Title: Targets and regulation of microRNA-652-3p in homeostasis and disease

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1. Abstract

microRNA are small non-coding RNA molecules which inhibit gene expression by binding mRNA, preventing its translation. As important regulators of gene expression, there is increasing interest in microRNAs as potential diagnostic biomarkers and therapeutic targets. Studies investigating the role of one of the miRNA – miR-652-3p – detail diverse roles for this miRNA in normal cell homeostasis and disease states, including cancers, cardiovascular disease, mental health, and central nervous system diseases. Here we review recent literature surrounding miR-652-3p, discussing its known target genes and their relevance to disease progression. These studies demonstrate that miR-652-3p targets *LLGL1* and *ZEB1* to modulate cell polarity mechanisms, with impacts on cancer metastasis and asymmetric cell division. Inhibition of the NOTCH ligand *JAG1* by miR-652-3p can have diverse effects on angiogenesis and immune cell regulation. Investigation of miR-652-3p and other dysregulated miRNAs identified a number of pathways potentially regulated by miR-652-3p. This review demonstrates that miR-652-3p has great promise as a diagnostic or therapeutic target due to its activity across multiple cellular systems.

Key Words: miR-652, cancer, cardiovascular disease, Notch signalling, mental health

2. Introduction

microRNAs (miRNA) are short 20-24 nucleotide non-coding RNA molecules which modulate gene expression. In the 27 years since the biomodulatory function of miRNA was first described in *C. elegans* [1], miRNA have been identified as a key element in eukaryotic cell regulation [2, 3]. Diverse networks of activity are being characterised for many miRNAs, including miR-652-3p, already known to modulate cell differentiation, proliferation, polarity, and apoptosis pathways [4-7].

In this review, we focus on miR-652-3p in cardiovascular disease, cancer, and other diseases. We describe the utilisation of miR-652-3p in biomarker panels, and we detail the validated gene targets of miR-652-3p and their conservation in humans and mice.

Ever developing knowledge in the field has made miRNA very interesting candidates for use as therapeutics and diagnostic tools. miRNA-based biomarker panels are already available for diagnosis of osteoporosis, cardiovascular disease, and several cancers [8]. Whilst no miRNA therapeutic has yet received FDA approval, several are in phase 1 and 2 clinical trials for both infectious and non-infectious diseases [8, 9]. As the literature surrounding miR-652-3p and its target genes continues to expand, its diverse cellular activities provide great potential as a diagnostic or therapeutic target.

3. Characteristics of miR-652

Human gene *MIR652* is located on the X chromosome, within an intron of *TMEM164*, encoding transmembrane protein 164 [10, 11]. As yet no publications have provided evidence that *TMEM164* is translated in humans. *MIR652* expression is controlled under the *TMEM164* promoter [12], and the pre-miR hsa-miR-652 may be generated by the spliceosome [13]. A second miRNA encoding gene *MIR3978* is also located on a *TMEM164* intron [14]. The encoded miRNA, miR-3978, has been associated with peritoneal gastric cancer metastasis [15], but has not been linked with miR-652-3p.

Expression of miR-652-3p is highest in human myeloid-lineage leukocytes, including circulating monocytes, neutrophils, and eosinophils [16-18]. Deep sequencing data from the FANTOM5 project suggests comparatively low expression of the pre-miR hsa-miR-652 in human lymphocytes [12], though the mouse homologue mmu-miR-652-3p has been shown to affect the differentiation of $CD4^+$ T cells [19]. Mature miR-652-3p is also expressed in human epithelial cells and dysregulation of miR-652 in epithelial cells has been associated with several cancers [20, 21, 7]. Extracellular miR-652-3p has been identified in circulating exosomes [22, 23], and numerous studies have quantitated miR-652-3p from human serum and plasma [24-30].

Dysregulated expression of the passenger strand miR-652-5p has been associated with diabetes and gastrointestinal cancers, and with a model of ischaemia [31-35]. However, deep sequencing data indicates expression of miR-652-5p is much lower than miR-652-3p [12], suggesting miR-652-3p is preferentially bound to Argonaute proteins during biogenesis [36].

Numerous studies are reporting an association or role of miR-652-3p in cardiovascular disease, cancers, mental health and the central nervous system (CNS), and immune regulation. The association of miR-652-3p with these diseases and known targets of miR-652-3p are reviewed here.

4. miR-652-3p in cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of death globally, responsible for 17.8 million deaths in 2017 [37]. miR-652-3p has been implicated in multiple studies of CVD with roles in pathways including atherosclerosis, and myocardial infarction.

Numerous studies have analysed the association of circulating miR-652-3p with CVD, focusing on heart failure. An early study found miR-652-3p upregulated in the plasma of 200 acute coronary syndrome patients [38]. When analysed in combination with existing prognostic markers NT-proBP and LVEF, low miR-652-3p concentration at initial admission was strongly predictive of readmission for heart failure. Ovchinnikova et al. found miR-652-3p expression was significantly downregulated in plasma of heart failure patients [39]. Expression was negatively correlated with heart failure severity and low miR-652-3p concentration was predictive of poor 180-day survival. A follow-up study found miR-652-3p

downregulated in heart failure patients, though not significantly [40]. Further, this study noted a correlation between lower miR-652-3p expression and increased incidence of atherosclerotic lesions [40]. With this evidence suggesting a role for miR-652-3p in human heart failure, studies were conducted in a rat hypertension model and a mouse ischaemic heart failure model [41]. In the rodent models, hypertension and heart failure did not induce significant changes in expression of the miRNAs previously reported to be differentially expressed in humans.

Recent studies have also suggested miR-652-3p as a biomarker of acute kidney injury in heart failure patients. Upregulated miR-652-3p, in conjunction with increased neutrophil gelatinase-associated lipocalin (NGAL), in both serum and urine of patients with heart failure was predictive of acute kidney injury onset [42]. Though, this finding was not seen in a separate study that did not find any correlation between miR-652-3p and NGAL [25]. These differences may be due to the population sampled, methods used to measure miRNA levels or other, as yet unidentified factors.

It has been suggested that miR-652-3p may play a role in regulating coagulation [23]. Low miR-652-3p expression in plasma was found to correlate with low platelet count in venous thromboembolism patients [43]. Low platelet count has been associated with an increased risk of recurrent embolisms [43, 44]. Additionally, low plasma miR-652-3p was associated with increased risk of adverse cardiac and cerebral events in end-stage kidney disease patients, suggesting an increased risk of thrombotic events [45].

