-3p	↑	-	[92]
	miR-423	↓	-	[92]
	miR-28-3p	↑	<i>IGF1, IGF2R, MAPK1, MAP2K3, RAF1</i>	[93]
	miR-146a-5p	↓	<i>SMAD4, TRAF6, IRAK1</i>	[94]
	miR-16-2-3p	↑	-	[92]
	miR-1-3p	↓	<i>KCNQ1 tv1</i>	[95]
	miR-23a/ miR-186	↓	-	[48]
	Diabetic complications	miR-4463	↑	Activates <i>PI3K/AKT</i> pathway
miR-196-3p		↑	-	[97]
miR-203-3p		↑	<i>SMAD1</i>	[98]
miR-20b-5p		↑	Regulates <i>Wnt9b/β-cell</i> signaling	[99]
miR-423		↓	<i>VEGF</i> signaling	[100]
miR-21		↑	<i>PPARα</i>	[101,102]
let-7b-5p		↓	<i>IRS1/Mt.Cytb</i> up-regulation	[103]
miR-1281		↑	<i>HDAC4</i>	[104]
miR-155		↓	-	[105]
Treatment	miR-122	↑	<i>CPT1A, LRP1, HINT1</i>	[106]
	miR-27b	↓ (human T2DM skeletal muscle) ↑ (diabetic mice)	<i>NAA15</i>	[107–109]
	miR-147	↑	<i>SLC22A3</i>	[110]
	miR-130a	↓	<i>MAP3K12</i>	[107,111]
	miR-210	↑	<i>NDUFA4</i>	[107,112]

### 3.1. Beta-Cell Function

Type 2 diabetes encompasses the combinatory effects of insulin resistance and a lack of insulin secretory response [113]. The aberrant expression of various miRNAs has been implicated in altered beta-cell function featuring T2DM pathophysiology. For instance, as an inhibitor of the *insulin*–*AKT* pathway, miR-143 presents itself as a novel biomarker for insulin tolerance and the development of T2DM [49], and miR-144 was shown to impair *insulin* signaling by negatively targeting *insulin receptor substrate 1 (IRS1)* [50]. Furthermore, miR-30d, miR-126-5p, and miR-146a-5p have all been identified as pancreas-enriched miRNAs and is implicated in diabetes pathogenesis, and the roles of miR-375, miR-21, miR-34a, miR-24.1, and miR-148 have also been investigated as potential biomarkers for T2DM [114]. In particular, the regulation of miR-375 was shown to be associated with beta-cell injury, highlighting its role in T2DM pathogenesis, and miR-15's involvement in beta-cell differentiation has also been reported [70].

As another miRNA that is directly associated with beta-cell function, miR-96 regulates pancreatic beta-cell function by inhibiting apoptosis and enhancing proliferation via targeting *forkhead box protein O1 (FoxO1)* and *SRY-box transcription factor 6 (SOX6)* [62]. The miRNA miR-199a-5p's role in hyperglycemia-induced beta-cell toxicity has also been the subject of study [63]. High glucose levels lead to an elevated expression of the miRNA, which then not only promotes reactive oxygen series (ROS) buildup but also induces apoptosis in beta cells via targeting the *sirtuin 1 (SIRT1)* protein. miR-124a2 is shown to target *FoxA2*, which is the master regulator of pancreatic development; however, the exact role it plays in pancreatic cell signaling, and hence in T2DM, remains to be fully elucidated [68]. The role of miR-9 in *insulin* secretion was shown to provide mediation via its targeting of *Onecut-2*, which is a transcription factor implicated in regulating beta-cell exocytosis [65].

Parallel to all these, some miRNAs have been shown to be protective against T2DM progression, such as miR-125b-5p, which enhanced the *JNK* pathway inhibition that mediated the beta-cell function in mice [64], and miR-155, which promoted *insulin* sensitivity, leading to *insulin*-mediated *AKT* and *IRS1* phosphorylation, which in turn increased glucose uptake and glycolysis [76]. It is known to target negative regulators of *insulin* signaling, including *histone deacetylase 4 (HDAC4)*, and was found to be downregulated in serum derived from T2DM patients.

### 3.2. Insulin Resistance

A considerable number of miRNAs are reported to play a role in insulin resistance, including miR-27a, miR-221, and miR-382-3p [71–73]. miR-27a, an exosomal miRNA derived from adipocytes, induces insulin resistance in skeletal tissue via inhibiting *peroxisome proliferator-activator receptor gamma (PPAR $\gamma$ )* and implicates obesity-associated cell signaling. Similarly, miR-221 was shown to negatively regulate insulin sensitivity by impairing the *phosphoinositide-3-kinase (PI3K)/AKT* pathway in an in vivo study based on male rats, where exercise induced elevated miR-382-3p levels, which reportedly suppressed the resistin protein, negatively regulating insulin resistance in rat models. miR-128-3p also induced insulin resistance, along with cardiovascular calcification via the *insulin gene enhancer protein 1 (ISL1)*-dependent *Wnt* pathway in type 2 diabetic rats [75]. Besides these, miR-145 also plays a role in insulin resistance by targeting the *PI3K/AKT* pathway [54], and a low expression level of miR-223 has also been associated with insulin resistance [89].

On the other hand, miR-18a was shown to improve insulin sensitivity by targeting *phosphatase and tensin homolog (PTEN)*, a negative regulator of the *PI3K/AKT* pathway, and hence, potentiating its role in treatment against T2DM [78].

