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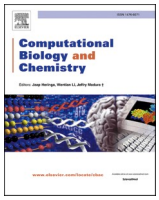

MicroRNA networks linked with BRCA1/2, PTEN, and common genes for Alzheimer's disease and breast cancer share highly enriched pathways that may unravel targets for the AD/BC comorbidity treatment

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ABSTRACT

MicroRNAs (miRNAs) are involved in the regulation of various cellular processes including pathological conditions. MiRNA networks have been extensively researched in age-related degenerative diseases, such as cancer, Alzheimer's disease (AD), and heart failure. Thus, miRNA has been studied from different approaches, *in vivo*, *in vitro*, and *in silico* including miRNA networks. Networks linking diverse biomedical entities unveil information not readily observable by other means. This work focuses on biological networks related to Breast cancer susceptibility 1 (BRCA1) in AD and breast cancer (BC). Using various bioinformatics approaches, we identified subnetworks common to AD and BC that suggest they are linked. According to our results, miR-107 was identified as a potentially good candidate for both AD and BC treatment (targeting BRCA1/2 and PTEN in both diseases), accompanied by miR-146a and miR-17. The analysis also confirmed the involvement of the miR-17-92 cluster, and miR-124-3p, and highlighted the importance of poorly researched miRNAs such as mir-6785 mir-6127, mir-6870, or miR-8485. After filtering the *in silico* analysis results, we found 49 miRNA molecules that modulate the expression of at least five genes common to both BC and AD. Those 49 miRNAs regulate the expression of 122 genes in AD and 93 genes in BC, from which 26 genes are common genes for AD and BC involved in neuron differentiation and genesis, cell differentiation and migration, regulation of cell cycle, and cancer development. Additionally, the highly enriched pathway was associated with diabetic complications, pointing out possible interplay among molecules underlying BC, AD, and diabetes pathology.

1. Introduction

Knowledge related to disease-gene-miRNA associations has revealed the existence of a genetic overlap between apparently unrelated diseases. This realization developed into a research niche, creating a global view of human diseasome (Amare et al., 2017; Carroll and Owen, 2009; Yunpeng Wang et al., 2016). Several genetic overlap or network overlap-related studies focus on diseases with high morbidity, mortality, and skyrocketing disease trajectories which include Alzheimer's disease (AD) (Desikan et al., 2015; Lin et al., 2020; Yokoyama et al., 2016) and breast cancer (BC) (Azamjah et al., 2019; Sung et al., 2021).

For AD, there are no drugs that can prevent or delay disease progression and no established biomarkers for early detection. Additionally, many clinical trials related to potential treatments have failed (Asher and Priefer, 2022). The problem associated with identifying treatment of AD lies in its complexity. Many changes in the cell cycle pathway, mitochondria, ROS regulating mechanisms, metallostasis, inflammatory responses, deficits in neurotransmitters, phosphorylated Tau, and

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chromosomal and hormonal imbalances characterize the AD cell (Reddy and Oliver, 2019; Smith et al., 1998). Moreover, these cellular changes involve more than 100 miRNAs (Absalon et al., 2013; P.H. Reddy et al., 2017).

On the other hand, the current mainstay BC treatment includes chemotherapy, radiotherapy, endocrine therapy, and targeted therapy, but these are limited in success due to BC heterogeneity (Petrović et al., 2021). Interestingly, Kesler and colleagues (Kesler et al., 2017) report that BC patients who underwent chemotherapy with a specific grey-matter brain structure might have an increased chance of developing AD (associated with older age and lower cognitive health). Additionally, reports show BC-AD comorbidity rates rise with age in BC patients (Mezencev and Chernoff, 2020). However, meta-analyses also report an inverse association between BC and AD, *i.e.*, AD incidence is lower among older cancer survivors than those with no cancer history (Ma et al., 2014; Zhang et al., 2015), but the interplay between AD risk and response to therapy in cancer survivors is quite complex (Mezencev and Chernoff, 2020). These findings are supported by experimental evidence showing down-regulated Pin1 (which maintains tau protein functioning in a 'normal state' and ensures proper APP cleavage in neurons) in the AD brains and resistance to breast cancer in Pin1 knockout mice (A. Driver and Ping Lu, 2010; Liou et al., 2003; Malter, 2023; Pastorino et al., 2006).

Despite this inverse association, biological signal pathways are shared by AD and BC; thus, effective treatment and interventions for AD may depend on mechanism-related research involving AD and BC. Here we propose, that the step toward for successful treatment might be one or more common denominators or miRNAs to be pursued as therapeutic targets. During the past decades, miRNAs emerged as potential drug targets, and one of their major characteristics is that they regulate up to thousands of genes simultaneously. This feature of miRNAs makes them perfect candidates in theory to treat one, two, or more diseases. Moreover, miRBase (version 21) data show 1881 human miRNA precursors into approximately 2588 mature miRNAs (Cammaerts et al., 2015). More than 1100 of these mature miRNA have been proven to exist in the human miRNome (Chang and Sharan, 2012), 60 % of these miRNA regulate critical pathways involved in the cell cycle, differentiation, apoptosis, development, and so on, and brain cells/tissue express about 70 % of the identified miRNA (Fineberg et al., 2009). These findings highlight the complexity of any brain-related disease as miRNAs are known to target "hub genes" that interact with several pathways (Albert et al., 2000; Casci, 2006; Chen et al., 2008).

There are no reports of the miRNAs functioning in both AD and BC. Thus, this *in silico* study aimed to unravel more of the miRNAs associated with regulating crucial genes involved in AD and BC pathogenesis and the underlying regulatory network. Additionally, we pinpoint key or hub miRNAs as they potentially represent new therapeutic targets for treating multiple diseases and consider whether we can repurpose existing drugs to treat diseases that share genetic overlap or treat comorbidities simultaneously.

1.1. Alzheimer's disease and miRNA

Thus far, miRNA-related research in AD primarily focuses on those proteins representing hallmarks of AD, such as APP, BACE1, and Tau (Absalon et al., 2013; P. Hemachandra Reddy et al., 2017; Satoh, 2012a). For example, APP and BACE1 mRNA gene expression occur with molecular events responsible for the production of Aβ through the aberrant expression or dysfunction of numerous miRNA such as miR-101, miR-153, miR-193b, miR-16, miR-15/107 family, miR-29a/b-1, miR-485, and so on (Faghihi et al., 2010; Hébert et al., 2009, 2008; Liang et al., 2012, p. 2; Liu et al., 2014, 2012; Parsi et al., 2015; Vilardo et al., 2010). Also, the hyperphosphorylation of endogenous Tau occurs with neurofibrillary pathology in AD. In this regard, Hebert and colleagues (Hébert et al., 2010) demonstrated the miR-16 family members (miR-16, miR-15, miR-195, miR-497, also known as miR-15 family members) whose levels reduce in Dicer-deficient mice, regulate ERK1 expression and tau phosphorylation in cultured mouse neurons. Furthermore, they show reduced miR-15a levels in the AD brain, which suggests miR-15a may be the critical regulator of tau phosphorylation (Hébert et al., 2010). Other miRNAs associated with TAU include miR-128 (Carrettiero et al., 2009), miR-146a (Li et al., 2011), miR-34a (Sarkar et al., 2019). Studies related to the established hallmarks (APP, BACE1, and TAU) provide a peripheral view of miRNA complexity in the AD cell. Research findings also suggest other proteins influence AD progression, especially core cell cycle proteins that regulate the post-mitotic cell processes (Atwood and Bowen, 2015; Bajic et al., 2015; Bajić et al., 2011; Frade and Ovejero-Benito, 2015; Hradek et al., 2015; Koseoglu et al., 2016; Bajic et al., 2016). However, miRNA networks for AD primarily involve processes that regulate the cell cycle, suggesting that the proteins involved in aberrant cell cycle entry (CCE) in AD and their associated miRNAs are crucial for AD pathogenesis (Absalon et al., 2013; Satoh, 2012a, 2012b). Thus, these CCE proteins and their associated miRNA may reveal a novel target/s for therapeutic interventions.