Research is ongoing to investigate the involvement of miR-652 in CVD. The most prominent CVD is atherosclerosis, a narrowing of blood vessels caused by a build-up of lipid plaque in the endothelium [46]. Early plaque generation is driven by phagocytosis of low-density lipoproteins by macrophages in the subendothelial space [47]. These macrophages promote atherosclerotic lesion formation through secretion of IL-1α [48]. Huang et al. observed miR-652-3p was upregulated in atherosclerotic plaque of both humans and mice [49]. miR-652-3p was found to target Cyclin D2 (*CCND2*) in human umbilical vein endothelial cells, inhibiting endothelial cell proliferation and enhancing atherosclerotic lesion formation. Cyclin family proteins are cell cycle regulators, and Cyclin D2 was shown to promote cardiac muscle repair in a mouse myocardial infarction model [50]. *In vivo* administration of an anti-miR-652-3p antagomir in mice decreased aortic lesion area, suggesting miR-652-3p inhibition as a therapeutic in atherosclerotic disease [49]. A further study from the same group found miR-652-3p upregulation was associated with dyslipidaemia [51]. Dyslipidaemia predisposes patients to atherosclerosis by lowering nitric oxide (NO) generation from endothelial cells [52]. The transcription factor, insulin gene enhancer protein (ISL1) increases NO production and stimulates vasodilation [53, 54]. miR-652-3p is overexpressed under hyperlipidaemic conditions and targets ISL1, decreasing NO production [51]. Administration of simvastatin, commonly given to treat dyslipidaemia, led to decreased miR-652-3p expression and rescued NO levels in hyperlipidaemic mice [51].

In vivo inhibition of miR-652-3p also limited cardiomyocyte hypertrophy and apoptosis in a mouse myocardial infarction model [55]. Hypertrophic cardiomyocytes upregulated miR-652-3p, inhibiting expression of NOTCH ligand JAG1 (Fig 1). Administration of a miR-652- 3p inhibitor in mice with cardiac hypertrophy resulted in increased cardiac angiogenesis, with no obvious organ toxicity [55]. Notch signalling plays diverse roles in cardiac development and repair, but it is also influential in the immune response [56-58]. *In vitro* Jag1-mediated Notch signalling was found to inhibit apoptosis of rat cardiomyocytes, and promote their proliferation [59]. Furthermore, *Mycobacterium bovis* BCG infection of mouse macrophages increased Notch signalling and inhibited macrophage apoptosis [60]. Additional research investigating the role of miR-652-3p in regulating the NOTCH pathway will be required to elucidate these mechanisms.

In an *in vitro* myocardial infarction model using primary mouse cardiomyocytes, downregulation of miR-652-3p allowed increased expression of MTP18, a controller of mitochondrial fission and apoptosis [61, 5]. This study determined miR-652-3p activity was regulated by the circular-RNA MFACR, which contains numerous miR-652-3p binding sites and acted as a miR-652-3p sponge. This circular-RNA has not been further investigated and as will be discussed later in this review, it is not clear whether miR-652-3p target sites are present in human *MTP18* mRNA transcripts. Together these studies indicate that miR-652-3p may have multiple roles to play in regulating CVD and further research in this area is warranted.

5. miR-652-3p in cancer

Given the wide range of critical cellular pathways controlled by miRNA, it is unsurprising that many miRNAs, including miR-652-3p, are dysregulated in cancer (Fig 2). For example, the miR-34 family is known to downregulate more than 30 oncogenes, and downregulation of miR-34 is associated with multiple cancer subtypes [62, 63]. This very broad influence makes miR-34 a prime target for drug development, though unfortunately no miR-34-based therapeutics have passed clinical trials to date [8]. Cancer is the most studied disease context of hsa-miR-652-3p expression, with miR-652-3p reported to possess both protective and oncogenic roles in different cancer types. These seemingly contradictory activities may be due to the types of tumours, the gene(s) targeted by miR-652-3p, or other as yet undetermined factors. The validation of numerous miR-652-3p target genes in different cancer settings illustrates the regulatory function miR-652-3p plays in key cell processes [6, 7, 20, 21, 64, 65].

Lung cancer

A four-miRNA diagnostic biomarker panel containing miR-652-3p was identified by Andersen et al., differentiating malignant pleural mesothelioma tumour tissue from non-neoplastic tissue [66]. The biomarker classifier analysed the downregulation of miR-126-3p, miR-143-3p, miR-145-5p, and miR-652-3p in tumour tissue, categorising tissue samples with an accuracy of 94% [66]. Another study found miR-652-3p was similarly downregulated in

squamous cell lung carcinoma tumour tissue [67]. Conversely, two other studies found miR-652-3p expression was upregulated in non-small cell lung cancer patient serum and tumour tissue, respectively [7,30]. These expression differences may be influenced by differences in the study size, subject ethnicity or the host response to different lung cancer subtypes. One major issue with measuring miRNA expression is data normalisation. These studies each used different housekeeper RNA to normalise qRT-PCR data, which can lead to conflicting results. A study analysing plasma miRNA of Chinese and Australian tuberculosis patients found the expression of several commonly used housekeeper miRNAs varied significantly between geographical cohorts [68]. Further studies are needed to determine an appropriate housekeeper in these lung cancers.

A 3-marker panel analysing increased serum expression of mir-660-5p, miR-652-3p, and a known lung-cancer biomarker protein Cyfra21-1 was developed for diagnosis of non-small cell lung cancer [30]. A receiver operating characteristic (ROC) curve for this panel had an area under the curve of 0.94 for distinguishing non-small cell lung cancer patients from controls.

The potential that miR-652-3p possesses as a biomarker in a number of cancers suggests this miR is important in cancer biology. How miR-652-3p influences cancer development is now starting to be elucidated.

miR-652-3p was found to be upregulated in tumour tissue of non-small cell lung cancer patients, and promoted tumour metastasis by targeting Lethal(2) giant larvae protein homologue 1 (*LLGL1*) [7]. LLGL1 is considered a tumour suppressor, largely because its activity in cell polarity maintenance prevents metastasis of cancerous epithelial cells (Fig 1) [69]. Upregulation of miR-652-3p in lung tumour cells, and the subsequent inhibition of LLGL1 expression led to an epithelial-to-mesenchymal transition in tumour cells, promoting cell migration and invasion [7]. Interestingly, downregulation of miR-652-3p in pancreatic cancer lines was also found to promote cancer cell proliferation and invasion. In this case miR-652-3p acted by targeting the tumour promoting expression of transcription factor zinc finger E-box-binding homeobox 1 (*ZEB1)* [20]. Increased ZEB1 expression promotes epithelial-to-mesenchymal transition and cell migration by inhibiting translation of *LLGL2*, which performs a similar function to *LLGL1* in many cell types [70-72]. These studies, indicate that *LLGL1* and *ZEB1* targeting by miR-652 can both promote or inhibit cell polarity maintenance. These differences may depend on cell type, tissue location, or disease state and clearly this subject requires further research.

Cell polarity maintained by LLGL activity also influences the polar distribution of NOTCH regulator protein NUMB during cell division (Fig 1), controlling Notch signalling in daughter cells [73]. Considering it also targets a NOTCH ligand, JAG1, miR-652-3p may be an influential regulator of the Notch signalling pathway.