### 3.3. Metabolism

miRNAs that are implicated in T2DM metabolism include miR-194's downregulation in T2DM-derived skeletal muscle [79]. This is associated with the uptake of glucose uptake, glycogen synthesis, increased glycolysis, the production of lactate, and glucose oxidation, mediated via an increased *AKT* and *glycogen synthase kinase 3 beta (GSK3 $\beta$ )*



phosphorylation, hence regulating glucose homeostasis. Furthermore, the role of miR-125a-5p in targeting *signal transducer and activator of transcription 3 (STAT3)*, and hence regulating hepatic glycolipid metabolism in T2DM, has also been reported [84].

### 3.4. Chronic Inflammation and Oxidative Stress

Other miRNAs, such as miR-146a, were shown to be indicative of inflammation and oxidative stress, establishing their implication in T2DM pathogenesis [115], whereas miR-424 negatively correlates with diabetic inflammation and oxidative stress by activating *kelch-like ech associated protein 1 (KEAP1)* and *nuclear factor erythroid 2-related factor 2 (NRF2)*, leading to higher superoxide dismutase (SOD) and glutathione (GSH) levels in T2DM patients [86]. Another two anti-inflammatory miRNAs, namely, miR-181b and miR-126-5p, are reported to negatively correlate with *nuclear factor kappa B (NF-κB)* expression and hence with T2DM [87]. Similarly, miR-21 is also associated with islet inflammation and the low expression of miR-223 correlated with oxidative stress as shown in the previously discussed study by Ding et al., besides the role of miR-199a-5p in ROS generation. The decreased expression of miR-126-3p corresponded with an increased expression of *vascular cell adhesion protein 1 (VCAM1)*, which is an endothelial inflammation marker, and decreased plasma antioxidant capacity in T2DM patients as compared to normal glucose tolerance (NGT) individuals [90].

### 3.5. Clinicopathological Features of T2DM

miRNA expression may also correlate with clinicopathological features that are associated with T2DM, including age, body mass index (BMI), gender, and ethnicity, such as the decreased expression level of miR-496 associated with the BMI-dependent upregulation of mTOR in elderly T2DM patients [91]. In a study published in 2019 on an Israeli Arab/Jewish mixed population, the expression levels of 12 candidate circulating miRNA biomarkers were determined using RT PCR expression analysis. It concluded that miR-486-3p was upregulated and miR-423 downregulated in patients with T2DM with respect to healthy individuals included in the investigation as controls [92]. Furthermore, the miR-28-3p and miR-423 upregulation, and miR-486-3p downregulation was reported for complicated T2DM as compared to early T2DM cases. The signatures of 4 miRNAs (miR-16-2-3p, miR-146a-5p, miR-30d, and miR-126-5p) were seen to be differentially expressed between early and complicated T2DM cases, with the addition of miR-423 only occurring for the male patients, highlighting the effect of sex differences on miRNA expression.

In another ethnic-group-specific study conducted on a Chinese Han population, miR-375 was reported as a potential biomarker with aberrant methylation in its promoter region that was positively associated with T2DM [116]. A different study also investigated its methylation in two different ethnic groups, the Han and Kazak populations, reporting differential expression and hence accounting for the difference in the incidence of T2DM between these two ethnicities [117].

### 3.6. Diabetic Complications

miRNAs have also been associated with diabetic complications. For example, the expression of miR-4463 is elevated in T2DM patients with arteriosclerosis [96]. It was shown to attenuate cell apoptosis via *peanut (PNUT)*-mediated *PTEN* nuclear localization and the activation of the cell survival *PI3K/AKT* pathway in hypoxic and/or hyperglycemic endothelial cells. In cases of diabetic neuropathy, increased miR-196-3p and miR-203 serum levels correlated with urinary albumin excretion, which is characteristic of T2DM [97]. The role of circulating exosomal miR-20b-5p in diabetic wound healing has also been assessed [99]. This miRNA plays a role in regulating the *Wnt9b/β*-cell signaling mediated suppression of human umbilical vein endothelial cell angiogenesis and cell functionality and slows wound healing. Hence, therapeutic targeting of this miRNA is shown to enhance angiogenesis and wound healing in T2DM mice models.

The potential role of miR-423 in diabetic vascular retinal proliferation has also been studied and may be accounted for by its interaction with *vascular endothelial growth factor (VEGF)* signaling [100]. The differential expression of miR-10b in limbal epithelial stem cells reportedly mediates diabetic alterations [118], whereas miR-146 has been implicated in inflammation-induced diabetic neuropathy [119], while miR-1281 directly targets *HDAC4* in diabetic retinopathy [104]. Moreover, miR-203-3p was found to target *SMAD1*, leading to the suppression of osteogenesis in diabetic patients [98] and the potential role of miR-15a in regulating initial retinal damage that is associated with early-stage T2DM has also been established [120].

In addition, single nucleotide polymorphisms (SNPs) in various miRNAs have also been studied, along with their role in diabetes and its associated complications. An miR-146a SNP is shown to be associated with diabetic microvascular complications of diabetic macular oedema in Caucasian patients [121], while the polymorphism rs767649 in miR-155 was found to be associated with diabetic retinopathy [105].

### 3.7. T2DM and Obesity

miRNAs associating with obesity and T2DM include miR-15, miR-143, and let-7b [122]. Furthermore, the expression of miR-448 has also been reportedly reduced in peripheral blood in T2DM patients who had undergone laparoscopic bariatric surgery, hence highlighting its role as a prognostic marker for obese T2DM patients [123].