One of the miRNAs described as a potential "hub" miRNA in AD for future therapeutics" is miR-26b. MiR-26b induces neuronal cell death in AD patients by executing several functions, including DNA replication, aberrant CCE, tau hyperphosphorylation, and apoptosis. It has been found that miR-26b is up-regulated early in AD neurons (Braak III stage that corresponds to MCI) by an unknown mechanism (Absalon et al., 2013,). Galimberti et al. (2014) confirmed the increased miR-26b levels in the CSF of AD patients compared to age-matched controls. Furthermore, Absalon and colleagues demonstrated that miR-26b directly binds to the tumor suppressor retinoblastoma 1 protein (pRb1), reducing its functionality as an E2F1 repressor which allows for transcriptional activation of aberrant CCE and pro-apoptotic gene targets (Absalon et al., 2013,). Typically, the nuclear complex consisting of p27, Cdk5, and p35 blocks the neuronal cell cycle by binding to E2F1, preventing its transcriptional activity (Zhang et al., 2010). Thus, inhibition of miR-26b may be a suitable therapeutic intervention for AD.

Nonetheless, finding a "hub miRNA" such as miR-26b is not a straightforward task, as we must identify the "hub genes" involved in AD pathogenesis before the "hub miRNA(s)" can be determined.

2. Methods and results

2.1. Unveiling "hub" miRNA potentially associated with BC-AD comorbidity

Today, several *in silico* tools can be used to conduct preliminary investigations into the role of miRNA and miRNA that may be associated with comorbidity. These tools include miRNET, DisGeNET, MirWalk, or miRPathDB (Chang et al., 2020; Kehl et al., 2020; Piñero et al., 2020; Sticht et al., 2018). We introduce two approaches to unveil "hub" miRNA potentially associated with BC-AD comorbidity. We will use the bioinformatics tools to identify miRNAs that regulate the common/shared genes and those that target networks with functional relevance to the two diseases based on enrichment and pathway analyses.

2.1.1. Approach 1 part A: evaluating genes shared between AD and BC

We used DisGeNET (https://www.disgenet.org/), a versatile platform for finding genes common to diverse diseases and comorbidities to identify genetic overlap (in terms of genes involved in AD and BC). In DisGeNET, we selected the disease-disease association (DDAs) option and used "Alzheimer's disease" and "Malignant neoplasm of the breast" as input data. Results from DisGeNET show, 3397 AD-associated, and 6941 BC-associated genes. AD and BC share 2204 common genes. We further found Breast cancer susceptibility 1 (BRCA1) and Breast cancer susceptibility 2 (BRCA2) included in the 2204 common genes.

Then, STRING, online protein network visualization software was used, to produce a common/shared genes network for AD and BC. We

removed all transport genes to reduce the number of nodes and then analyzed the full network. As parameters, we used high confidence (0.700) interaction score, ten as the maximum number of interactions, and only experiments, co-expression, and text mining as parameters for the interaction sources. We used the resulting interaction list under the "Export" option to identify the list of genes interacting with BRCA1. Using this list, we repeated the process, then used the "Clustering" option to perform K-means clustering, specifying 3 as the number of clusters. This analysis showed several critical genes experimentally connected to BRCA1/2. Results were presented in Fig. 1.

Moreover, it reveals physical and functional links between BRCA1, BRCA2, and Phosphatase and Tensin Homolog Deleted on Chromosome 10 (PTEN), suggesting relationships among these proteins involved in both diseases (Szklarczyk et al., 2017). However, the link between BRCA1/2 and PTEN is not based on experimental evidence but rather on BRCA1 and PTEN, and BRCA 2 and PTEN are frequently co-mentioned in PubMed abstracts to achieve scores of 0.738 and 0.731, respectively. Additionally, no co-expression data exist, but putative homologs are co-expressed in other organisms giving this link an additional co-expression score of 0.063.

Evaluating genes shared between AD and BC reveals a "BRCA1/2 – PTEN" mutation, promoter methylation status and PTEN loss of function-combinations and their interplay/connection and intersected pathways are very important topic in oncology (Kraya et al., 2022; Minami et al., 2014) as the *BRCA1* and *BRCA2* genes are a gene family that functions in cell cycle regulation and DNA damage repair as well as maintenance of telomeres integrity (McPherson et al., 2006), genome integrity in both mitochondria and nucleus (Okada and Ouchi, 2003), X chromosome inactivation (Jazaeri et al., 2004; Lose et al., 2008; Richardson et al., 2006) and survival of embryonic neuronal progenitors (Korhonen et al., 2003). Moreover, dysfunction of BRCA1 and/or BRCA2 proteins is generally known to increase the risk of breast cancer and several other cancer types. These proteins are involved in DNA repair/homologous recombination repair (HRR) (Creeden et al., 2021). However, BRCA1 is thought to play a more extensive role compared to BRCA2. That is, in the absence of functional BRCA1 or BRCA2, the DNA recombinase RAD51 does not relocate to the damaged DNA, but BRCA1 additionally interacts with CtIP affecting DNA-end resection, thereby playing a role in double-strand break repair (Cruz-García et al., 2014).

Evans et al. (2007) were the first to demonstrate increased BRCA1 levels in AD neurofibrillary tangles (NFT), suggesting that BRCA1 is involved in the CCE (Cell Cycle Exit) of affected neurons. The overall CCE mechanism and oxidative stress have been extensively researched and reviewed in AD (Castellani et al., 2006; Nagy et al., 1997; Nunomura et al., 2001). The BRCA1 increase in NFT was not accompanied by an overall rise in AD brains, as Suberbielle et al. recently demonstrated that reducing the levels of BRCA1 in mouse neurons results in DNA damage, neuronal shrinkage, and learning and memory deficits (Suberbielle