Breast cancer

Along with lung cancers, several studies have identified dysregulated expression of miR-652-3p in breast cancer patients, though no specific target genes have yet been identified. Cuk et al. found that miR-652-3p was upregulated in the plasma of 150 breast cancer patients [74]. miR-652-3p was part of a 7-miRNA panel identified which distinguished benign and malignant breast cancer [74]. The panel was particularly effective in young women (<50 years old), with an area under the ROC curve of 0.86. This study also found miR-652-3p levels correlated with tumour suppressor p53 expression, which is interestingly a predicted target of miR-652-3p on the TargetScan v7.2 database [75]. An additional study established a 4-miRNA serum signature including miR-652-3p which could also identify triple-negative breast cancer patients likely to relapse [29]. Increased expression of the 4 miRNAs was predictive of relapse within 36 months post-surgery.

Interestingly two studies found circulating miR-652-3p expression reduced in Luminal A type breast cancer patients [76, 77]. A biomarker panel analysing decreased miR-652-3p, miR-29a-3p, and miR-181a-5p concentrations in whole blood was able to identify Luminal A breast cancer, with an area under the ROC curve of 0.80 [77]. Indeed, low serum levels of miR-652-3p alone was able to identify both Luminal A and non-Luminal A breast cancers [76].

Discrepancies in circulating miR-652-3p expression reported in breast cancer may be due to the variation between serum and plasma, particularly considering miR-652-3p was identified in circulating exosomes, which are depleted in serum [22]. Alternatively, differences could be attributed to use of different reference controls in miRNA data normalisation. These studies used either small nuclear RNA U6 [74, 29] or miR-16-5p [77] as a housekeeping control, or no housekeeper at all in a ddPCR method [76]. Data normalisation methods can cause significant difference in experiment outcomes, and the use of U6 as a circulating housekeeping RNA has been questioned [78, 79]. A further consideration is the varying sizes the cohorts used. Studies reporting miR-652-3p overexpression in breast cancer used larger cohorts (n=110 and n=210) than those reporting miR-652-3p underexpression (n=59 and n=90). Other factors such as stage of disease at diagnosis, ethnicity, and age may all influence miR-652-3p expression. It may also be that miR-652-3p functions differently in different cancers due to other biological factors.

Gastrointestinal cancers

Gastrointestinal cancers make up 26% of all cancers globally with 5-year survival rates of 24-65%, depending on cancer subtype, and miRNA are already of major interest as diagnostic biomarkers in this field [80-82]. Recent studies have reported dysregulated miR-652-3p in multiple gastrointestinal cancers including oesophageal, gastric, and colorectal cancers.

A small study of two oesophageal cancer patients found high miR-652-3p levels in fixed tumour tissue correlated with poor prognosis [83]. Conversely, a later study by Zhen et al. found miR-652-3p was downregulated in oesophageal tumour tissue [65]. Whilst both

studies analysed squamous cell carcinoma tissues and used similar RNA quantification and data normalisation methods, tissue collection and processing varied significantly [83,65]. Larger studies accounting for comorbidities and environmental factors are warranted to investigate the role of miR-652-3p in oesophageal cancer. Zehn et al. found that transfection of a miR-652-3p mimic in oesophageal cancer cell lines decreased cell proliferation and invasion by targeting fibroblast growth factor receptor 1 (*FGFR1*) [65]. Overexpression of FGFR1 is associated with poor prognosis in several cancer types [84-86], and miR-652-3p appears to play a protective role in this context.

In addition to oesophageal cancer, miR-652 has also been associated with gastric cancer. miR-652-3p was upregulated in the serum of gastric cancer patients, determined through whole-genome sequencing [87]. Shin et al. also found miR-652-3p upregulated in plasma of 50 gastric cancer patients using qRT-PCR. This study identified miR-627-5p, miR-629-5p, and miR-652-3p as an effective diagnostic/prognostic biomarker panel for identification of gastric cancer [88].

Several other studies have found circulating miR-652-3p is increased in serum and plasma of colorectal cancer patients [89, 90]. Pre-cancerous colorectal adenoma could be identified using increased plasma miR-652-3p concentration [90], and an *in silico* analysis of microarray data found increased miR-652-3p concentration in colorectal tumour tissue was associated with poor prognosis [91]. Additionally, a conference abstract reported upregulated miR-652-3p in serum was also associated with poor prognosis in 43 colorectal cancer patients [89]. Interestingly, a further study found low serum miR-652-3p levels were associated with poor prognosis in 322 patients with stage I-III colorectal cancer [28].

These apparently conflicting results in colorectal cancer again highlight important issues with miRNA as biomarkers. miRNA expression can be influenced by many factors including diet, ethnicity, cancer subtype, and environmental factors [92, 93]. In this instance, miR-652-3p was upregulated in American cancer patients compared to healthy controls [90], but no difference was observed in a Chinese population [28]. Differences may also be dependent on the experimental method, as each study used differing sample matrices and methodologies (ddPCR versus qRT-PCR, versus microarray), each with their own miRNA normalisation strategy. Further studies including uniform approaches to normalise biomarker analysis are clearly required.

Other cancers

Dysregulation of miR-652-3p expression has been associated with numerous other cancers, and in many cases a miR-652-3p target gene has been experimentally validated.

miR-652-3p was found to be upregulated in urothelial cells in the urine of bladder cancer patients [94]. This study developed a large and specific 25-miR biomarker panel which included miR-652-3p for non-invasive bladder cancer diagnosis [94]. The role of miR-652-3p in this context is not yet clear. miR-652-3p has been shown to target *KCNN3*, encoding small

conductance calcium-activated potassium channel 3 (SK3). Treatment of the bladder cancer cell lines T24 and J83 with miR-652-3p mimics inhibited SK3 expression and promoted cancer cell invasion [6]. One study found that low SK3 expression in ovarian tumours was associated with poor patient survival [95]. However, a number of other studies have shown SK3 is overexpressed in primary tumours, and that high SK3 expression by cancer cells caused tumour cell invasion and metastasis [96-98]. SK3 expression in these T24 and J83 cell lines is low, compared to primary bladder cancer tissue [97] and this may account for the differences seen between the cell lines and primary cells. Whilst the activity of miR-652-3p in the T24 and J28 cell lines suggests that miR-652-3p does target *KCNN3* in bladder cancer, the in vivo effects of miR-652-3p on bladder cancer require further investigation.

Along with targeting SK3, miR-652-3p has been shown to directly target retinoic acid receptor-related orphan receptor alpha (*RORA*) in endometrial cancer cells [21]. Transfection of the Ishikawa human endometrial cancer cell line with a miR-652-3p mimic decreased RORA expression, leading to increased cell migration and proliferation. RORA was also targeted by miR-652-3p in gastric cancer, where miR-652-3p overexpression was associated with decreased survival [99]. RORA is commonly downregulated in cancers and is reportedly a regulator of p53 anti-tumour activity [100-102].

Downregulated miR-652-3p has also been seen in primary glioblastoma tissues with low miR-652-3p expression associated with poor overall survival [6]. Here miR-652-3p was acting as a tumour suppressor in glioblastoma cell lines, targeting the transcription factor forkhead-box k1 (*FOXK1*), inhibiting cell migration and promoting apoptosis. FOXK1 regulates a variety of cell processes, including aerobic glycolysis and cell differentiation, and is upregulated in many cancers [103]. Transfection of a glioblastoma cell line with a miR-652-3p mimic caused decreased tumour growth when xenografted into nude mice [6].