### 3.8. Diabetic Treatment

Ghrelin treatment of diabetic rats modulated miR-33a and miR-122's expression [124], and Liraglutinide was shown to induce increased miR-27b, miR-130a, and miR-210 serum levels in T2DM patients [103], reflecting on the possibility of a therapeutic agent's potential to modulate the miRNA regulation of genes. The expression of miR-147 was also shown to correlate with the metformin response in T2DM patients from a Pakistani population [110].

## 4. miRNAs in Breast Cancer

The aberrant miRNA regulation of genes that are critical for normal cell signaling is involved in various types of cancers, including breast cancer, via molecular mechanisms, such as chromosomal abnormalities, changes in transcriptional control and epigenetic regulation, and defective miRNA biogenesis machinery [125]. The study of atypically expressed miRNAs may hence be employed to develop potential diagnostic, prognostic, and therapeutic biomarkers for breast cancer. To date, there is an excessive number of miRNAs that have been discovered and are still being investigated for their potential role in breast carcinogenesis, including miR-15b, miR-10b, miR-16-2, miR-26a1, miR-17-92, miR-26a2, miR-26b, miR-126, miR-1246, miR-6861-5p, miR-1307-3p, miR-4634, miR-222, and miR-6875-5p [126–128].

Further to this, miR-362-3p was shown to have an anti-breast-cancer effect, with its expression being associated with higher survival rates in breast cancer patients [129]. At the molecular level, it negatively regulates the transcription of the *human ether a-go-go related gene (HERG)* potassium channels, which promote invasion and tumor proliferation; hence, its significance as a prognostic biomarker for breast cancer seems plausible. Moreover, the prognostic value of miR-383-5p has been highlighted by its role in inhibiting proliferation, migration, and invasion in breast cancer by targeting *lactate dehydrogenase A (LDHA)* expression [130]. Its downregulated expression is concluded to be associated with differentiation and lymph node metastasis, leading to overall poor survival.

Additionally, miR-127's role in *B-cell lymphoma 6 (BCL6)* targeting-mediated inhibition of breast cancer growth, migration, and invasion in breast cancer cells also explains its higher expression being associated with better prognosis in breast cancer patients [131]. Controversially, miR-186 has displayed both anti- and protumorigenic properties, yet its low expression in breast cancer patients has been associated with an overall poor

prognosis [132,133]. Exosomal miRNAs have also been implicated in breast cancer development [134] and miR-1282 has been shown to promote breast malignancy [135].

Moreover, numerous miRNAs have been studied for their serum levels to be employed as potential diagnostic and prognostic biomarkers for breast cancer. Khalighfard et al. found the expression levels of miR-21, miR-155, and miR-10b to be positively correlated with breast cancer, whereas let-7a showed the opposite correlation [136]. The study also showed these expression levels to respond to operative procedures, chemotherapy, and radiotherapy, all of which led to a decrease in the oncogenic miRNAs (onco-miRNAs) miR-21, miR-155, and miR10b and an increase in tumor suppressor miRNA (ts-miRNA) let-7a.

Numerous animal studies have supported miRNA's role in the abnormal cellular characteristics associated with cancer, including uncontrolled growth and proliferation, apoptotic resistance, and dedifferentiation [137], with miRNAs displaying their cancer-promoting or -inhibiting properties. Hence, they have the potential to switch on their oncogenic or tumor-suppressor activity under specific conditions. This section further discusses the miRNAs that are associated with breast cancer and its hallmarks' mediating molecular mechanisms, classifying them into ts-miRNAs and onco-miRNAs, and discusses the subtype-specific expression of various miRNAs, as summarized in Table 2.

#### 4.1. Tumor Suppressor MiRNA

Numerous ts-miRNAs have been identified so far. These include miR-140-5p, which has been implicated in a protective niche against breast cancer progression [143]. Although the underlying mechanism is not fully understood, a study reported that miR-140-5p targets *VEGFA*, hence inhibiting invasion and angiogenesis, and ultimately preventing breast cancer progression.

miR-590-5p, which is known to target *SOX2* for negative regulation, reduced the stemness and tumorigenic properties of breast cancer cells in vitro, corresponding with its downregulation [200]. Another miRNA with antitumorigenic properties, namely, miR-449b-5p, negatively impacted *Wnt/β-catenin* signaling by inhibiting *cell cycle alteration and expression-elevated protein in tumor (CREPT)*, which is a crucial oncogene, to induce cell cycle arrest and inhibit the invasion and growth of breast cancer cells, supported by reports of its low expression in breast cancer [138]. miR-216 also negatively regulated this particular pathway by decreasing both *Wnt* and *β-catenin* expression, leading to the suppression of proliferation and migration, and the induction of apoptosis by elevating *caspases 3/8*, *Bax*, and *P53* in MCF7 cells [139]. miR-590-5p, which is yet another miRNA that downregulates *Wnt/β-catenin* signaling, was shown to inhibit the progression of breast cancer by negatively correlating with cell migration, invasion, metastasis, and the epithelial mesenchymal transition (EMT) [140].

Further to this, miR-20a-5p also exhibited similar effects on breast cancer progression; however, it acts via targeting *high mobility group A2 (HMGA2)*, preventing its procarcinogenic effects [141]. Huang et al. also reported on miR-219-5p as a negative regulator of migration and EMT via targeting *myocardin-related transcription factor A (MRTF-A)* [142].