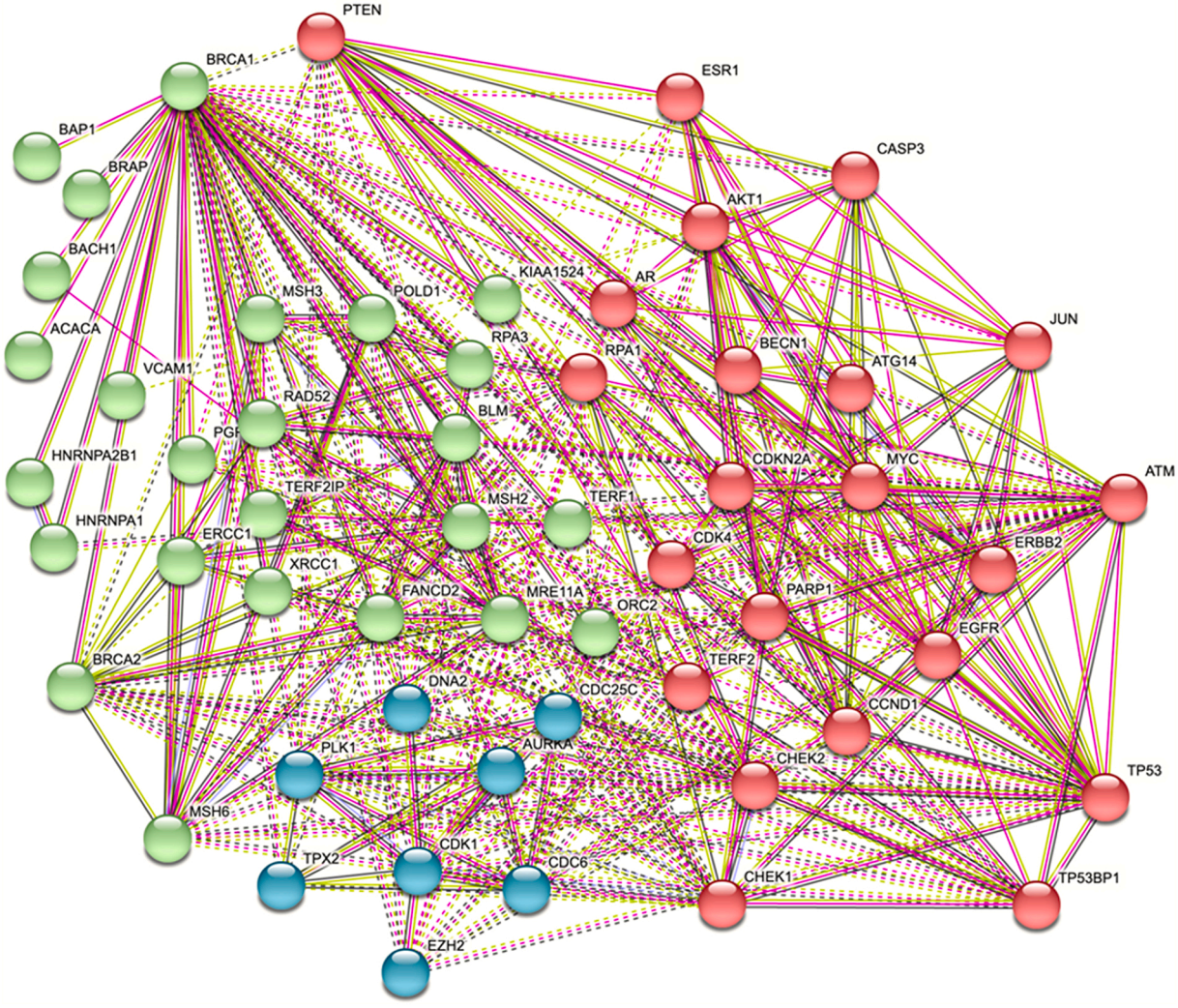

Fig. 1. A String generated network illustrating BRCA1 interactions in AD and BC pathogenesis. Proteins encoded by genes common for AD and BC pathogenesis. STRING software (Szklarczyk et al., 2017) confirmed and visualized the physical and functional relationship between BRCA1, BRCA2, and PTEN proteins.

et al., 2015). These characteristics are analogous to those found in Alzheimer's patients. Thus, they further compared the levels of neuronal BRCA1 in the brains of Alzheimer's patients to healthy brains of a control group and found neuronal BRCA1 levels were reduced by 65–75 % in Alzheimer's patients. The same authors further reported that the accumulation of Aβ in mice brains and cultured neurons reduced BRCA1 levels in neurons *via* activation of the NMDAR receptor, suggesting that the depletion of BRCA1 proteins may cause the defective DNA repair in AD brains (Suberbielle et al., 2015). Nakamura et al. (2020) have shown that BRCA1 and phosphorylated BRCA1-pBRCA1 (Ser1423) are present in phosphorylated tau inclusions, and pBRCA1 was especially associated with NFT in AD.

Additionally, BRCA1 working with the tumor suppressor molecules p53 again suggests a role for BRCA1 in the CCE hypothesis of AD (Nakanishi et al., 2015). Finding this genetic overlap of BRCA1 was unexpected due to breast cancer or cancer cells fast replicating aberrant cells compared to AD neuronal cells characterized by senescence. Nonetheless, targeting this BRCA1 "hub gene" to develop a therapeutic intervention that can reverse or prevent neurodegeneration seems a promising prospect.

Healthy cognitive activity is maintained by regulating oxidative damage through a preserved DNA damage repair mechanism. Cell-cycle dysregulation and cell death in post-mitotic neurons are different states of failed DNA damage repair (Silva et al., 2014). Several miRNAs have been associated with this oxidative stress damage control. However, their effect on BRCA 1 in the AD cell is unknown, even though more than half of human gene transcripts are silenced by a broad range of miRNAs (Davis and Hata, 2009). We could better understand 'hub' miRNA affecting BRCA1 in AD cells if we evaluate its genetic overlap with other diseases characterized by BRCA1 silencing, such as BC.

Regarding the potential PTEN involvement, PTEN is the second most frequently mutated gene in human cancer after p53. Moreover, PTEN, BRCA1, and p53 are known for maintaining genome integrity and are related to various subtypes of BC depending on the mutation of these crucial genes (Ali et al., 2017). In addition, BRCA1 and PTEN functionally cooperate to suppress tumor formation (Minami et al., 2014). Recent studies demonstrate that PTEN plays an essential role in maintaining chromosomal stability and that loss of PTEN leads to massive alterations of chromosomes and aneuploidy (Hou et al., 2017).

On the other hand, high levels of PTEN are expressed in embryos, adult brains, and postnatal development (Veleva-Rotse and Barnes, 2014). By inhibiting the PI3K/AKT pathway and PIP3, PTEN induces a "brake" mechanism that ceases cell growth and proliferation signals in the developing brain. These "networks" of growth and differentiation may play an essential role in the adult brain and neurodegeneration (Ogino et al., 2016). In AD, PTEN is highly expressed and co-localized with Aß. Still, PTEN does not influence Aß's aggregation, clearance, or processing modes. The synaptic AD model suggests that very early signs of memory impairment are due to hippocampal synaptic alterations, and Aß and PTEN have an essential role in these processes (Knafo et al., 2016). Still, how Aß and PTEN influence memory retention or loss is unknown. PTEN is of interest for its role in memory loss during the early stages of AD, as understanding this process might resolve an AD conundrum; why does a histology exam from a cohort of cognitively normal subjects in their 90's, exhibit pathological changes in the brain, and amyloid plaques as much or even more than AD patients?