While downregulation of miR-652-3p has been associated with poor survival in a number of cancers, overexpression of miR-652-3p has also been associated with increased tumour growth. Overexpression of mir-652-3p has been demonstrated in uveal melanoma tissues and in uveal melanoma cell lines [64]. Transfection of these cell lines with a miR-652-3p inhibitor led to decreased cell migration and increased expression of the validated miR-652-3p-target homeobox A9 (*HOXA9*). HOXA9 is a transcription factor regulating diverse processes, including embryonic development and haematopoiesis, and HOXA9 dysregulation is associated with several cancers [104-106]. Increased miR-652-3p expression in uveal melanoma promoted metastatic cell behaviour through modulating HOXA9 activity [64]. mir-652-3p has also been shown to target HOXA9 in human trophoblast cells [4], with inhibition of mir-652-3p leading to decreased trophoblast proliferation and migration.

Upregulated miR-652-3p has been seen in osteosarcoma tissue and osteosarcoma cell lines compared to osteoblast cell lines [107]. Jin et al. suggested miR-652-3p overexpression in osteosarcoma tissue may drive tumour malignancy by targeting the transcription factor Krueppel like factor 9 (KLF9) [108]. Dysregulation of KLF9 has been associated with

development of several cancers [109, 110]. Increased miR-652-3p expression in osteosarcoma cell lines inhibited KLF9 expression and promoted cancer cell invasion [108].

These recent studies highlight the diverse role of miR-652-3p, with both up- and downregulation of this miRNA associated with increased tumour growth and reduced survival. This apparent contradiction in function of miR-652-3p as both a tumour suppressor and tumour promoter is likely due to the multiple targets of miR-652-3p and how it acts on specific tumour or immune cells. Further research is required to fully understand how miR-652-3p is functioning in these different cancers and to determine the therapeutic potential of inhibiting or overexpressing miR-652-3p on tumour function.

6. miR-652-3p in mental illnesses and the central nervous system

Along with multiple roles in numerous cancers, miRNAs, including miR-652-3p, are also being recognised for their roles in mental illnesses and CNS diseases. Knowledge of how neuron function is regulated by miRNA is developing rapidly, with miRNA regulation, including that of miR-652-3p, being described in control systems in the central nervous system, through to neuronal diseases and mental illness [111-113].

A study of miRNA expression in post-mortem schizophrenia patient brain tissue found 6 miRNAs upregulated, including miR-652-3p [114]. A similar analysis found miR-652-3p noticeably upregulated in the frontal cortex of alcoholic patients [115]. In order to develop a non-invasive molecular method of schizophrenia diagnosis, Lai et al. measured miRNA levels in patients' peripheral blood mononuclear cells (PBMCs) [116]. miR-652-3p was upregulated in schizophrenia patients compared to controls, and formed part of a 7-miR biomarker panel able to robustly identify schizophrenia patients. However, a follow-up study found miR-652-3p was notably, but not significantly, upregulated in PBMCs of hospitalised schizophrenia patients [117]. Differing results between the 2 studies may be due a number of factors including recruitment methods, ethnicity, age, cohort size, concurrent medications or other comorbidities, and further studies in this area are required.

miR-652-3p has also been associated with a number of other mental illnesses and CNS conditions. miR-652-3p levels were elevated in the blood of bipolar disorder patients, while plasma miR-652-3p was decreased in patients diagnosed with the recently described internet gaming disorder [118, 119]. Both studies implicated miR-652-3p in dysregulation of the gamma-aminobutyric acid signalling pathway, associated with schizophrenia, bipolar disorder, and alcoholism [120]. The potential use of circulating cells and molecules as accessible markers of mental illness has been under investigation for some time [121], and the mechanisms by which psychiatric conditions interact with circulating leukocytes continue to be elucidated [122].

Studies have also shown an association between upregulated miR-652-3p and the onset of multiple sclerosis in both paediatric and adult patients [123]. Pleckstrin-2 (*PLEK2)*, an *in silico* predicted target of miR-652-3p, was downregulated in the paediatric multiple sclerosis

patients [123]. PLEK2 expression is associated with T cell movement and metastasis of numerous cancers [124, 125], potentially deepening the already discussed role of miR-652-3p as a regulator of cell migration.

Whilst no genes have yet been validated as miR-652-3p targets in nervous diseases, targets validated in other studies have implications in CNS disorders. SK3, targeted by miR-652-3p in bladder cancer [6], has been linked with schizophrenia and bipolar disorder [126, 127]. Additionally, changes in SK3 expression have been associated with myotonic dystrophy [128] and miR-652-3p was also reported to be upregulated in the serum of myotonic dystrophy patients [27].

7. miR-652-3p in other indications

The multifactorial actions of miR-652-3p also extend to reported roles in a number of other diseases. miR-652-3p was upregulated in PBMCs of paediatric patients with type 1 diabetes [35] and downregulated in plasma of pregnant women with pregestational and gestational obesity [26]. Low plasma miR-652-3p levels correlated with high blood glucose and increased weight gain during pregnancy. Similarly, downregulation of miR-652-3p in white adipose tissue was associated with insulin resistance in obese women [129]. Transfection of primary white adipose cells with a miR-652-3p mimic decreased expression of ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) and increased glucose incorporation into lipids. ENPP1 is a regulator of bone and soft tissue mineralisation, and has been associated with obesity, type 2 diabetes, and pathological calcification of soft tissues [130, 131]. Several additional studies have linked *in silico*-predicted miR-652-3p targets with fatty acid metabolism pathways [115, 123], suggesting further investigation into the involvement of miR-652-3p in cell metabolism is warranted.

Downregulation of serum miR-652-3p in liver cirrhosis patients was shown to be highly predictive of cirrhosis disease, but not the aetiology or stage of cirrhosis [18]. In a mouse model of fibrosis, miR-652-3p levels were decreased in the liver tissue suggesting a role for miR-652-3p in immune regulation [19]. Mouse $CD4^+$ T cells transfected with a miR-652-3p mimic expressed significantly lower levels of the Th17 cytokines, IL-17A and IL-22 [19]. In host immunity, down regulation of miR-652-3p may aid this early response to infection. These transfected $CD4^+$ T cells also displayed significantly lower levels of β-arrestin 1 (*ARRB1*), and a luciferase reporter assay confirmed ARRB1 was a target of miR-652-3p [19]. ARRB1 is ubiquitously expressed, and has known functions in T cell regulation [132], TLR signalling [133], and colorectal cancer progression [134], underpinning the role of miR-652-3p in immunoregulation and cancer metastasis [7, 20, 55].