Another miRNA that is downregulated in breast cancer is miR-322 [144]. It negatively regulates proliferation and was shown to induce apoptosis in vitro, corresponding with elevated levels of *Bax* and the downregulation of *BCL2*. It also reduced the invasiveness of breast cancer cells, decreasing their tendency to migrate, and was shown to correlate with *NFκB1* depletion. Similarly, miR-204 was also shown to inhibit proliferation and metastasis in MCF7 breast cancer cells in vitro, which was mediated by the induction of cell cycle arrest and apoptosis [145]. It significantly inhibited p-AKT and p-PI3K, which are two critical components of the pathway regulating cell survival. In line with this, miR-223's potential role in inhibiting proliferation and invasion in breast cancer via targeting *stromal interaction molecule 1 (STIM1)* was also studied [146], in parallel with its potential as a tumor biomarker by maintaining cell proliferation via the upregulation of *FoxO1* [201].



Table 2. miRNA and target gene regulation in breast cancer.

Breast Cancer (BC) Characteristic	miRNA	Expression	Target mRNA/Implicated Pathway	Reference
Tumor suppressor	miR-362-3p	↓	HERG potassium channels	[129]
	miR-383-5p	↓	LDHA	[130]
	miR-449b-5p	↓	CREPT	[138]
	miR-216	↓	Wnt/ $\beta$ -catenin signaling	[139]
	miR-590-5p	↓	SOX2	[140]
	miR-20a-5p	↓	HMGA2	[141]
	miR-219-5p	↓	MRTFA	[142]
	miR-140-5p	↓	VEGFA	[143]
	miR-322	↓	BCL2, NFkB1	[144]
	miR-204	↓	p-AKT and p-PI3K	[145]
	miR-223	↓	STIM1	[146]
	miR-33b	↓	Twist1, SALL4, HMGA2	[147]
	miR-31	↓	RDX, RhoA, ITGA5	[148]
	miR-143	↓	HER3	[149]
	miR-708-3p	↓	ZEB1, CDH2, Vimentin	[150]
	miR-503	↓	IGF-1R	[151]
	miR-148a	↓	BCL2	[152]
	miR-26a-5p	↓	RNF6, CDK4, CDK6, Cyclin D1	[153]
	miR-326	↓	SOX12	[154]
	miR-671-3p	↓	DEPTOR	[155]
	miR-140-3p	↓	RSU1	[156]
	let-7a(-5p)	↓	USP32	[157,158]
	miR-122	↓	IGF1R	[159]
miR-147	↓	AKT/mTOR pathway	[160]	
miR-186	↓	TWIST1	[132,133]	
miR-362-3p	↓	HERG potassium channels	[129]	
miR-145	↓	MUC1	[161]	
miR-146a	↓	EGFR	[162]	
Oncogenic	miR-21	↑	LZTFL1	[163]
	miR-370	↑	WNK2	[164]
	miR-9	↑	E-CAD, FoxO1, STARD13, LIFR	[165]
	miR-221	↑	PTEN, E-CAD	[166–169]
	miR-155	↑	MAPK7	[136,170]
	miR-421	↑	PDCD4	[171]
	miR-106a	↑	DAX1	[172]
	miR-15/miR-107/miR-182	↑	BRCA1 downregulation	[173]
	miR-526b/miR-655	↑	TCF21, PBRM1	[174]
	miR-409-5p	↑	RSU1	[175]
	miR-30d	↑	KLF-11/STAT3 pathway	[176]
Subtype-specific	miR-129	↓ (TNBC)	Lamin A	[177]
	miR-218	↑ (TNBC)	Lamin B1	[177]
	miR-200c	↓ (TNBC)	-	[178]
	miR-200b	↓	Ezrin-Radixin-Moesin; SPI	[179,180]
	miR-191	↑ (ER+)	sFRP1	[181,182]
	miR-122a	↑ (ER+)	-	[181]
	miR-213	↑ (ER+)	-	[181]
	miR-382-5p	↑ (ER+)	MXD1	[181,183]
	miR-222	↓ (ER+)	ER $\alpha$ , NOTCH3	[181,184,185]
	miR-497	↑ (TNBC, HER2+)	SMAD7	[186]
	let-7a-5p	↓ (TNBC)	GLUT12	[187]
	miR-18a	↑	HIF1 $\alpha$	[188–190]
miR-126-3p	↓ (TNBC)	RGS3	[191]	
miR-124a	↓ (IDC)	-	[192]	
Clinicopathology	miR-520g	↑	p53	[193]
	miR-4732-5p	↓	TSPAN13	[194]
Treatment	miR-663b	↑	TP73	[195]
	miR-7	↑	SETDB1, RELA/STAT3 pathway	[196–198]
	miR-1282	↓	-	[135]
	miR-27a	↑	AMPK2 $\alpha$	[199]

Moreover, other miRNAs that were shown to serve as negative regulators of breast cancer metastasis include miR-33b [147], miR-31 and miR-143 [202], miR-708-3p [150], and miR-204. miR-33b was shown to negatively correlate with lymph node metastasis and its

target genes, including *Twist1*, *spalt-like transcription factor 4 (SALL4)*, and *HMGA2*, through which, it inhibits self-renewal, migration, and invasion [66]. miR-31 was shown to be more potent in suppressing breast cancer metastasis and invasion as compared to miR-143, and miR-708-3p exhibited its tumor-suppressing activity by inhibiting EMT via targeting the EMT mediators *zinc finger E-box binding homeobox 1 (ZEB1)*, *cadherin 2 (CDH2)*, and *vimentin*, suppressing breast cancer metastasis and countering chemoresistance. Previously, miR-204 and miR-147 were also shown to mediate their tumor-suppressing effect on proliferation, invasion, and metastasis via targeting of the *PI3K/AKT* pathway [145,160].