Hypothetically, PTEN and its partners, BRCA1, p53, and underlining miRNA might express a 'normal' phenotype, suggesting apoptotic inhibition and conserve synaptic plasticity (no synaptic depression). Research that strengthens this hypothesis reported that when knock-in mice $PTEN^{\Delta PDZ}$ where removed, it rendered hippocampal synapses resistant to Aβ, so the cells do not go into depression or impaired LTP in the presence of Aβ (Knafo et al., 2016). The miR-17-92 cluster members were deregulated in BC in a BRCA1-dependent manner (Petrovic et al., 2017) and target PTEN (Basavaraju and de Lencastre, 2016; Hu et al., 2017). Concerning PTEN and its role in repair and brain synapses, BRCA1, miR-17 and/or miR17 cluster-associated changes will appear early in the disease. The Mir-17/92 cluster (miR-17, miR-18, miR-19, miR-19a, miR-19b-1, miR-20a) participates in cell cycle regulation, proliferation, and apoptosis (Mogilyansky and Rigoutsos, 2013). The cluster is important for normal development. It is expressed in embryonic cells, dysregulated in cardiovascular, immunological, and neurodegenerative diseases, and is important in aging (Estfanous et al., 2021). MiR-17/92 first targets the 3′UTRs of PTEN, E2F2, and E2F3. However, the E2F family (1,2,3) occupies the promoter region of miR-17, creating a biofeedback loop, as miR-17 can target E2F2 and E2F3 (Mogilyansky and Rigoutsos, 2013).

Here we suggest that p53, a hub protein found to regulate the CCE in AD (Satoh, 2012b), works in concert with BRCA1 and PTEN. Combination of PTEN and p53 deficiency ia associated with triple negative BC (Gasparyan et al., 2020, p. 53). Furthermore, the miR-17 cluster directly suppresses APP *in vitro* (Hébert et al., 2009), suggesting a novel role associated with PTEN. Note, that APP is deregulated in BC, which again highlights overlapping pathways in cancer and AD (Lim et al., 2014). From this aspect, these processes are in concert with up or down-regulation of miRNAs, as suggested, that the miR-17/92a cluster members are newly recognized partners for BRCA1 and the PTEN protein or as pointed out by Ohyashiki et al. (2011) that the cluster in itself presents cooperative results from the miRNAs through the TGF β signaling pathway. This means that several genes are targeted by several different miRNAs but form the same cluster.

Interestingly, all these molecules work in concert to execute apoptosis. In our view, the BRCA1 and PTEN deregulated phenotype in AD suggest that cluster members cooperate between themselves. There might be other clusters or individual miRNAs that compete for target genes.

MicroRNA profiling suffers from insufficient consensus in the research community. Hence, there is a strong demand for experimental and computational systems biology approaches to incorporate distinct information levels into a complex miRNA network in a given cellular environment. From our point of view, using groups of expressed miRNAs (P. Hemachandra Reddy et al., 2017; Satoh, 2012a, 2012b), the related targetome and several programs like MetaCore software, miRWalk (Dweep et al., 2011), UniPro UGene (Okonechnikov et al., 2012), is a constructive approach in which one may identify related pathways. Interestingly, searching for validated targets of 38 miRs and other groups, Satoh, 2012, reported that the most affected pathway was the cell cycle pathway. A significant relationship of canonical pathways by transcriptional regulation by p53, SMAD, CREB, and Rb/E2F has been reported (Katsel et al., 2013), and all of them play a pivotal role in cell cycle regulation. Also, there is a pathogenic convergence of BC and AD concerning the ectopic expression of the core cell cycle proteins that regulate the cell cycle through miRNA regulation (Du and Pertsemlidis, 2011).

2.1.2. Approach 1 part B: exploration of the miRNA-BRCA1-BRCA2-PTEN connection in AD and BC

Here, we used the online tool miRNET (https://www.mirnet.ca/) (Chang et al., 2020) to find miRNAs potentially associated with query terms of interest: BRCA1; BRCA2; PTEN; AD; BC. This approach will allow us to identify "hub" miRNAs that may regulate the BRCA1 network in AD brains. To explore potential miRNA involved in a complex network, we started by clicking "Multiple query types" in the miRNET tool and then checked the box for "genes" and "disease". Submitting these criteria leads to a page with a "Genes" and "Diseases" table. In the "Genes" tab, we selected "Official gene symbols" and entered BRCA1, BRCA2, and PTEN in the list, then in the "Disease" tab, we selected "Alzheimer's Disease" and "Breast cancer". Submitting this query opened a page with the interaction table. The interaction table showed 621 miRNAs linked to our queried genes and diseases. To focus our query on the more likely "hub" miRNAs associated with our query terms, we further added a "degree filter" of 2, and then proceeded to the visual network page. The

network page provides a visual representation of 28 miRNA linked to our queried genes and diseases. Of these miRNAs, five miRNAs (miR-147a, miR-107, miR-128-3p, miR-146a, and miR-124-3p) interact with at least four of the query inputs (Fig. 2a). We additionally used the "Functional Explorer" tool on the righthand side of the page to query the 28 miRNAs using the "miRNA Disease" database and found, with p-values lower than 0.001, ten and nine miRNAs associated with BC and AD, respectively. Eight of the miRNAs associated with BC and AD are common Fig. 2b).

Of the miRNAs that interact with at least four of the query inputs in Fig. 2a, only miR-107 and miR-124-3p were significantly and commonly associated with BC and AD. A significant decrease in miR-107 levels was detected in AD patients compared with healthy individuals and in beta-amyloid, (Aβ) (Aβ)-treated SH-SY5Y cells (Chen et al., 2020). The expression of miR-107 was shown to decrease in early AD, and the results of this study suggest miR-107 accelerates disease progression through the regulation of beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1) (Wang et al., 2008; Wei et al., 2020). Overexpression of miR-107 can reduce the negative effect of Aβ on apoptosis, viability, and neuroinflammation *via* fibroblast growth factor 7 (FGF7), and thus through the deactivation of the fibroblast growth factor receptor 2-phosphatidylinositol 3-kinase-protein kinase B (FGFR2/PI3-K/Akt) pathway (Chen et al., 2020). It has also been reported that miR-107 was dysregulated in peripheral blood and brain of AD patients. It was associated with the enlarged expression of cell-cycle proteins such as CDK6; it was related to the inhibition of dickkopf-related protein 1 in osteosarcoma. Dkk1 is a Wnt (Wingless and Int-1) signaling pathway that was also shown to be altered in AD, reflecting on increased tau phosphorylation (Swarbrick et al., 2019; Zhang et al., 2017). This association should be investigated in AD disease. MiR-107 might have a dual role in cancer. It might act as an oncogene and tumor-suppressor across various cancer types, resulting in its involvement in silencing multiple genes associated with cell cycle invasive and metastatic potential and response to chemotherapy (Luo et al., 2018). In breast cancer, miR-107 was described as either tumor suppressor or oncomiRNA. MiR-107 was markedly downregulated in both breast cancer cell lines and breast tumors. MiR-107 silences brain-derived neurotrophic factor (BDNF), and its downregulation was associated with decreased proliferation and invasion rates in MCF-7 and MDA-231 BC cells (Gao et al., 2017).

On the other hand, miR-107 levels were significantly higher within BC patients than in healthy control subjects; estrogen receptor-negative (ER-) individuals had higher miR-107 levels than ER+; overexpression of miR-107 in MCF-7 and MDA-MB-231 decreased invasive and migratory potential (Stückrath et al., 2015). MiR-107 has distinctive roles due to its numerous target genes. It is essential to investigate and find a specific group of BC patients where miR-107 alternations might reduce AD and BC progression. This might implicate that a miR-107 mimic might treat a particular subtype of BC in combination with AD.

