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Review

microRNA diagnostic panel for Alzheimer's disease and epigenetic trade-off between neurodegeneration and cancer

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ABSTRACT

microRNAs (miRNAs) have been extensively studied as potential biomarkers for Alzheimer's disease (AD). Their profiles have been analyzed in blood, cerebrospinal fluid (CSF) and brain tissue. However, due to the high variability between the reported data, stemming from the lack of methodological standardization and the heterogeneity of AD, the most promising miRNA biomarker candidates have not been selected. Our literature review shows that out of 137 miRNAs found to be altered in AD blood, 36 have been replicated in at least one independent study, and out of 166 miRNAs reported as differential in AD CSF, 13 have been repeatedly found. Only 3 miRNAs have been consistently reported as altered in three analyzed specimens: blood, CSF and the brain (hsa-miR-146a, hsa-miR-125b, hsa-miR-135a). Nonetheless, all 36 repeatedly differential miRNAs in AD blood are promising as components of the diagnostic panel. Given their predicted functions, such miRNA panel may report multiple pathways contributing to AD pathology, enabling the design of personalized therapies. In addition, the analysis revealed that the miRNAs dysregulated in AD overlap highly with miRNAs implicated in cancer. However, the directions of the miRNA changes are usually opposite in cancer and AD, indicative of an epigenetic trade-off between the two diseases.

1. Introduction

1.1. New concepts of AD and diagnostic challenges

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the main cause of dementia in the elderly. In 2015 around 47 million people have been reported to suffer from the AD-related dementia, and this number is forecasted to reach 131.5 million by 2050 (Prince et al., 2016). Due to the high prevalence and the generation of a huge socioeconomic burden, AD together with cancer are the major unmet health concerns in the 21st century (Hurd et al., 2013).

AD is perceived as a biological and clinical continuum. It starts with preclinical stage, manifesting with molecular alterations in the absence of clinical dementia (Anand et al., 2014; Cummings et al., 2016), and progresses through mild cognitive impairment (MCI) due to AD (prodromal AD) towards mild, moderate and severe dementia stages (Aisen et al., 2017; Jack et al., 2018). The main pathological hallmarks of AD are the oligomers and the aggregates of amyloid beta (Aβ) peptides, and intracellular deposits of hyperphosphorylated tau protein, known as neurofibrillary tangles (NFTs). However, other pathophysiological alterations have been also described. These include prominent activation of inflammatory and innate immune responses (Heppner et al., 2015; Zhao and Lukiw, 2018), as well as calcium dyshomeostasis, oxidative stress, mitochondrial damage, and alterations in the cell cycle regulatory mechanisms (Herrup, 2015; Pchitskaya et al., 2018; Wojsiat et al., 2018). The pattern of molecular alterations and associated neurodegeneration in the brain changes during the disease progression.

The profound understanding of mechanisms underlying AD and of the sequence of pathophysiological changes in the disease is essential for the development of novel, sensitive diagnostic approaches, allowing for the detection of the disease at an early, preclinical stage. The latter seems to be of a vital importance, given the failure of clinical trials aiming to treat symptomatic AD, when the neurodegeneration has already occurred and cannot be reversed. In addition, clinical AD presents with various neuropathological subtypes, differing by spatial distribution of brain atrophy, spread of NFTs or involvement of cerebral amyloid angiopathy, assumed to be caused by distinct AD molecular profiles (Elahi and Miller, 2017; Ferreira et al., 2018). Summarizing, the progress in the diagnostic paradigm from common symptoms and biomarkers to biomarkers allowing identification of disease subtypes and stages is critical for selection of personalized therapies and for the recruitment of patients for clinical trials.

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1.2. Prospects for blood-based biomarkers in AD

AD diagnosis is based mainly on clinical examination and neuropsychological testing, such as Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and evaluation of clinical dementia rate (CDR). In addition, in several centers it is supported by positron emission tomography (PET-amyloid, PET-tau, fluorodeoxyglucose-PET (FDG-PET)), magnetic resonance imaging (MRI) as well as by biochemical analysis of cerebrospinal fluid (CSF) for the levels of total and hyperphosphorylated tau protein and for the amounts of Aβ42 and Aβ40 peptides (Brier et al., 2016; Ewers et al., 2015; Villemagne, 2016; Wei et al., 2016a; Zimmer et al., 2014).

Despite the evident progress in AD diagnostics, current methodologies still have several limitations. They often require sophisticated, expensive equipment, not available in all clinical centers. The most commonly used in clinical practice, CSF assays, require lumbar puncture, which is an invasive procedure, not always safe and feasible, especially in the elderly. Therefore, it is not optimal for longitudinal studies. Some of these limitations can be overcome by the discovery and the implementation of blood-based biomarkers (Baird et al., 2015; Snyder et al., 2014; Thambisetty and Lovestone, 2010). Blood withdrawal and its biochemical analysis are relatively non-invasive and inexpensive, in contrast to the brain imaging and CSF collection, thus blood-based methods might be suitable for population screening and the selection of individuals at risk for further testing with more sophisticated approaches. Importantly, recent technological advances opened the possibility for ultrasensitive detection of low levels of Aβ and tau in the blood (Nabers et al., 2018; Nakamura et al., 2018; Neergaard et al., 2018). However, monitoring these biomarkers alone may not reflect complex molecular pathophysiology of AD. This might be better reflected by the changes in the levels of other proteins, including synaptic markers, metabolites and miRNAs (Geekiyanage et al., 2012; Leidinger et al., 2013; Nagaraj et al., 2017; Schipper et al., 2007; Sorensen et al., 2016; Tan et al., 2014b).

2. miRNA biogenesis, origin and function

miRNAs, due to their relatively high stability in biofluids, have recently received attention as one of the most promising blood-based biomarkers (Kroh et al., 2010; Roth et al., 2010). They represent a class of short non-coding RNA molecules, 19–24 nucleotide long, and play a pivotal role in the epigenetic regulation of gene expression, mainly at the post-transcriptional level. Their biogenesis occurs in a canonical or non-canonical manner (Abdelfattah et al., 2014; Bartel, 2018; Miyoshi et al., 2010). In brief, the canonical pathway of miRNA biogenesis starts in the nucleus with the generation of long pri-miRNA transcript by RNA polymerase II/III. This pri-miRNA transcript is processed by the protein complex called Microprocessor, composed of Drosha (RNAse III) and DGCR8 protein, to yield short hairpin pre-miRNA, which is exported to the cytoplasm in the process facilitated by Exportin-5-Ran-GTP. In the cytoplasm, a complex of Dicer (RNase III) and double-stranded RNA-binding protein (TRBP) is responsible for the cleavage of the hairpin pre-miRNA. The cleavage separates the hairpin loop and generates a mature double-stranded miRNA duplex with ~2 nucleotide-long 3′ overhangs on each end. This duplex is loaded onto the Argonaute (Ago) protein upon the acquisition by Ago of a high-energy conformation, in the process supported by chaperone HSCP70/HSP90 and ATP. Duplex binding induces the return of Ago to basic conformation and the release of a one strand of the miRNA duplex known as a passenger strand, which is next degraded. Ago forms a mature RNA-induced silencing complex (RISC) with the second, guide miRNA strand. Either arm of the pre-miRNA hairpin can become the guide strand. The choice depends on which strand of the duplex has a 5′ terminus preferred by the Ago binding pocket. miRNAs in silencing complex bind to the 3′ untranslated regions (3′ UTR) of the target transcripts based on specific sequence base pairing, and lower transcript expression by either mRNA degradation or translational inhibition (Bartel, 2018). Interestingly, recent results suggest that miRNAs can also target a 5′ UTR (Lee et al., 2009) or a coding region of a gene (Hausser et al., 2013), and can also play a role in translation enhancement (Saraiya et al., 2013; Ørom et al., 2008).

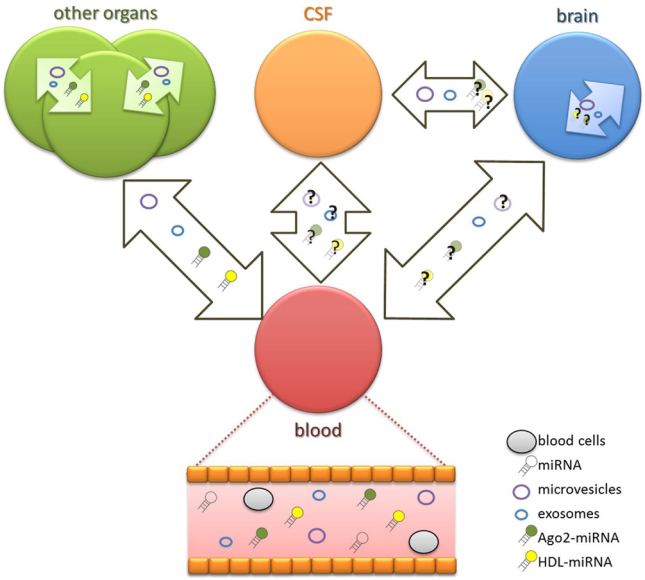

Fig. 1. miRNAs mediate cross-talk between blood, CSF, brain and periphery.
The scheme presents miRNA exchange between blood, CSF, brain and other organs mediated by miRNA shuttles (Ago protein, HDL, exosomes, microvesicles). The demonstrated involvement of particular miRNA shuttles in the cross-talk between blood and other organs, blood and brain, blood and CSF, CSF and brain, as well as inside organs is indicated, question marks denote lack of relevant data.

Recently, several non-canonical pathways of miRNA biogenesis have been described (Bartel, 2018; Ha and Kim, 2014; Winter et al., 2009). Some miRNAs are generated with the omission of the cleavage by Microprocessor or Dicer. Pri-miRNAs bypassing Microprocessor but requiring Dicer are produced either from certain introns called mitrons or from endogenous hairpin RNAs, such as shRNAs or chimeric hairpins. miR-451 is the best example of a short pre-miRNA-451 produced by Microprocessor which directly binds to Ago (Bartel, 2018).

Two decades of miRNA research resulted in the discovery of 48,885 mature miRNAs in 271 species registered in miRBase (Kozomara and Griffiths-Jones, 2014). In humans over 2500 mature miRNAs have been identified (www.mirbase.org) and predicted to regulate over 60% of transcripts (Friedman et al., 2009; Rajewsky, 2006). Since a single miRNA can target multiple mRNAs and a single transcript can be influenced by several miRNAs, the miRNA-mRNA regulatory network is very complex. Accordingly, changes in miRNA profiles can significantly affect cell physiology and such vital processes as cell proliferation, differentiation, DNA repair, apoptosis and metabolism (Faravelli and Corti, 2018; Vannini et al., 2018).