To date, the only communicable disease associated with miR-652-3p is *Mycobacterium tuberculosis* infection. Barry et al. found plasma miR-652-3p levels were lower in active tuberculosis patients compared to healthy controls, and that concentrations remained downregulated throughout the standard 6-month antibiotic treatment [24]. If the patient group was further stratified based on the success or failure of antibiotic treatment, pre-

treatment miR-652-3p levels were significantly lower in treatment failures compared to treatment successes. Additionally, the human monocyte cell line U937 downregulated miR-652-3p following lentiviral-transduction to express *M. tuberculosis* protein Hsp16.3 [17]. Whether the downregulation of miR-652-3p is part of the host immune response or bacterial pathogenesis remains to be elucidated. The expression of proinflammatory cytokines by *Mycobacterium bovis* BCG-infected macrophages is mediated by JAG1/NOTCH signalling [135], further suggesting a role for miR-652-3p in immune regulation [55].

8. miRNAs regularly associated with dysregulated miR-652-3p

To complement analysis of individual miRNA, investigation of miRNA commonly identified as dysregulated together can give insight into which pathways these miRNAs may regulate and can give insight into the physiological pathways altered in specific diseases.

Online Resource 1 details all miRNAs reported as either up- or downregulated where dysregulated miR-652-3p was also reported. Additionally, all studies identifying miR-652-3p as part of a disease biomarker signature are listed in Online Resource 2. Many miRNAs have been identified as dysregulated with miR-652-3p across multiple cancer types (Fig 2), and more still are dysregulated with miR-652-3p across cancer, CVD, and mental health and CNS disorders (Fig 3).

The miRNA most commonly associated with dysregulated miR-652-3p is mir-223-3p. Both were reported as dysregulated in breast cancer, bladder cancer, heart failure, and tuberculosis patients [24, 29, 40, 77, 94]. miR-223-3p regulates myeloid leukocyte differentiation and function [136], with reported functions as either a tumour promotor or suppressor in different cancers [137]. Similar to miR-652-3p, miR-223-3p can inhibit metastasis of cancer cells by targeting ZEB1 [138].

Multiple studies have also reported an association between significant changes in circulating mir-143-3p levels with miR-652-3p, with both miRNAs highly expressed in myeloid leukocytes [16]. Both miR-143-3p and miR-652-3p were reported to be upregulated in non-small cell lung cancer, mesothelioma, and CVD patients, and both downregulated in bladder cancer patients [23, 66, 67, 94]. miR-143-3p regulates the cell cycle by targeting MAPK7, and downregulation of miR-143-3p is associated with progression of several cancers [139, 140]. In a murine model, miR-143-3p expression was controlled by the Jag1/Notch1 pathway in vascular smooth muscle cells [141]. As miR-652-3p inhibits JAG1, this suggests miR-652-3p may regulate expression of miR-143-3p, through inhibition of JAG1 [55].

Similarly, miR-18a-5p has reported protective or pathogenic roles in different cancers [142], and dysregulated expression of miR-18a-5p has been reported with dysregulated miR-652-3p in lung, gastric, and bladder cancers [67, 88, 94]. Both miR-18a-5p and miR-652-3p are overexpressed in non-small cell lung cancer [7, 143]. Moreover, miR-18a-3p and miR-652-3p target RORA in glioma and endometrial cancer, respectively [21, 144], suggesting both miRNAs may regulate similar pathways.

Additional studies have suggested that miR-29a-3p dysregulation may be linked with both miR-181a-5p and miR-652-3p in breast, lung, and gastrointestinal cancers (Fig 2). Studies have shown both miR-181a-5p and miR-29a-3p target VEGF-A to supress angiogenesis in tumours [145, 146]. This is intriguing considering miR-652-3p has been associated with VEGF signalling in colorectal cancer [91], and suggests miR-652-3p could play a protective role in these tumours.

Another miRNA associated with miR-652-3p in multiple conditions is miR-107. Both have been reported to be upregulated in parallel in breast cancer, schizophrenia, and myotonic dystrophy [27, 29, 114]. miR-107 prevents cell cycle arrest and cancer progression by inhibiting CDK6 expression [147]. CDK6 itself is regulated by CCND2, a validated miR-652-3p-target, illustrating the involvement of miR-652-3p cell cycle maintenance [49]. In a similar fashion, a study in glioma cells showed hsa-miR-107 targets NOTCH2 [148], itself a receptor for the miR-652-3p target JAG1 [55]. Expression of miR-107 in macrophages is TLR and NF-κB dependant, and miR-107 was downregulated is response to LPS in mouse macrophages [149, 150]. Moreover, miR-107 and miR-652-3p were both downregulated in human macrophages expressing the recombinant mycobacterial antigen Hsp16.3 [17]. These co-dysregulation analyses highlight the diversity of pathways influenced by miR-652-3p and present interesting avenues for further investigation of miR-652-3p activity.

9. Interspecies conservation of miR-652-3p and its validated target genes

Common practical and ethical limitations associated with obtaining human samples make animal models an attractive alternative for scientific experimentation. Mice are among the most commonly used laboratory animals due to ease of colony maintenance and relatively short breeding cycle. Whilst mouse and human genomes are largely homologous [151], genetic differences between the species can greatly affect phenotypic and experimental outcomes [152].

In order to assess the use of mice as a model of miR-652-3p activity, we performed sequence alignments using the EMBOSS Needle global alignment tool (https://www.ebi.ac.uk/Tools/psa/) for all miR-652-3p targets validated in humans or mice: *ARRB1* [19], *CCND2* [49], *ENPP1* [129], *FGFR1* [65], *FOXK1* [6], *HOXA9* [4,64], *ISL1* [51], *JAG1* [55], *KCNN3* [6], *KLF9* [108], *LLGL1* [7], *MTP18* [5], *RORA* [99,21], and *ZEB1* [20].

mRNA sequences used in this analysis are detailed in Table S2. The mature miRNAs, hsa-miR-652-3p and mmu-miR-652-3p are 100% homologous [153]. However, the target sequences in the genes they are predicted to bind are not all conserved between humans and mice. For instance, the *RORA* 3'-UTR is conserved in mice, with only a single base difference in the binding region (Fig 4a). Target sequences in *ISL1*, *KLF9*, *ZEB1*, and *JAG1* are also well conserved in mice. However, single base differences are present in each gene corresponding to the miR-652-3p 5' seed sequence, known to be influential in miRNA-mRNA targeting [154]. The hsa-miR-652-3p target sites in human *LLGL1* and *ENPP1*, and the mmu-miR-652-3p target site in mouse *Arrb1* are all moderately conserved between the two

species, however, binding of the miR-652-3p seed sequence may be significantly impacted by 3' changes in the target genes. Conservation of 3'-UTR target sites in human *FGFR1* and *FOXK1* in mice is poor, and miR-652-3p is not expected to bind these sites. The validated target site for *Mtp18* in mice is not present in humans.