Another miRNA that might positively affect both disease progression is miR-124-3p (Table 1). Research has shown that miR-124-3p is downregulated in patients with AD, which was proven experimentally. External injection of miR-124-3p into AD mice significantly reduced Aβ

Table 1
The list of miRNAs molecules that modulate the expression of at least 5 genes in AD and BC.

List of miRNA molecules			
hsa-let-7a-5p	hsa-miR-1910-3p	hsa-miR-519d-3p	hsa-miR-6870-5p
hsa-let-7b-5p	hsa-miR-20b-5p	hsa-miR-5698	hsa-miR-6873-3p
hsa-let-7e-5p	hsa-miR-30b-3p	hsa-miR-6086	hsa-miR-6883-5p
hsa-miR-103a-3p	hsa-miR-34a-5p	hsa-miR-6127	hsa-miR-6884-5p
hsa-miR-106a-5p	hsa-miR-3689a-3p	hsa-miR-6133	hsa-miR-6893-5p
hsa-miR-106b-5p	hsa-miR-3689b-3p	hsa-miR-665	hsa-miR-7106-5p
hsa-miR-107	hsa-miR-3689c	hsa-miR-6731-5p	hsa-miR-7110-3p
hsa-miR-122-5p	hsa-miR-4430	hsa-miR-6779-5p	hsa-miR-8085
hsa-miR-124-3p	hsa-miR-455-3p	hsa-miR-6780a-5p	hsa-miR-8485
hsa-miR-1273h-5p	hsa-miR-4710	hsa-miR-6785-5p	hsa-miR-92a-3p
hsa-miR-149-3p	hsa-miR-4722-5p	hsa-miR-6808-5p	
hsa-miR-17-5p	hsa-miR-4728-5p	hsa-miR-6817-3p	
hsa-miR-185-5p	hsa-miR-504-3p	hsa-miR-6832-3p	

All miRNA-gene interactions are miRTarBase validated.

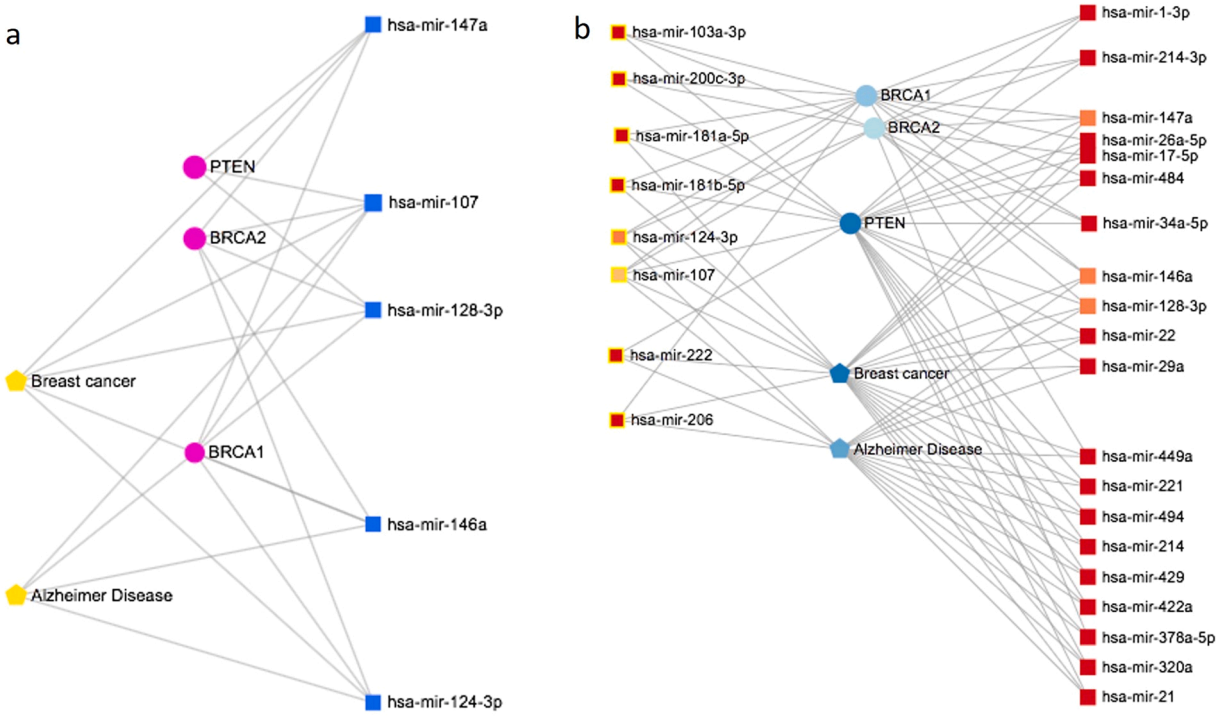

Fig. 2. MicroRNA shared between AD and BC. The results were obtained from miRNET tool (Chang et al., 2020). Network representations of a) the miRNA with four or more interactions and b) the miRNA associated with BC and AD based on the miRNET.

deposition and improved behavior (Zhou et al., 2019). The expression of miR-124-3p is downregulated in patients with BC as well. It has been shown that miR-124-3p significantly suppresses proliferation and invasion of BC cells through downregulation of expression of Cbl proto-oncogene, E3 ubiquitin-protein ligase (CBL) (Yanbo Wang et al., 2016).

Of the miRNAs that interact with *BRCA1,* miR-155 and miR-146a are probably the most studied regarding their involvement in BC pathogenesis. The BRCA1 protein decreases miR-155 levels and enhances the transcription of miR-146a (Kumaraswamy et al., 2015). Additionally, miR-146a and miR-146-5p induce BRCA1 translational repression, creating a negative feedback loop between miR-146a and *BRCA1*/BRCA1 in triple negative BC (Garcia et al., 2011). Genetic variants in the 3′UTR of BRCA1 were also shown to influence miR-146a –*BRCA1* binding (Chang and Sharan, 2012). BRCA1 inhibits miR-155 transcription by histone acetylation in the promoter of the mir-155 gene (Chang et al., 2011). Furthermore, miR-15/107/182 silences BRCA1 translation, resulting in absence of DNA repair. It is important to note that the representative miRNAs for BRCA1 regulation, such as miR-146a, miR-155, and miR-15/107, have been involved in early cancer formation phases. Moreover, elevated miR-146a levels characterize AD brains' hippocampus and superior temporal cortex. Notably, nuclear factor-kappa B (NF-κB) directly regulates the expression of miR-146a, and it targets the mRNA of complement factor H (CFH), a negative regulator of the inflammatory response in the brain (Lukiw and Alexandrov, 2012; Saba et al., 2014).

Knowing that dysregulated BRCA1 plays a crucial role in both AD and BC provides us with a starting point for identifying key miRNA (that targets BRCA1) that function in both BC and AD. Table S1 also lists miRNAs known to target *BRCA1* in BC and miRNAs differentially expressed in AD collated through a literature survey. In this table, we included miRNAs expressed in various brain regions which may be specific for the disease or brain tissue pathology, which may give direction to identify and characterize specific miRNA signatures as potential biomarkers for AD diagnosis and therapy (Hébert et al., 2009). The literature data lacks in information on miRNAs targeting *BRCA1/2* in AD. Additionally, miRTarBase (Chou et al., 2016; Kozomara and Griffiths-Jones, 2014) provides users with a list of 22 miRNAs that might target *BRCA1* mRNA, a few of which are not in the BC list, but are amongst the miRNAs differentially expressed in AD. MicroRNAs miR-107 and miR-124-3p are not included in this list of 22 miRNA that targets *BRCA1* mRNA.