Importantly, the miRNA action is not restricted to the cells where they have been generated. Numerous extracellular miRNAs have been detected. These are released in a regulated manner by donor cells and taken up by acceptor cells, and may play an important role in intercellular signaling (Hergenreider et al., 2012) (Fig. 1). The cell-free miRNAs are often encapsulated in membranous vesicles, including exosomes (small vesicles released by exocytosis, 30–100 nm), microvesicles (large vesicles released by shedding, 100 nm – 1 μm) and apoptotic bodies (50–500 nm). Alternatively, they might be complexed with one of four Ago proteins or associated with high density lipoprotein (HDL) (Creemers et al., 2012). All these shuttles protect circulating

extracellular miRNAs from degradation and allow their role as hormone-like epigenetic regulators transmitted by blood and regulating body organs (Fig. 1). However, unlike other organs, the brain and the CSF are separated from the blood by the blood brain barrier (BBB) and the blood cerebrospinal fluid barrier (BCSFB), respectively (Balusu et al., 2016; Banks, 2016). Nevertheless, recent findings indicate that exosomes containing miRNAs are capable of penetrating the BBB and mediating the cross-talk between the blood and the brain and between the brain and the CSF (Blandford et al., 2018; Kanninen et al., 2016; Mietelska-Porowska and Wojda, 2017; Vickers and Remaley, 2012) (Fig.1). The involvement of other shuttles, such as Ago complexes or HDL, and their significance for the cross-talk awaits investigation.

Although it is well-established that miRNAs are relatively abundant in the blood, the questions of their origin and destination remain unanswered. In theory, they can originate from any tissue and organ, including the brain and blood cells (Wang et al., 2017a; Wojda, 2016) (Fig. 1). Given the impairments of the BBB and the BCSFB in AD, the brain-derived or the CSF-derived miRNAs, packed in exosomes or associated with other shuttles, might be able to enter the blood stream in the disease (Gorlé et al., 2016; Morris et al., 2014; van de Haar et al., 2016). The opposite is also possible and circulating miRNAs may reach the brain, where they can regulate functions of brain cells. The miRNAs might reach the brain either by utilizing the molecular shuttles or might be released in the brain by whole blood cells, such as brain infiltrating monocytes and lymphocytes (Mietelska-Porowska and Wojda, 2017). This indicates a possibility of a reciprocal cross-talk between the brain and the periphery in AD, and points towards a diagnostic potential of blood-based miRNAs.

3. Evaluation of miRNA biomarker potential in AD

3.1. Study concept

In the current study, in order to evaluate the potentiality of circulating miRNAs as biomarkers for AD diagnosis, we analyzed miRNA data reproducibility, AD specificity of miRNA profiles, and searched for links between the miRNA alterations and AD pathology. The study concept was based on the assumption that AD molecular signature in the blood may include molecules originating from the brain and the CSF, as well as from peripheral tissues (Fig. 1). Our approach was opposite to the 'top-down' strategy, focusing on miRNAs altered in the brain and searching for their reflection in the CSF and in the blood (Millan, 2017). On the contrary, we used a 'bottom-up' approach. First, we identified repeatedly reported differential blood-based miRNAs. Next, we revised reports of the differential miRNA profiles in the CSF and the brain and searched for the overlap between the miRNA alterations in these specimens. Finally, we addressed the questions of AD specificity and of the functional implications of the miRNAs in the pathogenesis of the disease. To this end, we performed a cross-disease analysis and a computational prediction of genes and pathways regulated by the selected miRNAs.

3.2. miRNA profile in AD blood

Investigation into the role of miRNAs in AD pathogenesis and their applicability for AD diagnosis have led to the identification and the functional characterization of several miRNAs differentially expressed in various brain regions between control and AD subjects (Bekris and Leverenz, 2015; Clement et al., 2016; Hill and Lukiw, 2016; Lau et al., 2013; Millan, 2014, 2017; Puthiyedth et al., 2016; Reddy et al., 2017; Satoh, 2012; Zhao et al., 2015), and to the discovery of potential miRNA biomarker candidates in the CSF (Cogswell et al., 2008; Dangla-Valls et al., 2016; Lehmann et al., 2012; Li et al., 2016; Liu et al., 2018; Müller et al., 2016b; Sala Frigerio et al., 2013) and in the blood (Hu et al., 2016; Kumar and Reddy, 2016; Pan et al., 2016; Sheinerman et al., 2012; Tan and Yu, 2015; Tan et al., 2013; Wu et al., 2016). However, the most promising biomarker candidates have not been selected so far.

Multiple studies have addressed the alterations in the miRNA profiles in AD blood. The broad term "AD blood" is used in the literature and refers to whole blood and also to separate blood fractions, including blood cells, blood plasma or serum. The current review is based on this broad definition. Using search terms: "microRNA" or "miRNA" and "Blood" and "Alzheimer's disease" in Web of Science (Collection of such databases as: Web of Science™ Core Collection, Current Contents Connect, Data Citation IndexSM, BIOSIS Citation IndexSM, Derwent Innovations IndexSM, KCI-Korean Journal Database and MEDLINE), we shortlisted 265 studies published by 2018. Not all of these publications provided data adequate for comparisons. Therefore, out of these 265 studies, we selected the only ones which focused on miRNA profiles in whole blood, blood cells, plasma and serum of AD patients and compared them with the ones of healthy individuals or patients suffering from other disorders, such as Parkinson's disease, vascular disease and frontotemporal dementia. In addition, to ensure AD specificity of the potential biomarkers, we excluded comparisons of miRNA profiles in MCI versus other diseases and in AD versus MCI (Kayano et al., 2016; Sheinerman et al., 2013; Xie et al., 2017, 2015). This resulted in the list of 34 research reports, out of which we considered only these miRNAs which were identified as differential between AD and non-AD samples with statistically significant differences (P value of < 0.05 was used as a threshold for the statistical significance). Additionally, when both screening and validation experiments were performed, only the miRNAs confirmed for their differential expression in the validation step were shortlisted. Table 1 summarizes the results of the review of these 34 studies published in the last decade (years 2007–2017): 12 studies of serum samples, 1 study of exosomes extracted from serum, 1 study of postmortem-collected serum, 8 studies of plasma, 1 study of plasma derived exosomes, 6 studies of whole blood, and 5 studies of peripheral blood mononuclear cells (PBMC).

Despite the common goal to determine differential miRNA profiles in peripheral biofluids in AD, the studies were designed differently (Fig. 2). Fig. 2A shows publication years of all 34 reports that were selected for analysis. The first report was published in 2007 and as time progressed, the interest in this field has significantly increased, particularly in the second half of the last decade (Fig. 2A). During that time the preferences for cohort comparisons remained relatively stable (Fig. 2B). Several possible cohort comparisons were made: AD vs cognitively normal control (AC), AD vs other disease control (AO), AD vs cognitively normal control vs other disease control (ACO), AD vs MCI vs cognitively normal control (AMC), AD vs MCI vs cognitively normal control vs other disease control (AMCO), with the AC and AMC being the most frequent comparison (Fig. 2B). Unfortunately, only very few investigators performed validation experiments and used cohorts greater than 200 subjects, which might be the reasons for the lack of the reproducibility of the reported data (Fig. 2C and D). In terms of the conceptual design, around 50% of the studies employed a candidate approach, 18% used high throughput technologies and 32% combined these two strategies (Fig. 2E). Serum, followed by plasma, were the specimens of choice in the majority of the studies (Fig. 2F), and miRNA profiles were determined usually by reverse transcription quantitative polymerase chain reaction (RT-qPCR). However, other methodologies, including next generation sequencing (NGS), NGS + RT-qPCR, Nanostring + RT-qPCR or Microarray + RT-qPCR (Fig. 2H) were also used. Kits were preferred over the manual methods for RNA extraction (Fig. 2G) and spiked in cel-miR-39 and U6 RNAs were most commonly used as internal normalization controls for relative quantification in RT-qPCR (Fig. 2I). In recent years, there has been a small increase in the number of studies comprising pilot and verification steps (Fig. 2C) as well as an increased involvement of new methodologies for miRNA detection, such as NGS or NanoString (Fig. 2H).

From the 137 miRNAs differential in AD blood, only 36 have been reported at least twice (Table 2 and Fig. 3A). The most commonly found

Table 1
Blood-based miRNAs differential in AD reported in 34 independent studies in the last decade.

SOURCE	miRNAs (hsa-miR/ hsa-let)	Reference
Serum source		
Serum	137, 181c, 9, 29a, 29b, 125b, 29, 223, 519, 98-5p, 885-5p, 483-3p, 342-3p, 191-5p, 7d-5p, 135a, 200b, 30e-5p, 101-3p, 15a-5p, 20a-5p, 93, 93-5p, 106b-5p, 18b-5p, 106a-5p, 1306-5p, 3065-5p, 582-5p, 143, 143-3p, 335-5p, 361-5p, 424-5p, 15b-3p, 210, 31, 146a, 23a, 26b, 384, 501-3p, 455-3p, 3613-3p, 4668-5p, 5001- 5p, 4674, 4741, 122-5p	(Cheng et al., 2015; Dong et al., 2015; Galimberti et al., 2014; Geekiyanage et al., 2012; Hara et al., 2017; Jia and Liu, 2016; Kumar et al., 2017; Liu et al., 2014b, c; Tan et al., 2014a, b; Zhu et al., 2015)
Serum exosome	193b	(Liu et al., 2014a)
Post mortem serum#	34b-3p, 219-2-3p, 22-5p, 125b-1-3p, 1307-5p, 34c-5p, 34b-5p, 887, 182-5p, 135a-5p, 184, 30c-2-3p, 873-3p, 125a-3p, 671-3p, 21-5p, 1285-3p, 375, 3176, 127-3p	(Burgos et al., 2014)
Plasma source		
Plasma	7d-5p, 7g-5p, 15b-5p, 142-3p, 191-5p, 301a-3p, 545-3p, 34c, 15a, 370, 328, 138, 132, 34a, 146a, 125b, 590-5p, 142-5p, 194-5p, 107, 9, 151a-5p, 30b-5p, 486-5p, 33a-5p, 483-5p, 18a-5p, 320a, 320b, 320c, 502-3p, 103a-3p, 200a-3p, 1260a	(Bekris et al., 2013; Bhatnagar et al., 2014; Cosín-Tomás et al., 2017; Kiko et al., 2014; Kumar et al., 2013a; Nagaraj et al., 2017; Sorensen et al., 2016; Wang et al., 2015b)
Plasma exosomes	23b-3p, 24-3p, 29b-3p, 125b-5p, 138-5p, 139-5p, 141-3p, 150-5p, 152-3p, 185-5p, 338-3p, 342-3p, 342-5p, 548-5p, 659-5p, 3065-5p, 3613-3p, 3916, 4772-3p, 5001-3p	(Lugli et al., 2015)
Cells		
Whole blood	112, 161,7d-3p, 5010-3p, 26a-5p, 1285-5p, 103a-3p, 107, 532-5p, 26b-5p, 26b-3p, 28-3p, 30c-5p, 30d-5p, 148b-5p, 151a-3p, 186-5p, 425-5p, 550a-5p, 1468, 4781-3p, 5001-3p, 6513-3p, 7a-5p, 7e-5p, 7f-5p, 7g-5p, 15a-5p, 17-3p, 29b-3p, 98-5p, 144-5p, 148a-3p, 502-3p, 660-5p, 1294, 3200-3p, 135b, 29c, 106b-5p, 106a-5p, 9-5p	(Keller et al., 2016; Leidinger et al., 2013; Satoh et al., 2015; Yang et al., 2015b; Yılmaz et al., 2016; Zhang et al., 2016c)
PBMC	34a, 579, 181b, 520 h, 155, 517, 200a, 371, 7f, 29b, 339, 425, 154, 200b, 27b, 128	(Guedes et al., 2016; Ren et al., 2016; Schipper et al., 2007; Villa et al., 2011, 2013)