Yet another miRNA of particular interest is miR-503, which is known to inhibit *insulin-like growth factor 1 receptor (IGF-1R)*, altering insulin signaling, and hence, counteracting *IGF1R*'s role in breast cancer progression [151]. miR-148a targets *BCL2*, which is an anti-apoptotic factor, reducing its expression, and hence, leading to decreased proliferation and increased apoptosis, as reported in breast cancer cells [152]. Another study showed that miR-26a-5p downregulated *ring finger protein 6 (RNF6)*, *cyclin-dependent kinase 4 (CDK4)*, *CDK6*, and *cyclin D1* expression, upregulated *p21*, *p27*, and *p53* expression, and modulated *estrogen receptor alpha (ER $\alpha$ )* protein stability, leading to the inhibition of breast cancer growth [153]. This correlates with its low expression in breast cancer and association with overall poor survival in breast cancer patients. Furthermore, miR-326, with its tumor-suppressing activity, suppresses the proliferation, migration, and invasion of cancer, by targeting and regulating *SOX12*, and it was shown to be downregulated in breast cancer patients [154].

miR-671-3p, as shown in an in vitro study, is also downregulated in breast cancer cells, correlating with its *DEP domain containing mTOR interacting protein (DEPTOR)*-inhibition-mediated suppression of proliferation and invasion in MDA-MB-231, MCF-7, and SK-BR3 cells [155]. Another miRNA, miR-140-3p, which is underexpressed in breast cancer, inhibited cell cycle progression and proliferation in vitro, outlining its tumor-suppressing potential [156]. miR-146a also inhibited proliferation, invasion, and metastasis by directly targeting the 3' UTR region of *epidermal growth factor receptor (EGFR)* mRNA [162] and miR-145 by targeting the metastasis regulator gene *mucin 1 (MUC1)* [161,203]. Additionally, let-7a-5p and miR-21-5p were identified as potential noninvasive biomarkers for the diagnosis of breast cancer metastasis with reduced expression in breast cancer [157], while miR-361-3p's low expression was also implicated in promoting breast cancer [204].

#### 4.2. Oncogenic miRNAs

miRNAs that were shown to promote proliferation in breast cancer include miR-21 and miR-370 [163,164]. In vivo studies showed the miR-21 mechanism of action to associate with its target gene *LZTFL1*, which is a leucine zipper transcription factor. miR-370 also promotes cell proliferation and correlates with poor breast cancer prognosis; however, the underlying mechanism is still unclear, although its oncogenic activity has been associated with downregulating its downstream target *WNK2*.

Furthermore, miR-9 was implicated in breast cancer initiation and progression and was shown to promote metastasis in breast cancer [165]. Its expression and that of miR-221 in human breast cancer have been associated with poor differentiation, larger tumor size, lymph node metastasis, and an advanced stage [205].

Other miRNAs that are upregulated in breast cancer and positively associate with its progression include miR-155 via its potential targeting of *mitogen-activated protein kinase 7 (MAPK7)*, as shown by bioinformatics analysis and validation via a positively correlated expression pattern [170], and miR-421, which was found to be upregulated in MCF-7 and MDA-MB-231 breast cancer cell lines, as it promoted proliferation, migration, and invasion and inhibited apoptosis via its target gene known as *programmed cell death 4 (PDCD 4)* [171]. Moreover, miR-106a was shown to promote breast cancer by negatively regulating *dosage-sensitive sex reversal in the adrenal hypoplasia critical region on chromosome X gene 1 (DAX1)* [172].

In addition, miR-15, miR-107, and miR-182 mediate the reduced expression of *breast cancer type 1 susceptibility protein (BRCA1)*, leading to dysregulated DNA repair [173], while miR-526b and miR-655 expression corresponded to oxidative stress and the expression of *thioredoxin reductase 1 (TXNRD1)* in a previously published study, both of which were positively associated with breast cancer. While increased oxidative stress causes defects in DNA repair machinery, *TXNRD1* levels are regulated by *transcription factor 21 (TCF21)* and *polybromo 1 (PBRM1)*, which are two downstream targets of miR526b/miR-655 [174]. Furthermore, miR-30d exhibits its oncogenic potential by promoting breast cancer cell migration, invasion, and EMT by modulating the *kruppel-like factor 11 (KLF11)*–*STAT3* axis [176]. miR-409-5p is also upregulated in breast cancer and its inhibition is shown to mediate anticancerous effects via the subsequent upregulation of its downstream target, namely, *Ras suppressor protein 1 (RSU1)* [175].

#### 4.3. Clinicopathology of Breast Cancer and Its Subtypes

Different subtypes of breast cancer vary in their molecular expression profiles, including miRNAs such as the miR-124a, which is one of the most frequently methylated miRNA genes in cancer and is interlinked with tumor growth and aggressiveness in invasive ductal carcinoma [192]. Hence, miRNAs that are distinctly expressed in specific subtypes may be employed to diagnose a disease subtype and allow for better disease management and treatment. This has been validated by multiple studies, including the 46-miRNA signature that was already identified, which could differentiate between breast cancer subtypes [206].