Two separate studies have validated human *HOXA9* as a hsa-miR-652-3p target. Both studies listed the target sequence predicted by the TargetScan v7.2 database [75]. However, this target sequence is not present within any *HOXA9* mRNA transcripts in the Refseq database for either human or mouse [4, 64]. Rather, it is in a non-transcribed region over 600 bp downstream of *HOXA9* (Fig 4b). This non-transcribed region is also well conserved in mice. The predicted target sequence was validated in both studies using recombinant luciferase reporter constructs [4, 64]. miR-652-3p mimics and inhibitors modulated HOXA9 expression, as determined by western blot, suggesting there may be a second miR-652-3p target site in the *HOXA9* mRNA transcript, or that miR-652-3p could be targeting another protein upstream of HOXA9. Similar to the *HOXA9* target site, the validated miR-652-3p target site in the human *KCNN3* 3'-UTR is not present in known mouse *Kcnn3* mRNA transcripts (Fig 4c), but it is well conserved in the mouse genomic sequence downstream of *Kcnn3* (data not shown).

Though some validated 3'-UTR target sequences are not conserved between humans and mice, this does not necessarily mean miR-652-3p does not target these genes, as some miRNA are known to have several target sites within a single gene. Huang et al. predicted different miR-652-3p target sequences in human and mouse *CCND2*. Two predicted target sites in the human *CCND2* 3'-UTR are not well conserved in mice (Fig 4d), however a predicted target site in the mouse *Cnnd2* coding sequence is well conserved in humans [49]. Western blot data confirmed miR-652-3p targeted both human *CCND2* and mouse *Ccnd2* and the predicted target site in the mouse *Ccnd2* coding sequence was validated by a standard recombinant-gene luciferase assay [49].

Mouse models remain a valuable tool for the elucidation of miR-652-3p activity. The interspecies conservation of miRNA binding sites should be considered when developing investigative models of miRNA activity.

10. Conclusion

The current literature illustrates the diverse roles miR-652-3p plays in maintaining cellular processes, and its contributions to disease pathogenesis. Validated gene targets have implicated miR-652-3p in regulation of cell differentiation, metabolism, proliferation, and apoptosis, and aberrant miR-652-3p expression in these systems can lead to oesophageal, lung, uveal, bladder, endometrial, and pancreatic cancers. Dysregulation of miR-652-3p has been associated with several cardiovascular diseases, with a number of cardiac repair genes confirmed as miR-652-3p targets. The ability of miR-652-3p to target *JAG1*, *LLGL1*, and *ZEB1*, could profoundly influence cell polarity maintenance, cell fate determination, generation of inflammatory immune responses, and initiation or repression of cancer metastasis.

Although miR-652-3p has been identified as a potential biomarker in a number of mental health and central nervous system diseases, the mechanisms by which miR-652-3p is associated with these conditions are yet to be uncovered. The activity of miR-652-3p in infectious disease also remains poorly understood and its association with mycobacterial infection provides an excellent opportunity for further investigation. Continued investigation into the actions of miR-652-3p offers considerable opportunity to develop new diagnostic and therapeutic targets to treat a range of human diseases.

11. Declarations

Funding

MS was a recipient of a UTS Research Excellence Scholarship.

Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest.

Ethics approval

Not applicable

Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

Not applicable

Code availability

Not applicable

Authors' contributions

MS performed the literature search and data analysis, and wrote the manuscript; BS supervised and reviewed the work. All authors have read and approved this final version of the review.

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13. Figures

Fig 1 Regulation of cell polarity and Notch signalling by miR-652-3p. Organisation of cytoplasmic components in epithelial cells and mitotic cells is regulated by the co-inhibitory activity of the PAR complex (composed of PAR3, PAR6, and aPKC) and the Scribble complex (composed of Scribble (SCRIB), DAP-5, and LLGL1 or LLGL2). LLGL1/2 competes with PAR3 to bind aPKC in the apical zone. PAR3 binds and activates aPKC, initiating phosphorylation of LLGL1/2, deactivating LLGL1/2 and transporting it to the basolateral zone. Phosphorylated LLGL1/2 is reactivated and binds the scribble complex in the basolateral zone. ZEB1 prevents the expression of LLGL2, interfering with the regulation of the PAR complex. NOTCH-ligand JAG1 activates NOTCH, causing cleavage of the Notch intracellular domain (NICD) which translocates to the nucleus and activates transcription factors. NUMB inhibits Notch signalling by ubiquitinating NICD, directing it to the proteasome for degradation. During asymmetric cell division, active aPKC phosphorylates NUMB in the apical zone, driving transport of NUMB to basolateral zone. Asymmetric distribution of NUMB during mitosis influences daughter cell phenotype. miR-652-3p inhibits the activity of both ZEB1 and LLGL1, which can either promote or inhibit cell polarity and differentiation of dividing cells depending on cell type, tissue location, and disease. miR-652-3p also inhibits expression of JAG1, controlling Notch signalling activity.

Fig 2 Human miRNAs reported dysregulated with hsa-miR-652-3p in lung cancer, breast cancer, and gastrointestinal cancers. Lung cancers include non-small cell lung cancer and plural mesothelioma. Gastrointestinal cancer includes oesophageal cancer, gastric cancer, and colorectal cancer.

Fig 3 Human miRNAs reported dysregulated with hsa-miR-652-3p in cardiovascular disease, cancer, and mental health and central nervous system diseases. Cardiovascular disease includes acute coronary syndrome, heart failure, venous thromboembolism, and obesity. Cancer includes bladder cancer, breast cancer, oesophageal cancer, gastric cancer, mesothelioma, non-small cell lung cancer, and osteosarcoma. CNS and mental health disease includes alcoholism, bipolar disorder, internet gaming disorder, multiple sclerosis, myotonic dystrophy, and schizophrenia.

Fig 4 mir-652-3p target sequences are conserved between humans and mice. Yellow indicates bases bound by miR-652-3p, as described in published literature. **a** The 3'-UTR of validated miR-652-3p target genes in humans and mice. **b** The *in silico* predicted miR-652-3p target site in *HOXA9* reported in the literature is downstream of the transcribed mRNA. **c** The miR-652-3p target sequence in human *KCNN3* is conserved in the mouse genome, but is not included in known mouse mRNA transcripts. **d** The predicted miR-652-3p binding sites in the human *CCND2* 3'-UTR are moderately conserved in mice. The predicted miR-652-3p binding site in the mouse *Ccnd2* CDS is well conserved in humans.