The table summarizes differential miRNAs identified in various blood fractions. Summary of 12 serum, 1 serum exosomes, 1 post-mortem serum, 8 plasma, 1 plasma exosomes, 6 whole blood and 5 peripheral blood mononuclear cell (PBMC) studies is shown. hsa-let miRNAs are underlined to differentiate them from hsa-miR miRNAs. Naming convention with hsa-let miRNAs is maintained for historic reasons (www.mirbase.org). # Post mortem serum interval range: AD (1.5 to 7 h) and Controls (1.2 to 7.3 h) (Burgos et al., 2014).

as differential was hsa-miR-125b, which presented consistent down-regulation in six reports (Table 2). As shown in Fig. 3A, out of the 36 repeatedly reported miRNAs, 20 were reproduced with the same direction of change (concordant): 15 miRNAs were downregulated and only 5 miRNAs were concordantly upregulated. Discordant alterations were reported for each of the remaining 16 miRNAs (Fig. 3A). For further analysis of the data reproducibility, we compared how many times altered profiles of selected miRNAs were reproduced in different blood fractions (Table 2, Fig. 3B). Four blood fraction-based groups were created: serum (serum, serum exosome, postmortem serum), plasma (plasma and plasma exosomes), whole blood and PBMC (Table 2). 10 miRNAs (number 27–36 in Table 2) were found to exhibit altered levels only in one blood fraction (hsa-miR-181c, hsa-miR-135a, hsa-miR-93, hsa-miR-143 in serum, hsa-miR-138, hsa-miR-142-3p, hsa-miR-545-3p, hsa-miR-301a-3p in plasma, hsa-miR-155 in PBMC and hsa-miR-151a-3p in whole blood). The remaining 26 miRNAs (number 1–26 in Table 2) were shown to be altered in more than one blood fraction (source invariant repetition). The summary of the analysis for these 26 miRNAs is presented in Fig. 3B. As demonstrated in Fig. 3B, only 1 miRNA proved to be differential in all four sources (hsa-miR-29b); in turn, 2 miRNAs were reported as altered in plasma, serum and whole blood (hsa-miR-15a and hsa-miR-9); as much as 9 miRNAs were found to exhibit altered levels both in plasma and serum (hsa-miR-125b, hsa-miR-342-3p, hsa-miR-15b, hsa-let-7d-5p, hsa-miR-191-5p, hsa-miR-34c, hsa-miR-146a, hsa-miR-3065-5p and hsa-miR-3613-3p); only 4 miRNAs were differential both in serum and whole blood (hsa-miR-26b, hsa-miR-98-5p, hsa-miR-106b-5p and hsa-miR-106a-5p), and 5 differential miRNAs were reported both in plasma and whole blood (hsa-miR-107, hsa-let-7g-5p, hsa-miR-5001-3p, hsa-miR-502-3p and hsa-miR-103a-3p). As little as 2 miRNAs were found to exhibit altered levels both in whole blood and PBMC (hsa-let-7f and hsa-miR-425), and in plasma and PBMC (hsa-miR-34a and hsa-miR-200a-3p), and only 1 differential miRNAs was reported both in serum and PBMC (hsa-miR-200b) (Fig. 3B). This analysis revealed a variability in overlapping miRNAs among different blood fractions. Some similarities in miRNA profiles were noted in plasma and serum. Nevertheless, in part this might be the consequence of the plasma and the serum being the most commonly used blood fractions in search for AD biomarkers.

3.3. miRNA profile in AD CSF

Another source of circulating miRNAs is CSF. The first report of the alterations in the miRNA profiles in AD patients' CSF was published in 2008 (Cogswell et al., 2008). The authors analyzed CSF collected postmortem from 20 subjects (10 AD and 10 controls). This was followed by other studies, employing either screening or candidate approaches to discover and/or validate miRNAs differential in CSF. 80% of these studies were conducted in living individuals. Overall, CSF samples from a total cohort of 1690 individuals (disease subjects and controls) were analyzed in 26 studies listed in (Supplementary Table 1). Candidate approach as an experimental design, commercial kits for RNA extraction, RT-qPCR for RNA quantification and U6 snRNA as an endogenous control were most commonly used in the analyses. Unfortunately, only 4 out of the 26 studies employed two step strategy, comprising a pilot and a validation experiment (Dangla-Valls et al., 2016; Gui et al., 2015; Riancho et al., 2017; Sala Frigerio et al., 2013). This might underlie poor data reproducibility, with only 13 differential miRNAs reproduced in at least one independent study (Table 3).

Nevertheless, the analyses of CSF pointed to some interesting correlations between the miRNA alterations and the levels of P-tau, total tau and Aβ42 in CSF (Table 4). An inverse relationship between the levels of hsa-miR-27a-3p and T-tau and P-tau as well as a positive correlation with Aβ42 levels were observed (Sala Frigerio et al., 2013). Also, an inverse correlation between CSF exosomal hsa-miR-193b amount and Aβ42 levels was found (Liu et al., 2014a), and a negative correlation between the levels of CSF hsa-miR-384 and Aβ42 was

reported (Liu et al., 2014b). In addition, inverse relations were observed between hsa-miR-26b and T-tau and P-tau (Galimberti et al., 2014), and between hsa-miR-146a and T-tau and Aβ42 but not between hsa-miR-146a and P-tau (Denk et al., 2015). On the other hand, in another study no correlation was detected between the miRNA levels and Aβ42, T-tau and P-tau (Kiko et al., 2014). Correlations with other potential biomarkers, such as brain derived neurotrophic factor (BDNF) and DNA methyltransferase 3 (DNMT3), as well as amyloid and tau

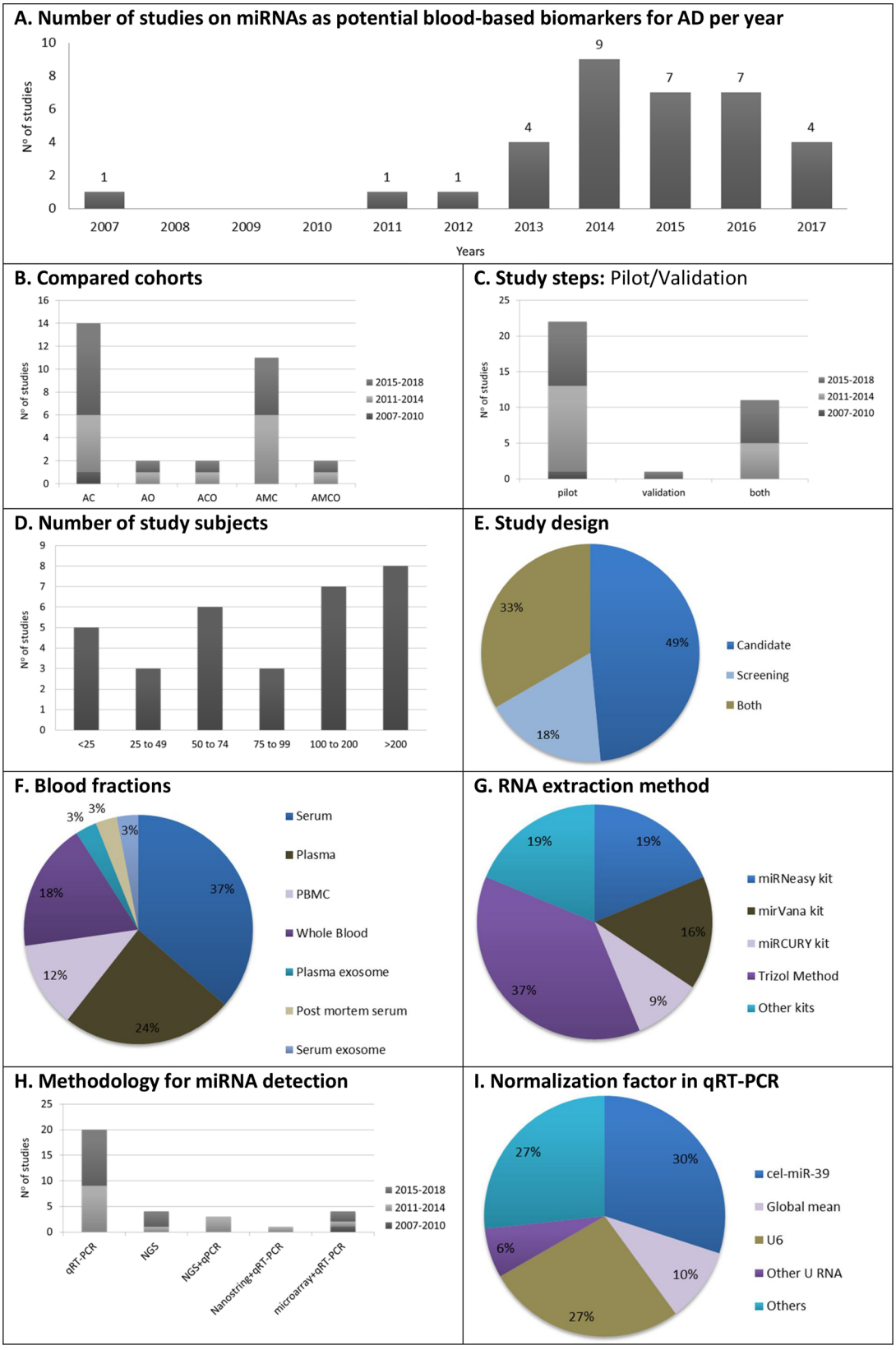

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Fig. 2. Characteristics of the last decade's studies on blood-based differential miRNAs in AD.
(A) All of the reviewed 34 studies investigating miRNAs as potential blood-based biomarkers for AD were published in the period 2007-2017. The number of studies in each year is shown. Since not all 34 studies were homogenously designed, the next individual panels show only the numbers of studies for which analyzed characteristics are available. **(B)** The bar graph presents distribution of cohort comparisons in various studies. Comparisons include Alzheimer's disease vs Cognitively normal control (AC), Alzheimer's disease vs Other diseases (AO), Alzheimer's disease vs Cognitively normal control vs Other diseases (ACO), Alzheimer's disease vs Mild cognitive impairment vs Cognitively normal control (AMC), Alzheimer's disease vs Mild cognitive impairment vs Cognitively normal control vs Other diseases (AMCO). **(C)** Study steps involved performing experiments either in a single pilot or a validation cohort or in both cohorts. **(D)** The bar graph presents distribution of studies involving various numbers of subjects. **(E)** Candidate (literature-based selection of limited number of miRNAs), screening (panels analyzing large number of miRNAs), or both strategies were applied to discover novel biomarkers. **(F)** Various blood fractions (serum, plasma, peripheral blood mononuclear cells (PBMC), whole blood, plasma exosomes, post-mortem serum and serum exosomes) were analyzed. **(G)** The pie chart shows distribution of various RNA extraction methodologies among the studies. **(H)** Methodologies used for miRNA detection included reverse transcription quantitative polymerase chain reaction (RT-qPCR), next generation sequencing (NGS), Nanostring and microarray approaches. **(I)** Either single RNA (such as cel-miR-39 and U6) or global mean of all miRNAs/group of miRNA expression were used as endogenous controls for data normalization.

pathology in the brain and severity of clinical dementia, have also been investigated. The amount of hsa-miR-29c in CSF was found to positively correlate with the levels of BDNF and inversely correlate with DNMT3 amount (Yang et al., 2015b). In turn, CSF hsa-miR-9 and hsa-miR-101 were inversely related with NFT and amyloid plaque density in post-mortem brains (Burgos et al., 2014). Finally, the relationship between hsa-miR-146a with MMSE score has been investigated, but no significant correlation was found (Müller et al., 2014).