Setijono et al. studied the downregulation of tumor-suppressing miR-129 and upregulation of oncogenic miR-218 in triple-negative breast cancer (TNBC), associating these two miRNAs to the deregulation of *lamin A* and *lamin B1*, respectively, which are common to human breast cancers [177]. Moreover, the reduced expression of miR-126-3p in TNBC cell lines corresponded with regulator of *G-protein signaling 3 (RGS3)*-inhibition-mediated suppression of cell proliferation, angiogenesis, migration, and invasion [191].

Another study on the aberrant expression of miRNAs in ER-positive breast cancer showed an increased expression of miR-191, miR-122a, miR-213, and miR-382-5p, and decreased expression levels of miR-125b-1, miR-125b-2, and miR-145 [181].

In a cross-subtype comparison, miR-200c was shown to be differentially expressed between TNBC and ER+/PR+ groups, with its expression being significantly lower in (TNBC) [178]. miR-200b was also found to be differentially expressed between two breast cancer cell lines, namely, MDA-MB-231 and MCF-7, with the expression being significantly higher in the latter and its expression negatively correlating with *Ezrin–Radixin–Moesin* mediated cell migration and invasion [179]. In another instance, miR-497 post-transcriptionally regulates *SMAD7*, and hence promotes proliferation, particularly in overexpressed HER2+ breast cancer and TNBC [186]. Contrary to this, miR-18a reportedly prevented distant metastases by directly targeting *hypoxia-inducible factor 1 alpha subunit (HIF1 $\alpha$ )* [188]; however, it has also been associated with poor overall survival, particularly in luminal breast cancers, and is overexpressed in TNBC [189,190].

Moreover, miRNA expression may also correlate with disease stage, grade, and other clinicopathological features. For instance, plasma miR-520g was found to be overexpressed in breast cancer patients, associating positively with lymph node metastasis, low differentiation grade, and invasion, and negatively with *p53* expression, signifying its prognostic value [193]. The expression of miR-106a, with its oncogenic potential, as already discussed, was also shown to positively correlate with higher tumor stage, lymph node and distant metastases, and overall poorer prognosis.

The dual, yet contradictory, role of miR-4732-5p has also been studied. Its significant downregulation in breast cancer samples reflects on its tumor-suppressing role in breast cancer initiation; however, it associates positively with clinicopathological features, such as high Ki-67 levels, grade, larger tumor size, lymph node metastasis, late clinical stage, and poor prognosis, indicating its oncogenic potential. It was shown to mediate these effects via its targeting and suppression of *tetraspanin 13 (TSPAN13)* expression [194].

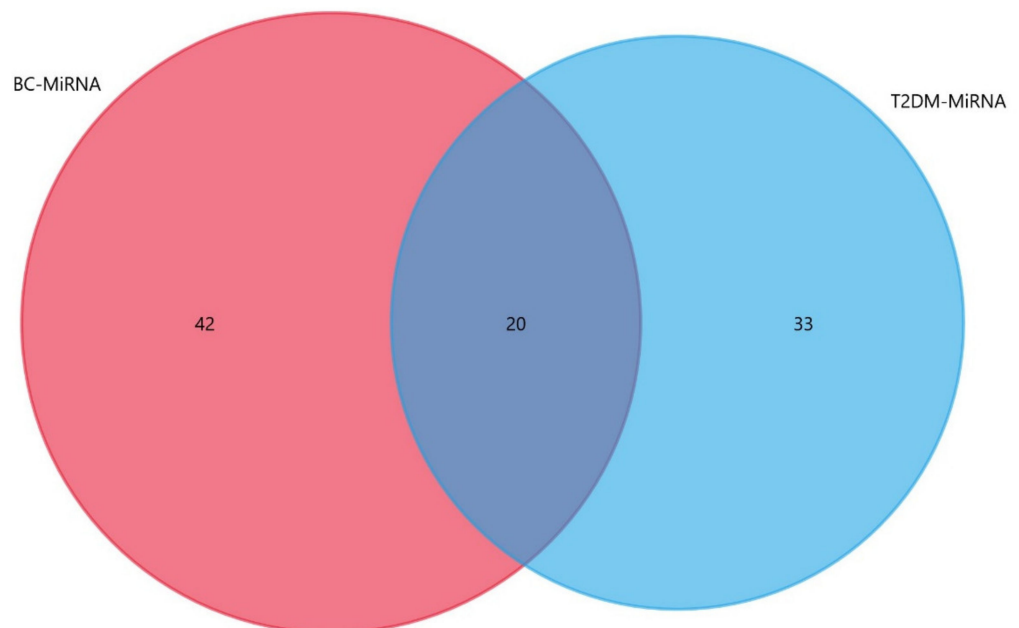
#### 4.4. Breast Cancer Treatments

miRNA regulation has also been implicated in crosstalk with breast cancer therapeutic agents. miR-663b was shown to play a role in tamoxifen resistance in breast cancer by implicating the downregulation of its direct target gene *tumor protein 73 (TP73)* in MCF-7 cells [195], while miR-7 not only associates with poor primary breast cancer prognosis but also correlates negatively with the tamoxifen response and overall poor post-relapse and progression-free survival [196].