Online Resource 1 miRNAs dysregulated with miR-652-3p

Online Resource 2 Identified disease biomarker signatures utilising miR-652-3p

Online Resource 3 Sequences used for inter-species alignment analysis of validated miR-652-3p target genes

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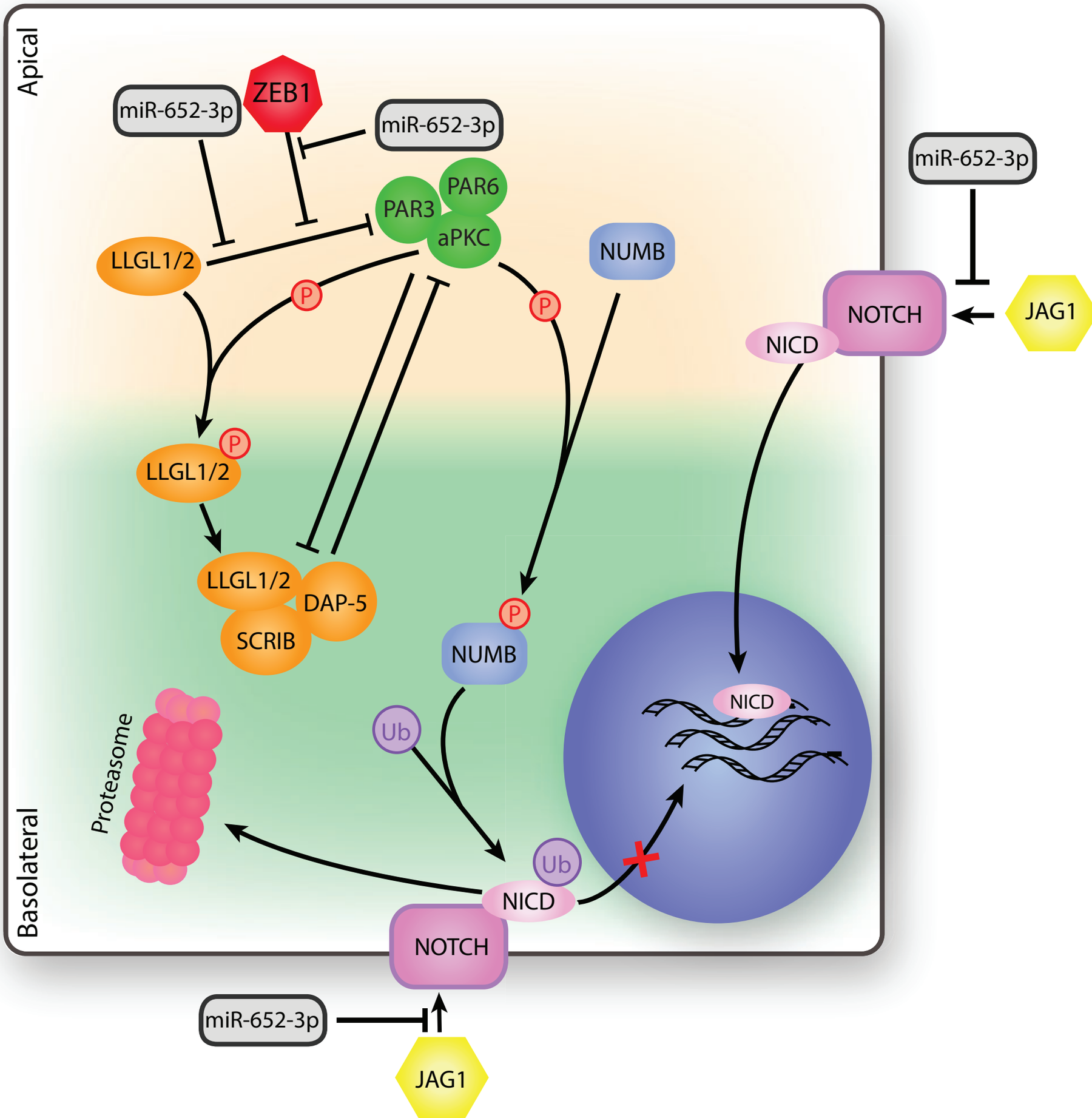
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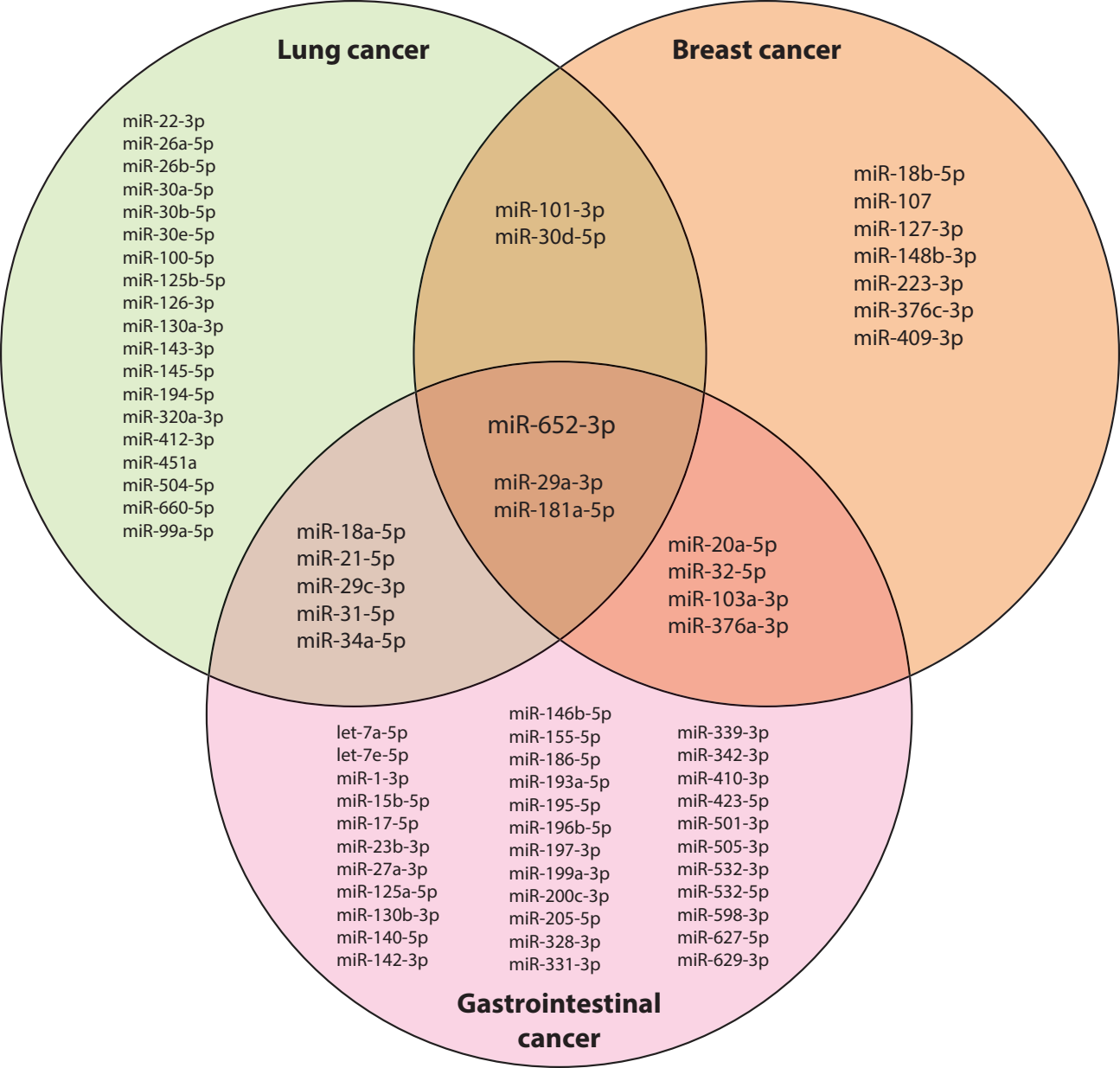