3.4. Similarities between miRNA alterations in AD blood, CSF and brain

As the next step, we aimed to identify differential miRNAs in both biofluids in AD: blood and CSF, and found 37 miRNAs altered in these two specimens (Fig. 4, top). Only 3 out of these have been reported in at least two independent studies both in AD blood and CSF, and these were also found as altered in AD brain (Fig. 4, bottom). These included: hsa-miR-146a, hsa-miR-125b and hsa-miR-135a. The literature search revealed that increased hsa-miR-146a levels have been found in the hippocampus and in the superior temporal lobe neocortex of AD patients (Cui et al., 2010; Lukiw and Alexandrov, 2012; Lukiw et al., 2008; Sethi and Lukiw, 2009) and up-regulated hsa-miR-125b expression has been observed in the cerebellum, hippocampus, medial frontal gyrus (Cogswell et al., 2008), temporal lobe neocortex (Lukiw and Alexandrov, 2012; Sethi and Lukiw, 2009) and frontal cortex (Banzhaf-Strathmann et al., 2014) in AD (Fig. 5). On the other hand, reduced hsa-miR-125b and hsa-miR-135a levels have been observed in the grey matter of AD patients (Wang et al., 2011) (Fig. 5). The overlap between the differentially expressed miRNAs in various specimens may suggest their considerable implication in the disease pathomechanism and point towards a cross-talk between the brain and the periphery. However, it needs to be noted that although altered in all the specimens, the most probable candidates were not always changed in the concordant direction. This might be due, at least in part, to some intrinsic differences among the studied populations or various patient selection criteria, or to the different proportions of miRNA shuttles affecting the miRNAs levels in various biological fluids.

3.5. Overlap between miRNA signatures in AD and other diseases

Subsequently, in order to critically review the potential of miRNAs as AD biomarkers and to ensure their disease specificity, we looked at their implication in other disorders. The analysis revealed that the 36 miRNAs repeatedly found to be differential in AD blood (Table 2) were also reported to present altered levels in blood in other diseases (Supplementary Table 2). As shown in this table, the majority of the miRNAs were reported as biomarker candidates in different types of cancer. For example, altered levels of hsa-miR-200b were reported in ovarian cancer in serum, in colorectal cancer in plasma and in prostate cancer in whole blood. Some blood-based miRNAs were reported to be altered both in some types of cancer and metabolic disorders, e.g. hsa-miR-138 was found to be associated with ovarian cancer and diabetes. Interestingly, a group of several miRNAs out of the 36 miRNAs differential in AD blood also proved to be associated both with cancers and with other neurological diseases, e.g. altered blood levels of hsa-miR-98-5p were reported in non-small cell lung cancer and in schizophrenia, of hsa-miR-34a in several cancers as well as in schizophrenia and major depressive disorder, and of hsa-miR-106b-5p in epilepsy, autism spectrum disorder and schizophrenia (Supplementary Table 2).

Of special interest are the results for the 3 miRNAs identified as the best potential biomarkers for AD (hsa-miR-146a, hsa-miR-125b and hsa-miR-135a) (Table 5). Several publications indicate mechanistic links of these miRNAs with both AD and other diseases. For example, hsa-miR-125b has been demonstrated to be downregulated in AD brain, where it might be responsible for the upregulation of the cyclin dependent kinase 5 (cdk5) expression and tau hyperphosphorylation. At the same time, its alterations in several cancers and involvement in the regulation of mitogen-activated protein kinase (MAPK) signaling and cell proliferation have been also reported (Banzhaf-Strathmann et al., 2014). In turn, hsa-miR-146a has been indicated as one of main miRNAs associated with cellular senescence and inflammation and implicated in mechanisms underlying age-related chronic diseases (Olivieri et al., 2013). Finally, hsa-miR-135a has been reported as a tumor suppressor in cancers (Tang et al., 2014; Zhang et al., 2016a).

These findings raise a question: how is it possible that the same miRNAs are implicated in the pathophysiology of different diseases? The prominent reason for this might be the low ratio of the total number of miRNAs to the total number of genes, which is estimated to be around 1:10 in humans. This leads to the situation that each miRNA may target several transcripts in a tissue- and physiological conditions-specific manner, and the set of the targeted transcripts is likely to be distinct in various health conditions (Afonso-Grunz and Müller, 2015). All these indicate that the individual miRNAs should not be used as standalone biomarkers. However, when combined in a form of a panel they might present diagnostic potential.

3.6. Targets of the miRNAs differential in AD blood

To discern the transcripts targeted by the shortlisted 36 miRNAs, reproducibly altered in AD blood, we performed bioinformatics analysis using miRTarBase (Chou et al., 2016, 2018). Only experimentally validated targets were taken into account to strengthen findings. The search led to the identification of 720 potential gene targets of the selected miRNAs. The identified gene targets (Corresponding Genes) were denoted as CORGENEs and were grouped into three categories: 1) targeted by 15 down-regulated miRNAs (miR-down − CORGENE), 2) regulated by 5 up-regulated miRNAs (miR-up − CORGENE) and 3) targeted by 16 miRNAs exhibiting discordant alterations (miR-dis − - CORGENE) (Table 6A and Fig. 6A). The first group comprised 293 genes, out of which 42 were regulated by more than one miRNA from the list. The second group consisted of 265 targets, out of which 17 were regulated by more than one miRNA from the pool. Finally, the miRNAs exhibiting discordant alterations were found to target 321 genes, with 57 of them regulated by more than one miRNA from the set (Table 6A and Fig. 6A). The common targets among the groups of

Table 2
36 blood-based miRNA candidate AD biomarkers selected based on the reproducibility. (For interpretation of the references to colour in this Table legend, the reader is referred to the web version of this article.)

No	miRNA (hsa-miR/ hsa-let)	Direction & No. of Reports	Plasma	Serum	Blood	PMBC	Reference
1.	125b	Down-6	yes	yes	-	-	(Burgos et al., 2014; Galimberti et al., 2014; Jia and Liu, 2016; Kiko et al., 2014; Lugli et al., 2015; Tan, L. et al., 2014a)
2.	29b	Down- 4	yes	yes	yes	yes	(Geekiyanage et al., 2012; Lugli et al., 2015; Satoh et al., 2015; Villa et al., 2013)
3.	34a	Dis-4	yes	-	-	yes	(Bhatnagar et al., 2014; Cosín-Tomás et al., 2017; Kiko et al., 2014; Schipper et al., 2007)
4.	342-3p	Down- 3	yes	yes	-	-	(Cheng et al., 2015; Lugli et al., 2015; Tan, L et al., 2014b)
5.	7f	Dis-3	-	-	yes	yes	(Leidinger et al., 2013; Satoh et al., 2015; Schipper et al., 2007)
6.	15a	Dis-3	yes	yes	yes	-	(Bekris et al., 2013; Cheng et al., 2015; Satoh et al., 2015)
7.	107	Down-3	yes	-	yes	-	(Leidinger et al., 2013; Wang et al., 2015; Yılmaz et al., 2016)
8.	26b	Dis-3	-	yes	yes	-	(Galimberti et al., 2014; Leidinger et al., 2013; Satoh et al., 2015)
9.	9	Dis- 3	yes	yes	yes	-	(Geekiyanage et al., 2012; Tan, L. et al., 2014a; Yılmaz et al., 2016)
10.	15b	Down-3	yes	yes	-	-	(Cheng et al., 2015; Cosín-Tomás et al., 2017; Kumar et al., 2013)
11.	7d-5p	Down-2	yes	yes	-	-	(Kumar et al., 2013; Tan, L et al., 2014b)
12.	7g-5p	Down-2	yes	-	yes	-	(Kumar et al., 2013; Satoh et al., 2015)
13.	191-5p	Down- 2	yes	yes	-	-	(Kumar et al., 2013; Tan, L et al., 2014b)
14.	98-5p	Down-2	-	yes	yes	-	(Satoh et al., 2015; Tan, L et al., 2014b)
15.	34c	Up- 2	yes	yes	-	-	(Bhatnagar et al., 2014; Burgos et al., 2014)
16.	200b	Dis-2	-	yes	-	yes	(Guedes et al., 2016; Liu et al., 2014c)
17.	146a	Down-2	yes	yes	-	-	(Dong et al., 2015; Kiko et al., 2014)
18.	5001-3p	Dis-2	yes	-	yes	-	(Lugli et al., 2015; Satoh et al., 2015)
19.	3065-5p	Dis- 2	yes	yes	-	-	(Cheng et al., 2015; Lugli et al., 2015)
20.	425	Up- 2	-	-	yes	yes	(Ren et al., 2016; Satoh et al., 2015)
21.	106b-5p	Dis- 2	-	yes	yes	-	(Cheng et al., 2015; Yılmaz et al., 2016)
22.	106a-5p	Dis-2	-	yes	yes	-	(Cheng et al., 2015; Yılmaz et al., 2016)
23.	502-3p	Dis-2	yes	-	yes	-	(Nagaraj et al., 2017; Satoh et al., 2015)
24.	103a-3p	Down- 2	yes	-	yes	-	(Leidinger et al., 2013; Nagaraj et al., 2017)
25.	200a-3p	Up- 2	yes	-	-	yes	(Nagaraj et al., 2017; Schipper et al., 2007)
26.	3613-3p	Dis-2	yes	yes	-	-	(Kumar et al., 2017; Lugli et al., 2015)
27.	142-3p	Down- 3	yes				(Cosín-Tomás et al., 2017; Kumar et al., 2013; Nagaraj et al., 2017)
28.	181c	Down- 2		yes			(Geekiyanage et al., 2012; Tan, L. et al., 2014a)
29.	155	Up-2				yes	(Guedes et al., 2016; Schipper et al., 2007)
30.	138	Dis-2	yes				(Bekris et al., 2013; Lugli et al., 2015)
31.	135a	Dis- 2		yes			(Burgos et al., 2014; Liu et al., 2014c)
32.	151a-3p	Up-2			yes		(Leidinger et al., 2013; Satoh et al., 2015)
33.	93	Dis- 2		yes			(Cheng et al., 2015; Dong et al., 2015)
34.	143	Dis- 2		yes			(Cheng et al., 2015; Dong et al., 2015)
35.	545-3p	Down- 2	yes				(Cosín-Tomás et al., 2017; Kumar et al., 2013)
36.	301a-3p	Down- 2	yes				(Kumar et al., 2013; Nagaraj et al., 2017)

The table lists blood-based miRNAs differential in AD, reported more than once in independent studies of the last decade. miRNAs with repetition counts ≥ 2 among different blood fractions are shaded in grey (No. 1- 26), miRNAs with repetition counts ≥ 2 among the same blood fractions are left unshaded (No. 27-36). The table also lists the direction of changes: Down - concordantly downregulated shown in green, Up - concordantly upregulated shown in red and Dis - discordantly reported shown in blue.

miRNAs are also shown (Table 6A and Fig. 6A).