#### 5. miRNA's Regulatory Reigns on the T2DM–Breast Cancer Association

With a non-exhaustive list of miRNAs implicated in these two complex, metabolic diseases, particularly in breast cancer, several miRNAs have been identified as mediating aberrant gene regulation, contributing to both diseases' progression. Previously, miR-448 was shown to play a role in determining the adhesive and angiogenic potential of endothelial progenitor cells (EPCs) and is known to suppress viability and invasion. Moreover, circulating miRNAs with an endocrine function include miR-122-5p, which is dominantly expressed in the liver and shows tumor suppressor properties [159,207], whereas the loss of miR-145 expression was shown to contribute toward breast cancer development and progression in patients with both breast cancer and T2DM [208]. Additionally, miR-148 and miR-125b have also been implicated with both diseases.

In continuation with this, the miRNAs discussed earlier in this review, i.e., 53 for T2DM and 62 for breast cancer, were utilized to identify a 20-miRNA signature that is common to both T2DM and breast cancer by employing a Venn diagram analysis performed on Funrich software [209], as shown in Figure 2.



**Figure 2.** Signature miRNA overlap between T2DM and BC regulatory miRNA Networks. Each circle represents a disease-specific miRNA subset, with the intersection representing a signature of 20 miRNAs that are common to both T2DM and breast cancer.

These miRNAs that are common to both T2DM and breast cancer are miR-18a, miR-223, miR-33b, miR-143, miR-145, miR-147, miR-186, miR-27a, miR-21, miR-9, miR-221, miR-222, miR-155, miR-15, miR-182, miR-30d, miR-126-3p, miR-146a, miR-122, and miR-124a. This miRNA overlap between the miRNA regulatory networks of T2DM and breast cancer signifies the potential implication of each of these miRNAs in T2DM–breast cancer (BC) crosstalk, hence providing a window to further probe into the miRNA-mediated

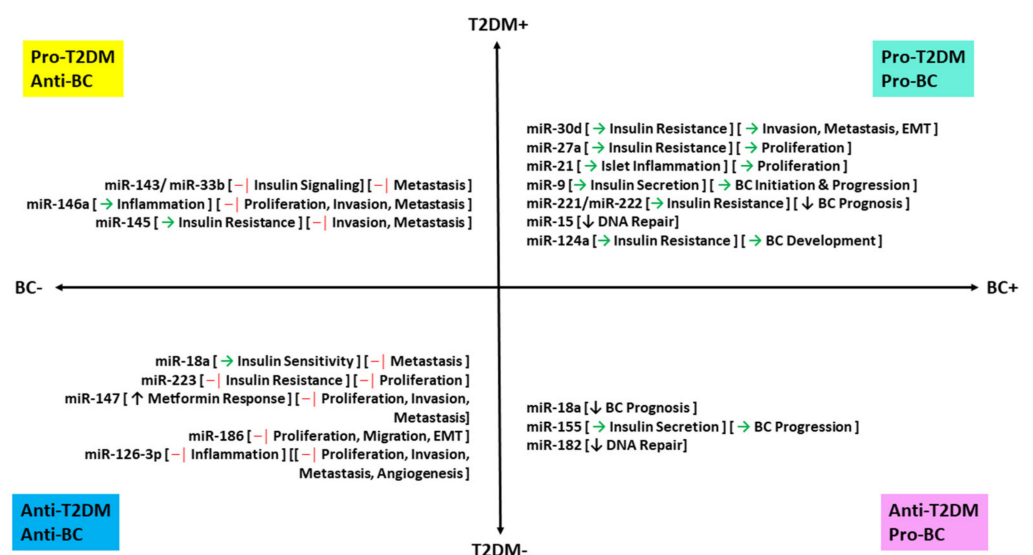
molecular basis of the T2DM–BC association. Therefore, understanding their role in T2DM, breast cancer, and the comorbid state is crucial.

So far, the roles of miRNA-124a and miR-30d have already been established in patients with both breast cancer and diabetes, with their expression levels positively correlating with diabetic characteristics, including the insulin resistance index, BMI, and glycosylated hemoglobin [210]. Another study has implicated it in pancreatic development and insulin secretion [211]. Their expression levels are also shown to correlate with clinical–pathological features of breast cancer in patients with both comorbidities [212], and the development of breast cancer with T2DM; however, the underlying mechanism is still not clear. Another study correlated these miRNAs' expression with the downregulation of *caveolin-1* (*CAV1*)-mediated activation of *estrogen receptor* signaling and its crosstalk with *insulin* signaling to increase the serum *insulin* level [213].

Similarly, another two miRNAs that activate the *estrogen receptor* by downregulating *CAV1* are miR-221 and miR-222, and the overexpression of these two miRNAs is associated with poor breast cancer prognosis and is positively correlated with the insulin resistance index [214]. Besides their implication in T2DM and breast cancer individually, these are also aberrantly expressed in patients with both diabetes and postmenopausal breast cancer [215]. At the molecular level, the decreased expression of *CAV1* also leads to decreased insulin sensitivity, and hence, the development of insulin resistance and *estrogen* signaling contributes to breast cancer.

Furthermore, Liraglutinide's inhibitory effect on the miR-27a level, and subsequently elevated levels of *AMP-activated kinase 2 alpha* (*AMPK2α*) in MCF-7 cells, was also reported [199], and miR-122, besides its role in T2DM etiology, has also been implicated in breast cancer. It was found to target *IGF1R*, inhibiting cell proliferation and tumorigenesis [159].

Hence, out of the 20 miRNAs identified, previously published literature has already discussed 6 of these miRNAs in the context of the T2DM–BC dual relationship. As for the remaining 14 miRNAs, relating the expression patterns of each of these for either disease may provide clues into their potential role in mediating the phenotypic changes underlying the T2DM–BC crosstalk, as illustrated in Figure 3.