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miR-99a-5p
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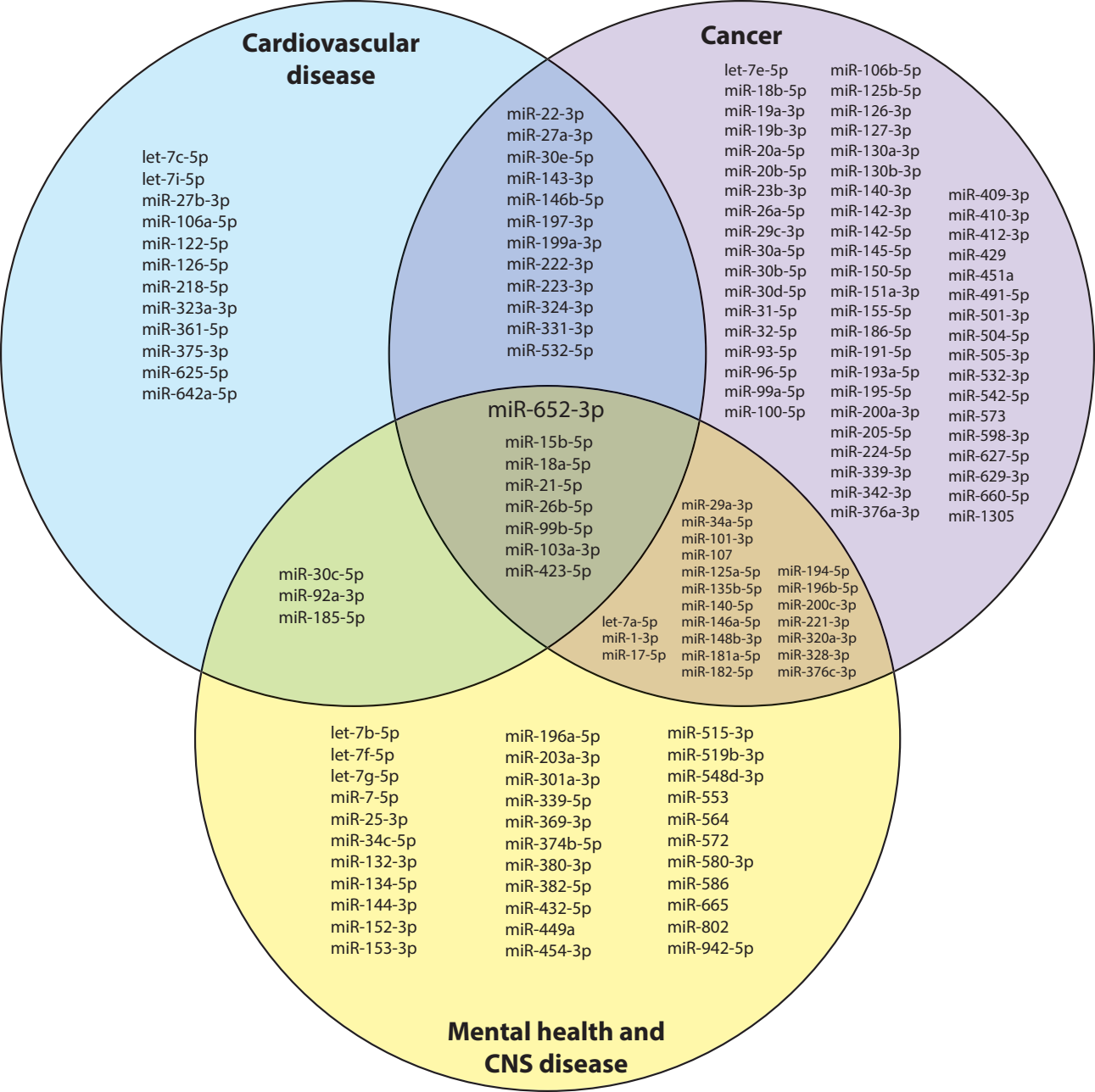
Gastrointestinal cancer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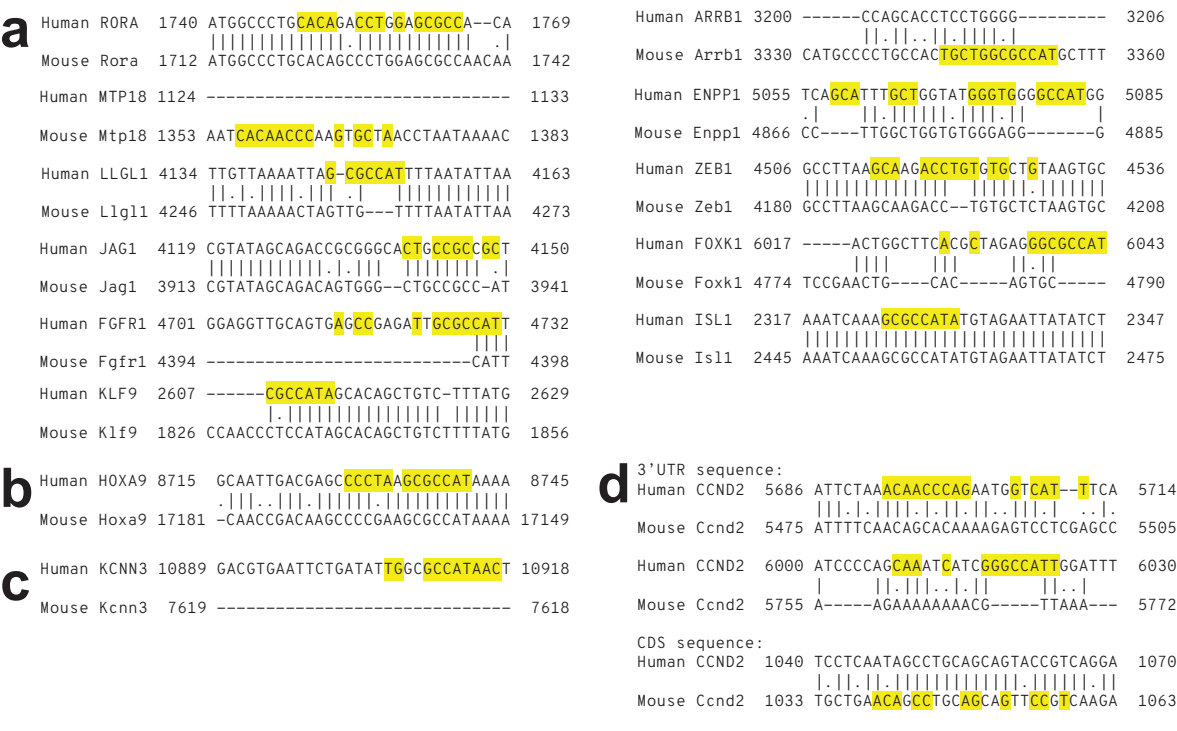
Mental health and CNS disease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