These promising data led us to perform further gene enrichment analysis. To this end, we searched for genes regulated by at least 4 out of the 36 miRNAs, and found 25 such targets (Table 6B and Fig. 6B). Earlier, 8 of them, namely cyclin D1 (*CCND1*), vascular endothelial growth factor A (*VEGFA*), *MYC*, high mobility group protein HMGI-C (*HMGA2*), cyclin-dependent kinase inhibitor 1 A (*CDKN1 A*), *DICER1*, interleukin 13 (*IL13*) and phosphatase and tensin homolog (*PTEN*), have been predicted to be implicated in AD pathophysiology (Keller et al., 2016). Our analysis broadened this list (Table 6B).

In order to get greater insight into the pathways regulated by the shortlisted 36 miRNAs, their 720 target genes were assigned to the physiological processes using WEB-based Gene SeT AnaLysis Toolkit (WebGestalt). WebGestalt is a web-based tool utilizing data from the pathway databases, including the KEGG pathway, Wiki pathway, Common pathway and Disease association pathway (Table 7).

Functional enrichment analysis was performed with $p < 0.0001$ after false discovery rate (FDR) correction for multiple testing (Wang et al., 2013, 2017b; Zhang et al., 2005). As demonstrated in Table 7 and Supplementary Table 3, pathways implicated in cancer pathogenesis

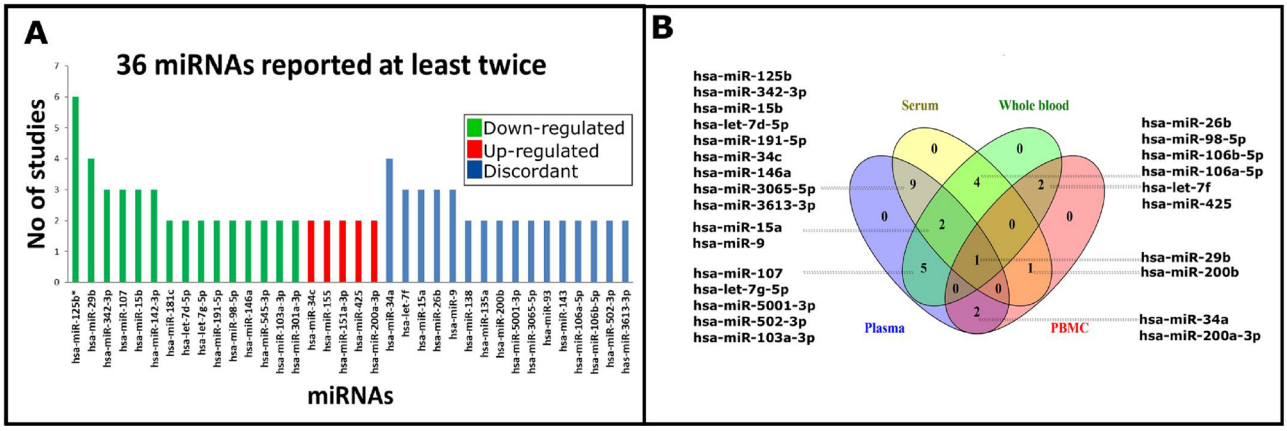


Fig. 3. 36 miRNAs reproducibly reported as differential in AD blood.
(A) The bar graph presents direction of changes of 36 blood-based differential miRNAs repeated at least once in independent studies. concordant (upregulation shown in red color and downregulation shown in green color) – the same directions of changes were observed in independent studies; discordant (shown in blue color) – opposite direction of changes was observed in independent studies. **(B)** The scheme demonstrates the distribution of 26 miRNAs out of 36 differential in AD listed in Table 2 among various blood fractions (plasma, serum, whole blood and PBMC). Numbers indicate how many common miRNAs were reported in different blood fractions. Listed are these miRNAs which were reported at least in two different sources.

were among the top hits. This might point towards molecular links between cancer and AD.

3.7. Inverse miRNA signatures in cancer and AD

To elucidate the relationship between cancer and AD on the epigenetic level, we compared the directions of miRNA changes between the two diseases. 20 miRNAs, which exhibited reproducible concordant alterations in AD (Table 2, Fig. 3A), were taken into account to compare with meta-analysis of circulating blood miRNAs in cancer (He et al., 2015) (Fig. 7). This analysis revealed the same 6 miRNAs in serum and 7 miRNAs in plasma that are altered in both conditions. Although the same miRNAs are altered in AD and several types of cancer, they show opposite directions of changes (Fig. 7). This is in line with the data stemming from proteomic studies and functional analyses of the disease pathomechanisms (Shafi, 2016; Tabarés-Seisdedos and Rubenstein, 2013). For example, dysregulation of the cell cycle and of the cell cycle associated programmed cell death is observed in both conditions. However, while in cancer cells escape from apoptosis and proliferate, in AD peripheral cells exhibit growth arrest (Behrens et al., 2012; Bialopiotrowicz et al., 2011; Braidy et al., 2016; Checler and Dunys, 2012) and mature brain neurons show abortosis and re-entry into the cell cycle without mitosis (Herrup, 2015; Herrup and Arendt, 2002; Yang et al., 2003; Zekanowski and Wojda, 2009). In addition, loss of function of tumour suppressor gene *TP53* on one hand is a prerequisite for cancer development but on the other might provide neuroprotection (van Heemst et al., 2005). In consonance with that, people with *TP53* mutations that confer less vigorous apoptosis present 41% increased survival despite a higher risk of death from cancer (van Heemst et al., 2005). Analogously, upregulation of Wnt cell survival pathways and ubiquitin proteasome and increased expression of peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1) promote oncogenesis, while loss of their function results in neuronal death and neurodegeneration. Finally, APP might be implicated not only in AD pathogenesis but also in carcinogenesis as a possible oncogene (Shafi, 2016; Tabarés-Seisdedos and Rubenstein, 2013) and mutations in *MAPT* might be susceptibility factors for cancer (Rossi et al., 2018).

The hypothesis that AD and cancer are characterized by changes in the expression of the same genes but in an opposite direction is further supported by epidemiological data (Musicco et al., 2013; Ou et al., 2013). These point towards inverse associations between AD and hematologic malignancies, colorectal and lung cancer (the smoking-related type in particular) (Driver et al., 2012; Roe et al., 2010). Interestingly, pancreatic cancer appears to be an exception. Its miRNA profile does not follow the inversion rule (Fig. 7), and accordingly, there is a co-occurrence of the pancreatic cancer and AD (Burke et al., 1994). Epidemiological link between AD and cancer has been also indicated by a large scale retrospective study (over 15 years) on a cohort

Table 3
13 miRNAs differential in AD CSF selected based on the reproducibility.

No	miRNA (hsa-miR)	Direction & No. of Reports	Reference
1.	**146a**	Dis-7	(Alexandrov et al., 2012; Denk et al., 2015; Kiko et al., 2014; Lukiw et al., 2012; Lusardi et al., 2017; Müller et al., 2014, 2016b)
2.	**125b**	Dis-5	(Alexandrov et al., 2012; Dangla-Valls et al., 2016; Galimberti et al., 2014; Kiko et al., 2014; Lusardi et al., 2017)
3.	**29a**	Dis-3	(Kiko et al., 2014; Lusardi et al., 2017; Müller et al., 2016a)
4.	**29c**	**Down-3**	(Gui et al., 2015; Sorensen et al., 2016; Yang et al., 2015a, 2015b)
5.	**136-3p**	Dis-2	(Burgos et al., 2014; Gui et al., 2015)
6.	**127-3p**	**Down-2**	(Burgos et al., 2014; van Harten et al., 2015)
7.	**30a-3p**	Dis-2	(Cogswell et al., 2008; Lusardi et al., 2017)
8.	**139-5p**	**Down-2**	(Burgos et al., 2014; van Harten et al., 2015)
9.	**135a**	Dis-2	(Cogswell et al., 2008; Liu et al., 2014c)
10.	**206**	Dis-2	(Riancho et al., 2017; van Harten et al., 2015)
11.	**9-5p**	**Down-2**	(Burgos et al., 2014; Riancho et al., 2017)
12.	**141**	Dis-2	(Cogswell et al., 2008; Riancho et al., 2017)
13.	**598**	Dis-2	(Burgos et al., 2014; Riancho et al., 2017)

The miRNAs were selected from 26 independent CSF studies of the last decade. Only these reported ≥ 2 times are listed. The direction of changes is shown: Down - concordantly downregulated, Up - concordantly upregulated and Dis - discordantly reported.

Table 4
Correlations between the levels of the CSF-based miRNAs and conventional biomarkers differential in AD.

Study	miRNA (hsa -mir/hsa-let)	Correlation markers	Nature of correlation	Statistics
Correlation observed with respect to conventional CSF markers (Aβ42, T-tau and P-tau)				
(Sala Frigerio et al., 2013)	27a-3p	Aβ42,T-tau and P-tau	Positive correlation with Aβ42; Inverse correlation with T-tau and P-tau	Spearman rank correlation Cohort 1: Aβ42; r = 0.4361, p = 0.0055 T-tau; r = -0.6025, p < 0.0001 P-tau; r = -0.5304, p = 0.0005 Cohort 2: Aβ42; r = 0.4692, p = 0.0059 T-tau; r = -0.3829, p = 0.0279 P-tau; r = -0.4030, p = 0.0201
(Liu et al., 2014a)	193b	Aβ42	Inverse correlation	Spearman rank correlation Aβ42; r = -0.442, p < 0.05
(Liu et al., 2014b)	384	Aβ42	Inverse correlation	Spearman rank correlation Aβ42; r = -0.571, p < 0.05
(Galimberti et al., 2014)	26b	T-tau and P-tau	Inverse correlation	Spearman rank correlation T-tau; r = -0.440, p = 0.022 P-tau; r = -0.469, p = 0.013
(Denk et al., 2015)	146a	Aβ42 and T-tau	Inverse correlation	Pearson correlation Aβ42; r = -0.5364, p = 0.0101 T-tau; r = -0.5142,p = 0.0171
(Liu et al., 2018)	7b	T-tau and P-tau	Positive correlation	Pearson correlation T-tau; r = 0.7411, p < 0.0001 P-tau; r = 0.5458, p < 0.0001
Correlation observed with respect to other AD pathology markers				
(Burgos et al., 2014)	9 and 101	neurofibrillary tangles and plaque density (in Brain)	Inverse correlation	Pearson correlation
(Yang et al., 2015a)	29c	CSF proteins (BDNF & DNMT3)	Positive correlation with BDNF and inverse correlation with DNMT3	NA
Correlation not observed				
(Müller et al., 2014)	146a	MMSE	Nil	Nil
(Kiko et al., 2014)	29a, 29b, 34a, 125b and 146a	Aβ42,T-tau and P-tau	Nil	Nil

The table reviews the studies correlating miRNA and protein biomarkers in AD CSF. Aβ – amyloid beta, BDNF - brain derived neurotrophic factor, DNMT3 - DNA methyltransferase 3, MMSE - Mini-Mental State Examination, NA - not available.