2.2. Approach 2: exploration of miRNA enrichment and pathway analysis in AD and BC

We have used MirWalk 3.0 (Sticht et al., 2018), an online tool developed by the bioinformatical service of the Medical Faculty Mannheim, Heidelberg University. One of the options on the platform is to predict miRNA molecules that might be involved in the development of different diseases, based on validated miRNA-gene interactions in disease ontologies. We used the "Diseases" option on the index page (http://mirwalk.umm.uni-heidelberg.de/). Before running the query, we have selected "Human" as a species. Two separate queries were run for AD and BC (selected under the "Select disease" drop-down menu). After running a query (by clicking on "Proceed"), we saved the results in a.csv file (by clicking on the "Export" button)". The whole procedure has been followed for both AD and BC diseases. Initially, the query revealed 465,344 entries related to the AD ontology and 284,914 entries for BC ontology. Each entry represents an interaction (predicted or validated) between a miRNA molecule and a gene (mRNA) for a particular disease. We restricted the analysis only to MirTar base (Huang et al., 2020) validated miRNA-gene interactions (entries with a "MIRT" number under the "validated" column). After excluding non-validated interactions, we have left with 7744 entries for AD and 6708 entries for BC (Supplementary data 1). We have filtered the data to find entries with common miRNA molecules for AD and BC, which regulate at least five genes in both diseases. After cleaning up the data end removing multiple entries, we identified 49 miRNA molecules, which modulate the expression of at least five genes in both BC and AD (Table 1). Those 49 miRNAs regulate the expression of 122 genes in AD and 93 genes in BC (26 common genes for AD and BC), presented in Table 2. The interaction networks have been generated for all miRNA molecules and their corresponding genes (Fig. S1) using Cytoscape 3.9.1 software (Shannon et al., 2003).

According to the analysis, the most prominent miRNA molecules are mir-17-5p (regulating expressions of 20 genes) and miR-92a-3p (regulating expression of 19 genes). As previously discussed, the miR-17-92 cluster plays an important role in developing both diseases. Additional miRNA recognized as a significant modulator in both diseases is miR-149-3p (regulates expression of 18 genes). In breast cancer, the expression of miRNA-149 plays a dual role. Two isoforms of miR-149 (miR-149-3p and miR-149-5p) have different roles in tumorigenesis and the biology of the cell, both targeting tumor suppressors and oncogenes (He et al., 2018).

On the other hand, the expression of miR-149 is downregulated in patients with AD. Targeting BACE-1 mRNA may reduce the accumulation of Aβ protein (Du et al., 2021). Additional experiments should be performed to confirm or reject the hypothesis of targeting miR-149 as a protentional therapeutic in treating AD and BC.

The analysis has confirmed the involvement of the previously discussed miRNA-107 and miR-124-3p in the regulation of both AD and BC by targeting multiple genes in both diseases. Another interesting miRNA molecule might be miR-6785, regulating 15 genes associated with AD and/or BC. According to our knowledge, there has been no research investigating the role and expression of mir-6785 in AD or BC. However, it is published that the expression of the TMED10 gene (Transmembrane P24 Trafficking Protein 10), targeted by mir-6785, is significantly downregulated in patients with AD, which leads to increased amyloid-β (Aβ) production (Shin et al., 2019). On the other hand, the same miRNA is silencing the expression of TERF1 (Telomeric Repeat Binding Factor 1) and OGG1 (8-Oxoguanine DNA Glycosylase) genes, both related to the development of different types of cancer. TERF1 gene plays an essential role in telomere maintenance, and its downregulation is associated with prostate cancer development (dos Santos et al., 2021). Mutations and different polymorphisms in OGG1gene are associated with BC development. OGG1 protein is involved in the base excision repair (BER) pathway and plays an important role in maintaining genome integrity (Lloyd, 2022).

However, some miRNAs targeting several genes in AD and BC might have a different role in the genesis of the diseases. For example, miR-106b (regulating the expression of several genes in AD and BC) is downregulated in AD, promoting disease development and progression, while it is up-regulated in BC, inducing cell migration, invasion, and proliferation (Li et al., 2017; Liu et al., 2016). So, a specific biological contest should be considered for each miRNA candidate, which requires further experimental analysis.

To investigate and predict biological processes and signaling pathways regulated by 49 miRNA candidates, we performed pathway analysis using the miRPathDB 2.0 online tool (Kehl et al., 2020). The enrichment pathway analysis was based on Gene Ontology - Biological processes (GO PB) and KEGG databases, under the "Custom heat map calculator" option on the miRPathDB 2.0 platform (Kehl et al., 2020). All 49 miRNAs have been entered in a field for the miRNA list. As evidence, "Predicted (union)" has been used in both analyses. For GO BP analysis, a minimal number of significant miRNAs to show a pathway was set to 20, and a minimal number of significant pathways so that miRNA appear, was set up to 40. The results have shown that most biological processes were restated to neuron differentiation and neuron genesis and cell differentiation and migration processes. MAP kinase and Ras kinase signaling pathways were also enriched. Among the most significant miRNA molecules were previously discussed well-known miRNAs

Table 2
The list of genes targeted by candidate miRNA molecules related to disease.