**Figure 3.** Regulatory miRNA overlap in T2DM and breast cancer. Symbols: → represents activation, −| represents inhibition, ↑ represents upregulation, and ↓ represents downregulation.

For instance, miR-122, miR-143, miR-223, miR-33b, miR-145, miR-147, miR-18a, miR-124a, and miR-155 are differentially expressed; miR-21, miR-9, miR-27a, miR-15, and miR-182 are upregulated miRNAs; miR-186, miR-126-3p, and miR-146a are downregulated



miRNAs in both diseases. Their expression, coupled with the subsequent implication on their target genes, may provide insight into the potential roles of these miRNAs as diagnostic, prognostic (particularly quadrant I in Figure 3), or therapeutic biomarkers (especially those falling into quadrant III in Figure 3) for comorbid patients. However, the roles of each of these miRNAs need to be studied in patients with both comorbidities to fully understand their potential niche in diabetes–breast cancer crosstalk.

In summary, there are numerous miRNAs, some of which were previously established, along with the additional miRNAs identified here, which may be implicated in mediating T2DM-induced breast carcinogenesis and T2DM onset in diabetic patients. To validate this overlap in the T2DM and BC miRNA regulatory networks, it is necessary to conduct further research on the potential role of miRNAs associated with T2DM, in breast carcinogenesis, and of those associated with breast cancer in the onset of T2DM in breast cancer patients, along with the identification of other novel miRNAs to fully comprehend the extent of the miRNA-mediated gene regulatory network underlying the molecular bridge between diabetes and breast cancer.

## 6. Future of miRNAs in T2DM and Breast Cancer

With several complexities underlying T2DM and breast cancer, the miRNAs highlighted in this review may just be a small sample of those involved. Many other miRNAs are associated with T2DM and breast cancer; however, their association and the underlying mechanisms are not fully clear. These include miR-155, which was shown to be downregulated in T2DM patients [105]; miR-330, which positively associates with T2DM pathogenesis [216]; miR-802-5p [217], miR-126, and miR-146a with T2DM [218]. Similarly, molecular mechanisms underlying numerous other miRNAs implicated in breast cancer are not fully understood and further investigation is required to establish their roles as potential diagnostic or prognostic markers, and even potential therapeutic targets for breast cancer.

## 7. Conclusions

With increasing molecular evidence establishing the T2DM–BC association, a considerable number of miRNAs have been implicated in mediating this inter-disease transitional crosstalk, highlighting a significant overlap in the miRNA regulatory networks underlying diabetes and breast cancer. This study identified a 20-miRNA signature that is common to both T2DM and breast cancer, of which, 6 were previously implicated in the T2DM–BC association. However, to fully acknowledge the depth of this relationship, there is a pressing need for further in-depth molecular studies to elucidate the roles of each of these miRNAs identified in the T2DM–BC association. These may then be employed to provide novel therapeutic targets and thereafter counter the elevated risk of breast cancer in diabetic patients and enhance the prognosis in breast cancer patients with the onset of diabetes.

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## Abbreviations

RNA	Ribonucleic acid
DNA	Deoxyribonucleic acid
DCGR8	DiGeorge critical region
ORP8	Oxysterol binding related protein 8
IRS	Insulin receptor substrate
RUNX2	Runt-related transcription factor 2
ERK	Extracellular-signal-regulated kinase

Mtpn	Myotrophin
TGF- $\beta$ 1	Transforming growth factor beta 1
VAMP2	Vesicle associated membrane protein 2
JNK	c-Jun N-terminal kinase
SYTL4	Synaptotagmin-like 4
GLUT4	Glucose transporter type 4
Wnt	Wingless-related integration site
PDK4	Pyruvate dehydrogenase kinase 4
CRAT	Carnitine O-acetyltransferase
CPT1A	Carnitine palmitoyltransferase 1A
HADH	Hydroxyacyl-coenzyme A dehydrogenase
Pclo	Piccolo presynaptic cytomatrix protein
VCAM-1	Vascular cell adhesion molecule 1
mTOR	Mechanistic target of rapamycin
MAP2K3	Mitogen-activated protein kinase kinase 3
TRAF6	Tumor necrosis factor (TNF) receptor associated factor 6
IRAK1	Interleukin 1 receptor-associated kinase 1
KCNQ1	Potassium voltage-gated channel subfamily Q member 1
SMAD1	Human homologue of Mad and Sma
Mt.Cytb	Mitochondrial cytochrome B
LRP1	Low-density lipoprotein receptor-related protein 1
HINT1	Histidine triad nucleotide-binding protein 1
NAA15	N-alpha-acetyltransferase 15
MAP3K	Mitogen activated protein (MAP) kinase kinase kinase
NDUFA4	Nicotinamide adenine dinucleotide (NADH)-dehydrogenase (ubiquinone) subunit
RT PCR	Real-time polymerase chain reaction
RDX	Radixin
RhoA	Ras homolog family member A
ITGA5	Integrin alpha-5
USP32	Ubiquitin specific peptidase 32
E-CAD	E-cadherin
STARD13	Steroidogenic acute regulatory protein (StAR)-related lipid transfer domain protein 13
LIFR	Leukemia inhibitory factor (LIF)- receptor subunit alpha
SP1	Proximal specificity protein 1
MXD1	MYC associated factor X (MAX) dimerization protein 1
NOTCH3	Neurogenic locus notch homolog protein 3
SETDB1	SET domain bifurcated histone lysine methyltransferase 1

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