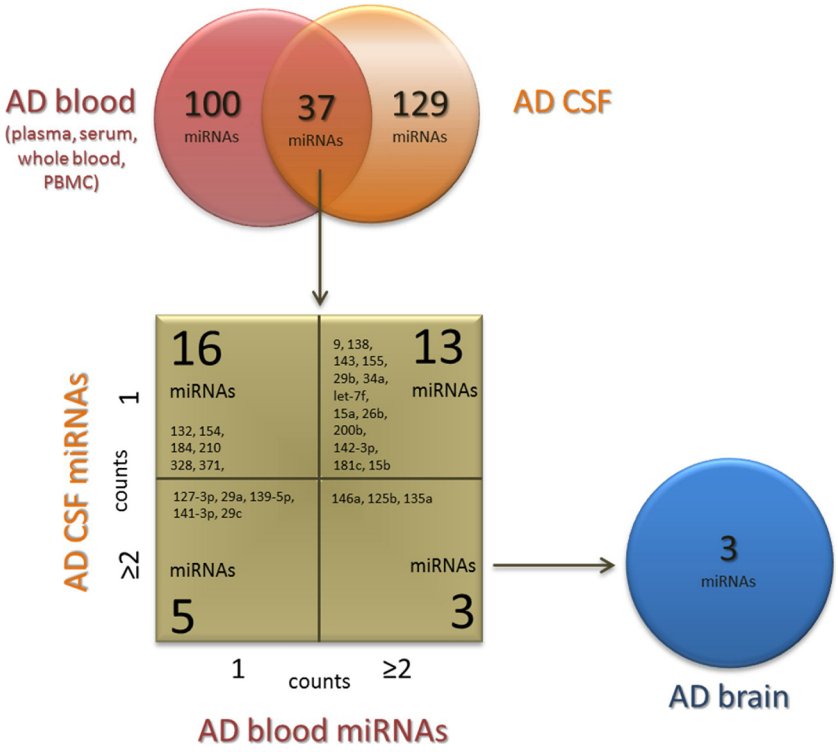


Fig. 4. miRNAs differential in AD across the blood, the cerebrospinal fluid and the brain: the bottom-up analysis. Top circles depict the overlap between potential miRNA biomarker candidates detected in the blood (red circle) and in the CSF (orange circle) in multiple studies. The corresponding 2 × 2 matrix shows the numbers and the names of overlapping miRNAs based on how many times they were independently reported in the blood and in the CSF (1 time or at least 2 times). Only 3 miRNAs were found to be reported at least two times both in the blood and in the CSF and these 3 miRNAs were also reported in the brain (blue circle). The arrows indicate the direction of the bottom-up analysis from the blood and the CSF to the brain.

of 3.5 million elderly US veterans. The results of this analysis demonstrated that survivors of most types of cancer had reduced risk of subsequent AD but a higher risk of other diseases, such as non-AD dementia, stroke, osteoarthritis and macular degeneration (Frain et al., 2017). On the other hand, survivors of prostate cancer and melanoma did not follow this rule and presented an increased risk of AD. Finally, a meta-analysis of five studies showed a 50% decreased risk of AD in patients with a history of cancer and a 36% decreased risk of cancer in patients with AD (Catalá-López et al., 2014a, b).

The inverse relationship between cancer and neurodegeneration has

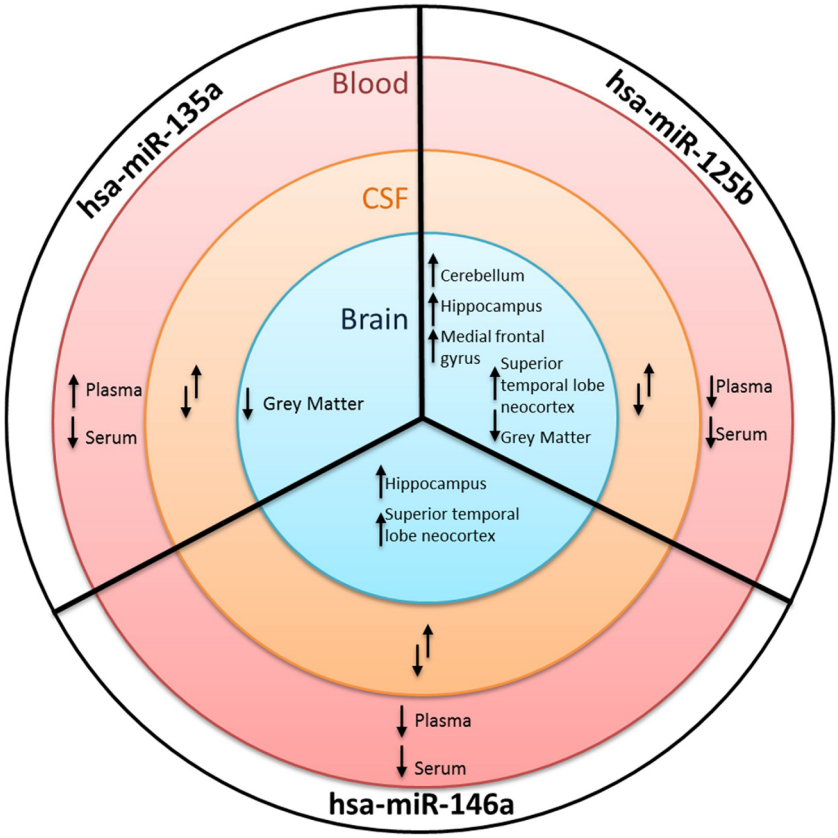


Fig. 5. Direction of changes of 3 differential miRNAs (hsa-miR-146a, hsa-miR-125b and hsa-miR-135a) in AD blood, CSF and brain.
Three clockwise parts of the circle show data for hsa-miR-135a, hsa-miR-125b, and hsa-miR-146a (from left to right) in AD blood, CSF and brain (outer circle – blood, middle circle – CSF, inner circle - brain). Each arrow represents one independent report on the dysregulation of a given miRNA. Arrows directed upwards present upregulation and arrows directed downwards indicate downregulation of miRNAs. hsa-miR-135a was reported as dysregulated in blood twice: as downregulated in serum and upregulated in plasma. In CSF hsa-miR-135a was reported once as downregulated and once as upregulated, and in brain grey matter hsa-miR-135a was reported as downregulated. hsa-miR-125b was reported twice as downregulated in plasma and serum, however in CSF it was once reported as upregulated and once as downregulated. Discordantly altered levels of hsa-miR-125b were also independently reported in various regions of the brain. hsa-miR-146a was reported independently twice, as downregulated both in plasma and serum, however in the CSF two independent reports showed discordant direction of change in this miRNAs' levels. In different brain regions several reports showed upregulation of hsa-miR-146a.

Table 5
Cross-disease analysis of miRNAs differential in AD blood, CSF and brain.

No	miRNAs	Reported as potential diagnostic candidate (Source; Disease)
1.	**hsa-miR-146a**	**Serum:** Aging (Kangas et al., 2017), Adenocarcinoma (Lv et al., 2017), Hepatocellular carcinoma (Devhare et al., 2017), Ankylosing spondylitis (Qian et al., 2016), Dengue (Ouyang et al., 2016), Parkinson's disease (Ma et al., 2016a), Psoriasis (Yang et al., 2016b), Hepatocellular carcinoma (Motawi et al., 2015), Thyroid Cancer (Graham et al., 2015), Acute kidney injury (Aguado-Fraile et al., 2015), Uveal melanoma (Ragusa et al., 2015), Juvenile idiopathic arthritis (Kamiya et al., 2015), Non-small-cell lung cancer (Wang et al., 2015a), Type 2 diabetes (Baldeón et al., 2014), Graves ophthalmopathy (Wei et al., 2014), Type 2 diabetes (Yang et al., 2014), Polycystic ovary syndrome (Long et al., 2014), Non-small cell lung cancer (Wu et al., 2014), Rheumatoid arthritis (Filková et al., 2014), Lymph node metastasis in gastric cancer (Kim et al., 2013), Pancreatic cancer (Li et al., 2013), Acute coronary syndrome (Oerlemans et al., 2012), Systemic lupus erythematosus (Wang et al., 2010a), Sepsis (Wang et al., 2010b) **Plasma:** Autoimmune thyroid diseases (Otsu et al., 2017), Coronary artery disease (Wang et al., 2016), Cancer Metastasis (Markou et al., 2016), Age-related macular degeneration (Ménard et al., 2016), Juvenile idiopathic arthritis (Ma et al., 2016b), myocardial fibrosis in hypertrophic cardiomyopathy (Fang et al., 2015), Rheumatoid arthritis (Ormseth et al., 2015), Breast cancer (Stückrath et al., 2015), Exercise training (Wardle et al., 2015), Breast cancer (Kumar et al., 2013b), Peripartum cardiomyopathy (Halkein et al., 2013), Systemic lupus erythematosus (Wang et al., 2012), Eosinophilic esophagitis (Lu et al., 2012), Exercise training (Baggish et al., 2011) **PBMC:** Autoimmune thyroid diseases (Otsu et al., 2017), Allergic rhinitis (Luo et al., 2016), Type 2 diabetes (Lenin et al., 2015), Multiple sclerosis (Ma et al., 2014), Myasthenia gravis (Lu et al., 2013), Rheumatoid arthritis (Pauley et al., 2008) **Natural killer cells:** Chronic fatigue syndrome/Myalgic encephalomyelitis (Brenu et al., 2012) **Blood leukocytes:** Systemic lupus erythematosus (Dominguez-Gutierrez et al., 2014) **Mononuclear leukocytes:** Sjögren's syndrome (Zilahi et al., 2012) **CD4(+) T cells:** Oral lichen planus (Yang et al., 2016a), Rheumatoid arthritis (Li et al., 2010) **Regulatory T (Treg) cells:** Ulcerative colitis (Mohammadnia-Afrouzi et al., 2016) **Whole blood:** Head and neck squamous cell carcinoma (Lerner et al., 2016), Rheumatoid arthritis (Mookherjee and El-Gabalawy, 2013), Breast cancer (Alshatwi et al., 2012) **Exosomes of monocyte-derived macrophages:** Tuberculosis (Mortaz et al., 2016)
2.	**hsa-miR-125b**	**Serum:** Sepsis (Reithmair et al., 2017), Glioblastoma multiforme (Regazzo et al., 2016), Endometriosis (Cosar et al., 2016), Epithelial ovarian cancer (Zuberi et al., 2016), Hepatitis B virus infection (Ninomiya et al., 2016), osteoporotic fracture (Panach et al., 2015), Breast cancer (Matamala et al., 2015), Aerobic exercise (de Gonzalo-Calvo et al., 2015), Prostate cancer (Roberts et al., 2015), Hepatitis B virus infection (Akamatsu et al., 2015), Ewing's sarcoma (Nie et al., 2015), Hepatocellular carcinoma (Zuo et al., 2016), Glioma (Wei et al., 2016b), Non-alcoholic fatty liver disease (Pirola et al., 2015), hepatitis B virus related hepatocellular carcinoma (Giray et al., 2014), Osteoporosis (Seeliger et al., 2014), Spinocerebellar ataxia type 3/Machado-Joseph disease (Shi et al., 2014), Breast cancer (Mar-Aguilar et al., 2013), Non-small-cell lung cancer (Ma et al., 2012) **Plasma:** Viral encephalitis (Gao et al., 2017), Acute myocardial infarction (Jia et al., 2016), Asthma and Allergic rhinitis (Panganiban et al., 2016), Breast cancer (Matamala et al., 2015), Acute myocardial infarction (Huang et al., 2014), Type 2 diabetes (Ortega et al., 2014), Obesity (Ortega et al., 2013) **PBMC:** Rheumatoid arthritis (Hruskova et al., 2016) **Whole blood:** Obstructive renal injury (Wang et al., 2017d), Stroke(Sepramaniam et al., 2014) **Serum exosomes:** Sepsis (Reithmair et al., 2017), Melanoma (Alegre et al., 2014) **T cells:** Systemic lupus erythematosus (Luo et al., 2013)
3.	**hsa-miR-135a**	**Serum:** Colorectal cancer (Wang et al., 2017c), Non-small cell lung cancer(Zhang et al., 2016b), Endometriosis (Cho et al., 2015) **PBMC:** Coronary artery disease (Hoekstra et al., 2010)