Gene	Disease	Gene	Disease	Gene	Disease	Gene	Disease
ABCA1	AD	CSNK1D	AD	IRS1	AD	REL	BC
ADAM10	AD	CSNK2A1	BC	KAT2B	BC	RHOA	BC
ADAM17	AD	CST3	AD	KAT7	BC	RHOB	BC
ADAM9	AD	CTNNB1	AD	KCNC4	AD	RHOC	BC
ADIPOQ	AD&BC	CTSB	BC	KCNMA1	AD	RNF20	BC
ADIPOR2	BC	CYB5R3	BC	KDM4A	BC	RUNX3	BC
ADSL	BC	CYP19A1	AD&BC	KMT2D	BC	SHMT1	BC
AIFM1	AD	CYP1A2	BC	LDLR	AD	SIRT1	AD
AKAP5	AD	CYP2C19	BC	LIPC	AD	SIRT3	AD
AKT1	BC	DUSP6	BC	LNPEP	BC	SIX1	BC
ANG	AD	DYNC1H1	AD	LRP8	AD	SLC25A4	AD
APC	AD&BC	E2F1	AD	LRPAP1	AD	SLC8A1	AD
APP	AD	ECE1	AD	MAP2K3	BC	SNCG	AD&BC
ARID1A	BC	EEF2K	AD	MAPK1	AD&BC	SNRPA	AD
ATM	AD&BC	EGF	AD	MAPK9	AD	SOD2	AD&BC
ATP5F1A	AD	EGFR	BC	MBL2	AD	SOX6	AD
ATP7A	AD	EIF2AK2	AD	MDM2	BC	STAT3	AD&BC
ATR	AD	EIF2S1	AD	MDM4	AD	TARDBP	AD
BACE1	AD	ELK1	AD	MFN1	AD	TERF1	BC
BACE2	AD	EPHA4	AD	MGMT	BC	TFAM	AD
BAIAP2	AD	ERCC1	BC	MKI67	BC	TGFB1	BC
BAK1	AD	ESR1	AD&BC	MMP2	AD	THRA	BC
BARHL1	AD	ESR2	AD&BC	MRE11	AD	TIMP2	AD
BCL2L1	AD&BC	F11R	BC	MYC	BC	TIMP3	BC
BCL2L2	AD	FANCA	BC	NCAM1	AD	TK1	BC
BDNF	AD	FANCC	BC	NCOA3	BC	TMED10	AD
BRCA1	BC	FAS	AD&BC	NCOR2	BC	TNF	AD&BC
BRIP1	AD&BC	FGF1	AD	NDUFA5	AD	TNFRSF1A	AD
BTG2	BC	FGF2	BC	NGFR	AD	TP53	BC
C3	AD	FGFR1	AD	NOD2	BC	TP73	BC
CAMK2A	AD	FOXO3	AD	NOS1	AD	TSC1	BC
CAPN1	AD	FXYD6	AD	NRGN	AD	VEGFA	AD
CASP8	AD&BC	FYN	AD	OGG1	BC	WNT1	BC
CASP9	AD&BC	GLUD1	AD	OPA1	AD	WNT7B	BC
CAV1	AD&BC	GLUL	AD	PAWR	AD	WT1	AD&BC
CCL5	AD	GRB2	BC	PDGFB	AD	XIAP	BC
CCNE1	BC	GRIN2B	AD	PIK3R1	AD	XPO5	BC
CCNG1	AD	GSR	AD	PLCG1	AD&BC	XRCC3	BC
CCR5	AD&BC	GSTM3	AD	PLPP4	BC	XRN1	AD
CD40LG	AD	HIF1A	AD	PMEPA1	BC		
CDC25C	BC	HIVEP3	AD	PPARA	AD		
CDC42	AD	HSP90AA1	AD	PPARGC1A	AD		
CDH1	BC	ICAM1	AD&BC	PPM1D	BC		
CDK4	BC	IDE	AD	PPP1R9B	AD		
CDKN1B	BC	IGF1	AD&BC	PPP2R2B	AD&BC		
CDKN2A	BC	IGF1R	AD&BC	PTEN	BC		
CEBPB	AD	IGFBP3	AD&BC	PTGES3	BC		
CLOCK	AD	IL6R	AD	PTK2B	BC		
CLU	AD&BC	IL6ST	AD	RAD51	BC		
CSNK1A1	AD	IREB2	AD	RCAN1	AD		

Genes as potential targets for miRNAs from Table 1. Genes are associated with Alzheimer's disease (AD) and/or breast cancer (BC).

such as miR-17, miR-107, and miR-124, and some miRNA molecules that have not been associated with AD or BC in previous studies. However, molecules like miR-6127, miR-6870, or miR-8485 are potentially involved in regulating all related biological processes (Fig. 3a). Since the KEGG database is more specific, minimal numbers of significant miRNAs and pathways were set up to 10. The most enriched pathways were related to cancer-related pathways, such as "Pathways in cancer" and "microRNAs in cancer", but also pathways such as "Axon guidance", related to brain development. Also, several signaling pathways were enriched, regulating cell mobility and proliferation processes such as Ras, ErbB, Rap1, Hippo, Wnt, FoxO, and MAPK. The most prominent miRNAs such as miR-5698, miR-6870, or miR-6127 have not been associated with the development and progression of AD or BC so far (Fig. 3b). Two more analyses have been performed on the same dataset and against the same bases (GO BP and KEGG) but considering only interactions with experimental evidence (strong and/or week). The analysis confirmed that the miRNAs such as miR-34a, miR-92a, miR-107, miR-124-3p involved in the regulations of related neurological processes as well as signaling pathways related to the regulation of cell cycle and cancer development, including p53 signaling pathway, TGFβ signaling pathway, and PI3K/Akt signaling pathway. These pathways might play important roles in the development of AD and BC.

To increase confidence in our findings, we further validate the results. In the validation process, we compared our significant miRNA molecules against the disease dataset by performing miRNA enriched analysis using TAM 2.0 tool available on the www.lirmed.com/tam2 website (Li et al., 2018; Lu et al., 2010). Since the TAM 2.0 tool uses pre-mature miRNAs as input data, we had to convert the annotations of processed miRNAs to pre-mature miRNA annotations. Fig. 3**.** Heat maps of significantly enriched pathways on significant miRNAs in AD and BC from miRPathDB 2.0 (Kehl et al., 2020). a) Heat map of significantly enriched pathways in GO BP database, based on predicted miRNA-gene interactions. b) KEGG base. Darker blue shades represent higher scores of enrichment.

The analysis was performed under the "Analysis" tab on the website. In step one, we entered all selected miRNAs (n = 49). The field under

Fig. 3. Heat maps of significantly enriched pathways on significant miRNAs in AD and BC from miRPathDB 2.0 (Kehl et al., 2020). a) Heat map of significantly enriched pathways in GO BP database, based on predicted miRNA-gene interactions. b) KEGG base. Darker blue shades represent higher scores of enrichment.

step two remained empty (default background data were used). The "Overrepresentation" radio button has been checked in the step tree. Step four has been left as default. In step five, the "Up and down" (taking into consideration the direction of miRNA expression) and "Mask non-standard terms" checkboxes have been checked, and then ran the analysis. The results have shown that in both, Breast Neoplasms were significantly overrepresented (-log10 (FDR) > 5.5). Also, among the significantly enriched disorders was type 2 diabetes mellitus (T2DM) (-log10 (FDR) > 5.5), which development might be driven through similar pathways responsible for the development of AD (mainly through the PI3K/Akt signaling pathway). In some cases T2DM progress into AD, named type 3 diabetes (T3D), a neuroendocrine disorder. Altered metabolic pathways for beta-cell development, amyloid beta degradation, and PI3K/AKT pathway may underlie T3D pathology (Mittal et al., 2016) (Fig. 4). The process has been repeated with a change in step three - the "Underrepresentation" radio.

Furthermore, we performed pathway analysis based on genes regulated by 49 miRNAs in BC and AD from previous analysis by STRING online software (Szklarczyk et al., 2017). High confidence (0.700) interaction score and high FDR stringency (1 %) were used for the analysis. Two separate analyses were done, one for genes dysregulated in BC (n = 93) (Supplementary Fig. 2a) and another for genes dysregulated in AD (n = 122) (Supplementary Fig. 2b). However, there were 26 overlapping genes dysregulated in AD and BC. According to the analysis, in KEGG pathways “Alzheimer’s disease” pathway was one of the most prominent (-log10 (FDR) > 16) (Supplementary Fig. 2b). Besides, “Pathways in cancer” as well as pathways detected in previously performed miRNA enrichment analysis (Ras, FoxO, Rap1, and MAPK) was also significant, all with around ten times more significant genes than expected by chance (Fig. S2a, S2b).

Enrichment analysis of GO BP has revealed that the processes related to response to organic substances and response to oxidative stress, along with processes related to the regulation of apoptosis and cell cycle control, are significantly enriched in both AD and BC (data not shown).