The table presents the biomarker potential for non-AD diseases of the 3 miRNAs differential in the AD blood, CSF and brain (miR-146a, miR-125b and miR-135a).

been recently related to the ageing process (Aramillo Irizar et al., 2018). It has been reported that transcriptomic changes associated with aging are similar to these observed in neurodegeneration but opposite to the ones seen in cancer, and that there is a shift from cancer to degenerative chronic diseases as main causes of death during aging. All these data point to an antagonistic trade-off between cancer and degeneration, and reflect a shift from the major biological objective to maintain reproduction towards the need for individual survival. Our analysis adds to this view an epigenetic level of this antagonistic relationship, reflected in miRNA signatures.

The general term cancer refers to common processes underlying different types of cancer. Despite that different types of cancer and neurodegeneration are biological entities characterized by distinctive molecular characteristics, our data support previous observations that cancer and AD share some key features. These include alterations in cell fate and metabolic processes, and might be associated with ageing (Olivieri et al., 2013; Aramillo Irizar et al., 2018). From this perspective, relationship between miRNA profiles in adult brain in AD and in adult brain cancer (glioma) is particularly interesting, especially given that microglia undergo a neoplastic transformation in glioma and that microglia also play key role in AD pathogenesis (Shi and Holtzman, 2018). The comparison of miRNA molecular signatures in both brain pathologies in different brain areas and in the blood is needed.

3.8. Required improvements and advantages of miRNA panel for AD diagnostics

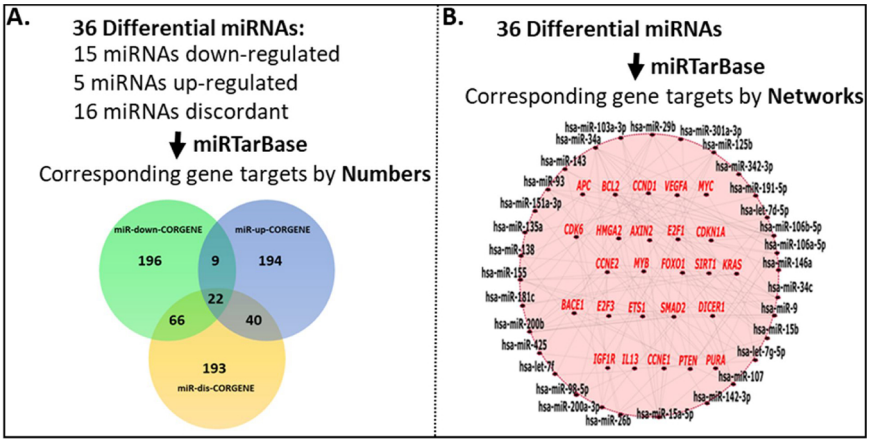
Despite significant progress in miRNA research, miRNA biomarker field still suffers from poor data reproducibility. This might be due to the lack of the standardization of pre-analytical, analytical and post-analytical factors (Kumar and Reddy, 2016; O'Bryant et al., 2015, 2017).

The main sources of analytical variability across the studies are sample collection and analysis protocols, including variability of reagents, laboratory materials, equipment and its calibration as well as procedures for sample handling, storage and processing. Various blood fractions used as miRNA source, different methods for miRNA isolation, detection and data normalization all may cause inconsistencies in miRNA profiling. Hemolysis and sample freeze-thaw cycles should be avoided as these may release miRNAs from blood cells and significantly change miRNA profiles. Whole blood vs serum vs plasma differ by processing and additives such as citrate and EDTA or heparin, which may influence stability and detectability of miRNAs (O'Bryant et al., 2015; Zhao et al., 2017). EDTA but not heparin is compatible with subsequent qRT-PCR, currently the most sensitive, cost-effective and one of the fastest methods of miRNA analysis. All these make the qRT-PCR one of the most commonly used miRNA analysis methods, often combined with RNA microarrays. Nevertheless, NGS is more suitable for identifying novel miRNAs and the novel NanoString methodology allows for the simultaneous measurement of miRNAs and mRNA targets within the same sample. Another important factor that might influence the analysis is the choice of the normalization controls, either endogenous or exogenous. So far no optimal normalization strategy exists (Kumar and Reddy, 2016; Zhao et al., 2017) and the employment of several normalizers is recommended. Finally, little is known on the influence of patient diet and health status on protein, lipid and vesicular miRNAs shuttles in body fluids. Such pre-analytical factors require further investigations. Overall, the establishment of the guidelines and

Table 6
Gene targets of the 36 blood-based miRNA AD biomarker candidates.

Analysis	No	Genes
A. Genes enriched with stratification of miRNAs based on their direction of regulation (concordantly up/down and discordant)		
Genes regulated by more than 1 down-regulated miRNA	**42** (out of 196)	AGO1,AKT2,AXIN2,BACE1,BAK1,BCL2,CAV1,CCNE1,CCNJ,CDK6,CDKN2 A,DAPK1,DICER1,DNMT1,E2 F2,FOXO1,GRN,HMGA1,HMGA2,IFNG,IL1 A,IL13,KLF4,KRAS,LAMC2,MCL1,-MMP15,MMP24,MPL,MYB,MYC,NKIRAS2,NOTCH2,PRKCE,PTEN,RAC1,RAD51,SMAD4,SNCG,TET2,TGFBR1,VEGFA
Genes regulated by more than 1 up- regulated miRNA	**17** (out of 194)	BCL2,CCND1,CCNE2,CEBPB,CSF1R,CTNNB1,GRB2,INPP5D,JARID2,MAFB,MYB,MYC,PICALM,PTEN,RUNX2,SMAD2,THRB
Genes regulated by more than 1 discordant miRNA	**57**(out of 193)	APC,APP,ATG16L1,AXIN2,BACE1,BCL2,BCL2L11,BMI1,CASP7,CCND1,CCND2,CCNE1,CCNE2,CD44,CDK6,CDKN1 A,CREB1,CYP19A1,DNMT3 A,E2 F1,E2 F3,ETS1,EZH2,FOSL1,FOX-O1,FOXP1,HNF4A,IGF1R,JAG1,KAT2B,LIMK1,MAPK9,MMP13,MYB,MYC,NAMPT,NOTCH1,NR2C2,PHLPP1,PRDM1,PRTG,PTEN,PTGS2,PURA,RB1,RBL2,ROCK2,RUNX3,SIRT1,SMA-D7,STAT3,TGFBR2,VEGFA,WNT1,XIAP,ZBTB4,ZEB2
Common genes in "miR-down-CORGENE" and "miR-up-CORGENE"	**9**	ARNTL,BMF,E2 F2,FADD,MAPK14,NOTCH4,RAC1,RAD51,TAB2
Common genes in "miR-down-CORGENE" and "miR-dis-CORGENE"	**66**	APP,BACE1,BCL2L11,BMPR2,BRCA1,CASP3,CCND2,CDKN1 A,CDX2,COL1 A1,COX2,CREB1,CXCR4,CYP19A1,DICER1,DNMT3 A,DNMT3B,E2 F1,EIF2C1,ELAVL1,EZH2,FAS,FN1,FOX-O1,GRN,HDAC4,HK2,HMGA1,HMGA2,HOXA10,HSPA1B,ID2,IFNG,IGF1R,IL13,ITGB1,JAK1,KDR,KLF4,L1CAM,LATS2,LOX,MDM4,MMP2,MMP13,MPL,MXD1,NFKB1,NOTCH2,PRD-M1,PRTG,PTGS2,PURA,RECK,ROCK1,ROCK2,RUNX3,SERPINE1,SIRT1,SIRT7,SMAD7,SOX4,SP1,TNF,TUSC2,VEGFA
Common genes in "miR-up-CORGENE" and "miR-dis-CORGENE"	**40**	BAP1,BCL6,CCNE2,CSF1R,CTNNB1,ELMO2,ERBB2IP,FGF7,FOSL1,FOXO3,GALNT7,HNF4A,HOXB5,KLF11,KLHL20,LEF1,MATR3,MET,NANOG,NOTCH1,PTPRD,RASSF2,RIN2,SHC1,-SMAD5,SNAI1,SOX2,SPI1,SRF,TCF7L1,ULBP2,VAC14,WASF3,WDR37,WEE1,YY1,ZAP70,ZEB1,ZEB2,ZFPM2
Common genes in "miR-down-CORGENE", "miR-up-CORGENE" and "miR-dis-CORGENE"	**22**	APC,AXIN2,BCL2,CCND1,CCNE1,CDK4,CDK6,CEBPB,E2 F3,ETS1,HIF1 A,KRAS,MYB,MYC,MYCN,NTRK3,PDGFRA,PDGFRB,PTEN,SMAD2,TP53,TP53INP1
B. Genes enriched without stratification of miRNAs based on their direction of regulation (up/down)		
Genes targeted by atleast 4 miRNAs out of all 36 miRNAs	**25**	APC,AXIN2,BACE1,BCL2,CCND1,CCNE1,CCNE2,CDK6,CDKN1 A,DICER1,E2 F1,E2 F3,ETS1,FOXO1,HMGA2,IGF1R,IL13,KRAS,MYB,MYC,PTEN,PURA,SIRT1,SMAD2,VEGFA

A, Lists of genes targeted by the 36 miRNAs repeatedly differential in AD blood, included in various subgroups based on their direction of changes and the number of data reproduction (Fig. 6A). B, List of experimentally validated genes regulated by at least 4 out of the 36 miRNAs repeatedly differential in AD blood, without stratification based on the concordant vs discordant changes (Fig. 6B). The analysis was performed using miRTarBase (Chou et al., 2016, 2018).



miRNAs are noted on the circumference.

Fig. 6. Functional analysis of the 36 miRNAs differential in AD blood.
This figure presents analysis of gene targets of the 36 repeatedly reported differential miRNAs in AD blood. They were identified based on miRTarBase and listed in Table 6. **(A)** Gene targets were grouped by overlap/non-overlap among concordantly and discordantly differential miRNAs and numbers of gene targets in each group are shown. miR-down − CORGENE is a pool of gene targets regulated by the 15 concordantly downregulated miRNAs, miR-up − CORGENE is a pool of gene targets regulated by the 5 concordantly upregulated miRNAs, miR-dis − CORGENE is a pool of gene targets regulated by the 16 discordant miRNAs. Common genes in each pool are listed in Table 6**A. (B)** Enriched miRNA-gene target network for the 36 differential miRNAs in AD blood is presented. Gene targets regulated by at least 4 out of the 36 miRNAs listed in Table 6**B** are shown inside the circle and corresponding

Table 7
Pathway enrichment analysis for the gene targets.

miR-CORGENES	KEGG Pathway	Wikipathway	Common Pathway	Disease Association Pathway
miR-down-CORGENES	Pathways in cancer, Pancreatic cancer, Focal adhesion, Prostate cancer, Small cell lung cancer, Chronic myeloid leukemia, Bladder cancer, Melanoma, Glioma, Colorectal cancer	Integrated Pancreatic Cancer Pathway, Focal Adhesion, Signaling Pathways in Glioblastoma, Senescence and Autophagy, Androgen receptor signaling pathway, Muscle cell TarBase, Lymphocyte TarBase, MAPK signaling pathway, DNA damage response, miRNA regulation of DNA Damage Response	Integrin family cell surface interactions, Beta1 integrin cell surface interactions, TRAIL signaling pathway, Sphingosine 1-phosphate (S1P) pathway, Proteoglycan syndecan-mediated signaling events, PDGF receptor signaling network, IFN-gamma pathway, ErbB receptor signaling network, Signaling events mediated by Hepatocyte Growth Factor Receptor (c-Met), Glypican 1 network	Cancer or viral infections, Neoplasms, Neoplastic Processes, Neoplasm Metastasis, Epithelial cancers, Carcinoma, Breast Diseases, Breast Neoplasms, Neoplasm of unspecified nature of digestive system, Gastrointestinal Neoplasms
miR-up-CORGENES	Pathways in cancer, Colorectal cancer, Endometrial cancer, Prostate cancer, Melanoma, Glioma, Small cell lung cancer, Pancreatic cancer, Chronic myeloid leukemia, Wnt signaling pathway	Lymphocyte TarBase, Integrated Pancreatic Cancer Pathway, TGF beta Signaling Pathway, DNA damage response (only ATM dependent), Muscle cell TarBase, Epithelium TarBase, Signaling Pathways in Glioblastoma, Wnt Signaling Pathway and Pluripotency, Wnt Signaling PathwayB Cell Receptor Signaling Pathway	S1P1 pathway, Class I PI3K signaling events mediated by Akt, EGF receptor (ErbB1) signaling pathway, Arf6 signaling events, Internalization of ErbB1, Nectin adhesion pathway, Signaling events mediated by focal adhesion kinase, IL5-mediated signaling events, Class I PI3K signaling events, IFN-gamma pathway	Cancer or viral infections, Cell Transformation Neoplastic, Neoplasms, Neoplastic Processes, Neuroectodermal Tumors, Brain Neoplasms, Carcinoma Small Cell, Disease Progression, Colonic Neoplasms, Skin Neoplasms
miR-dis-CORGENES	Pathways in cancer, Prostate cancer, Chronic myeloid leukemia, Melanoma, Small cell lung cancer, Focal adhesion, Glioma, Bladder cancer, Pancreatic cancer, p53 signaling pathway	Signaling Pathways in Glioblastoma, Integrated Pancreatic Cancer Pathway, miRNA regulation of DNA Damage Response, DNA damage response, Lymphocyte TarBase, Adipogenesis, Senescence and Autophagy, G1 to S cell cycle control, DNA damage response (only ATM dependent), miRNAs involved in DDR	TRAIL signaling pathway, Glypican pathway, Glypican 1 network, Syndecan-1-mediated signaling events, IFN-gamma pathway, Plasma membrane estrogen receptor signaling, Signaling events mediated by Hepatocyte Growth Factor Receptor (c-Met),IGF1 pathway, PDGF receptor signaling network, Signaling events mediated by VEGFR1 and VEGFR2	Cancer or viral infections, Neoplasms,, Neoplastic Processes, Cell Transformation Neoplastic, Carcinoma, Carcinoma Small Cell, Neoplasm Metastasis, Epithelial cancers, Neoplasm Invasiveness, Neoplasm of unspecified nature of digestive system

Gene targets were grouped into the following categories: miR-down − CORGENES, miR-up − CORGENES and miR-dis − CORGENES (Fig. 6A) and analyzed for pathway enrichment using WEB-based Gene SeT AnaLysis Toolkit (WebGestalt) (Wang et al., 2013, 2017b; Zhang et al., 2005).

their cross-validation across cohorts and methodologies remain critical for the development of better biomarkers for AD.

Especially important is the formulation of key pre-analytical standards as clear subject recruitment criteria. Considering that 30% cognitively normal people show initial signs of Aβ pathology in the brain, all recruited individuals, including non-demented control subjects, should undergo detailed neuropsychological evaluation, complemented either with CSF analysis or brain imaging. Unfortunately, in

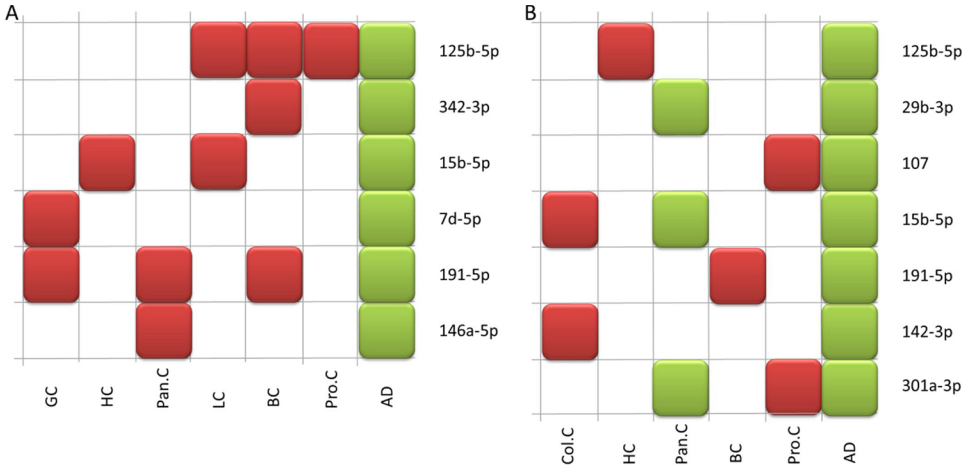


Fig. 7. Comparison of the direction of changes of blood-based miRNAs differential in cancer and AD.
(A) The figure presents the direction of changes of serum-based miRNAs differential in AD and cancer. **(B)** The figure presents the direction of changes of plasma-based miRNAs differential in AD and cancer.
The red color represents upregulation while the green color represents downregulation.
GC- Gastric cancer; Col.C- Colorectal cancer; HC- Hepatocellular carcinoma; Pan.C- Pancreatic cancer; LC- Lung cancer; BC-Breast cancer; Cer.C- Cervical cancer; Pro.C-Prostate cancer.
The 20 concordant miRNAs differential in AD blood were evaluated in the light of the data from a meta-analysis of blood-based miRNAs differential in cancer (He et al., 2015).

the reviewed reports results of CSF and/or imaging biomarker assays were lacking for a number of subjects from both control and AD groups. Moreover, often non-homogenous AD stages and subtypes were compared (Aisen et al., 2017; Dubois et al., 2016). In addition, a verification step in statistically sufficient numbers of subjects should become a gold standard for the biomarker discovery studies to exclude false positive hits and to increase data reproducibility.

Another reason for the inconsistencies between independent reports might be the sensitivity of miRNA signatures to subtle changes related to disease stages and subtypes as well as to genetic and epigenetic background. This sensitivity should not be seen as a disadvantage but rather as a strong advantage of the miRNA-based biomarkers which may accurately reflect complex network alterations. These features make blood-based miRNA panel uniquely suited for the diagnostics of multifactorial AD pathology and for the design of personalized therapeutic strategies.

4. Conclusions

The presented analysis of 34 studies from the last decade, involving a total cohort of 4106 participants, determined 36 circulating miRNAs to be repeatedly altered in the blood of AD patients, regardless of the study design. These 36 miRNAs, emerging predominantly from the analyses of samples obtained from patients presenting with marked clinical symptoms of AD, may represent the most promising biomarker candidates for a diagnostic panel for symptomatic AD. However, the miRNA signatures of pre-symptomatic AD and MCI due to AD are still missing.

These selected miRNAs, circulating in the blood, may originate both from the brain (hsa-miR-146a, hsa-miR-125b and hsa-miR-135a) and the periphery (the majority, e.g. hsa-miR-29b, hsa-let-7f, hsa-miR-34a, hsa-miR-200a-3p, hsa-miR-200b from PBMC), and thus may represent well the systemic nature of the disease. Although their exact role in the disease pathogenesis and their assignment to disease pathways remain uncertain, increasing understanding of the complex miRNA regulatory networks raises a possibility that the miRNA profiles will facilitate the determination of major biological pathways contributing to the pathology in a particular patient and aid the design of personalized therapeutics.

In addition, our analysis revealed that there is a considerable overlap between the sets of miRNAs altered in cancers and in AD. However, the direction of their changes is usually opposite in these disorders. This inverse relationship between cancer and AD on the epigenetic level fits well with the inverse transcriptomic changes identified recently in cancer and neurodegeneration (Aramillo Irizar et al., 2018) and may account for a shift from cancer to neurodegeneration as the main cause of death during aging.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article. No writing assistance was utilized in the production of this manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2018.10.008.

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