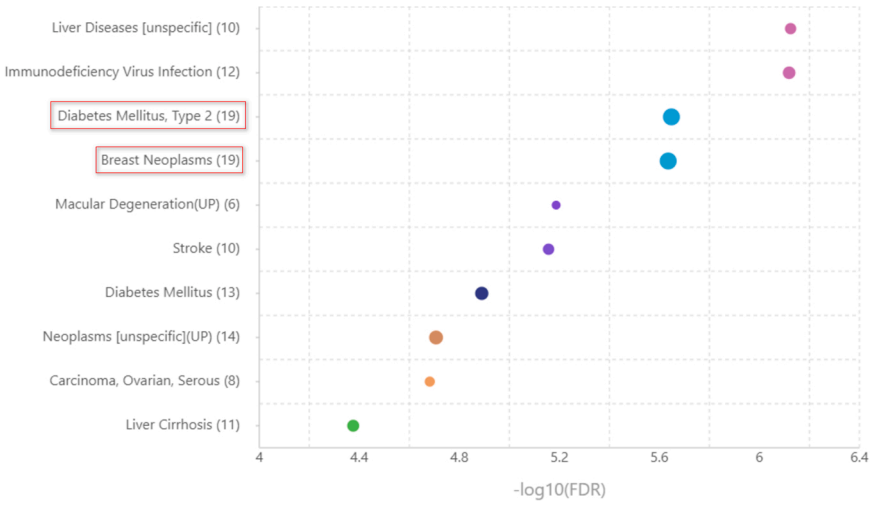

Fig. 4. MiRNA-disease analysis. Comparison of significant miRNA molecules against the disease dataset with TAM 2.0 tool (Li et al., 2018; Lu et al., 2010). Alzheimer's disease and type 2 diabetes mellitus pathogenesis were significantly associated with 49 selected miRNAs (AD -log10 (FDR) > 5; DM2 -log10 (FDR) > 20).

Interestingly, the p53 signaling pathway, MAPK signaling pathway, as well as PI3K-Akt signaling pathway, appeared as highly enriched in both AD and BC-disease.

Additional enrichment analysis was performed against the DisGeNET database to confirm the involvement of selected genes in the development of AD and BC. For that purpose, the Enricher tool (https://maayanlab.cloud/Enrichr/) was used (Chen et al., 2013; Kuleshov et al., 2016; Xie et al., 2021). After submitting all genes related to AD and BC in the gene list (n = 189), results for the DisGeNET database have been found under the "Diseases/Drugs" tab. According to the results, "Alzheimer's disease" and "Breast Carcinoma" along with other breast cancer-related diseases, appeared as the most enriched diseases (Fig. 5).

3. Conclusions

Targeting miRNAs regulating the PTEN-BRCA1 axis might enable us to treat AD in its early phases and postpone neuronal cell death in its terminal stages. According to the literature review and *in silico* analysis, targeting miR-107 might be a good candidate for both AD and BC treatment at the same time, accompanied by miR-146a, miR-124-3p, miR-335-5p, and miR-17. Functional analysis should be performed to select the best potential targets to treat one or both diseases simultaneously. The *in silico* disease ontology analysis has confirmed the involvement of previously described miR-17 (along with other members of the miR-17-92 cluster), miR-124-3p, miR-107 in AD and put a new light on poorly researched miRNAs such as mir-6785, mir-6127, mir-6870 or miR-8485.

The pathway analysis of the candidate miRNAs discovered that the same set of miRNAs is involved in regulating pathways and processes, which might be important factors in the development of both AD and BC. In addition, miRNA-disease enrichment analysis confirmed the significance of candidate miRNAs in BC-related diseases and diabetes mellitus conditions, which share a lot of commonly dysregulated genes with AD. This finding might also give directions towards finding pathways which should be targeted to prevent progression of T2DM into T3D/AD.

The pathway analysis performed on the genes commonly regulated by candidate miRNAs widely confirmed previous findings. The most enriched pathways were those related to regulating the cell cycle and processes that regulate the cellular response to oxidative and chemical stress. Particularly significant pathways might be p53, MAPK, and PI3K-Akt signaling pathways, involved in the root of the pathogenesis of both

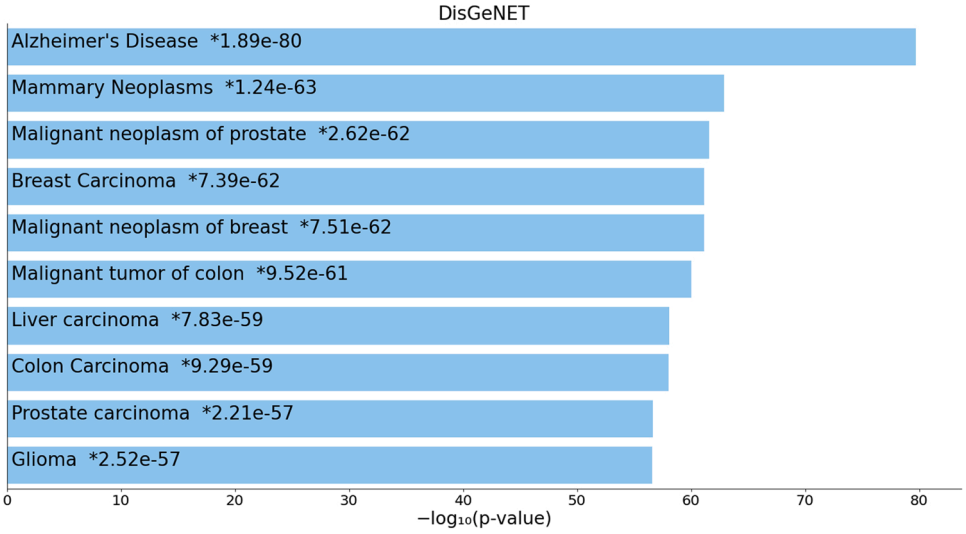

Fig. 5. Gene-disease enrichment analysis on DisGeNet database. "Breast cancer" and "Alzheimer's disease" have been sorted among the most enriched diseases. The X-axis represents the negative logarithm (base 10) of the p-value.

AD and BC diseases. In addition, enrichment analysis performed against the DisGeNET database (the starting point in Approach 1), confirmed that the same set of genes highly enriched AD and BC-related diseases.

However, it is well known that some miRNAs and proteins might have opposite roles in the development and progression of different diseases. Furthermore, some miRNAs might have a dual role in the disease's progression, depending on the particular conditions or other factors that influence the disease. This process revealed a highly enriched pathway associated with diabetic complications that suggests there might be interplay among pathways underlying the pathology of this systemic disease AD, BC, and T2DM. So, further experimental analyses are required to confirm or reject the hypothesis that a particular miRNA might be a protentional target for treating specific diseases such as AD and BC.

CRediT authorship contribution statement

NP, AŠ, and VB designed, analyzed the work, and wrote the manuscript; ME contributed to the work analysis and data interpretation; GP, TG, and EI, drafted the work, wrote parts of the manuscript, and critically revised it. NP, AŠ, VB, ME, GP, TG, and EI approved the final version of the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declaration of Competing Interest

The authors have no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.compbiolchem.2023.107925.

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