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REVIEW – CANCER RESEARCH

Expression profiles and prognostic value of miRNAs in retinoblastoma

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Abstract
Current cure rates for retinoblastoma (RB) are very high in developed countries. Nonetheless, in less privileged places worldwide, delayed diagnosis and refusal to adhere to treatment still endure an obstacle to improve overall patient survival. Thus, the access to consistent biomarkers for diagnosis at an earlier stage may facilitate treatment and improve outcomes. Over recent years, much attention has been focused on miRNAs, key post-transcriptional regulators that when altered, largely contribute to carcinogenesis and tumor progression. Many of the ~2500 microRNAs described in humans have shown differential expression profiles in tumors. In this review, we summarize current data about the roles of miRNAs in RB along with their value as diagnostic/prognostic factors using electronic databases such as PubMed. We reviewed the importance of miRNA in RB biology and discussed their implications in clinic intervention. Several miRNAs have pointed out reliable diagnostic and prognostic molecular biomarkers. The emergence of targeted therapies has significantly improved cancer treatment. In the near future, the modulation of miRNAs will represent a good treatment strategy.

Keywords miRNA · Cancer · Children · Retinoblastoma · Solid tumor · Review

MicroRNA biogenesis and function

MicroRNAs (miRNA) are small noncoding RNAs with about 18–24 nucleotides that act as post-transcriptional negative regulators by degrading or repressing mRNAs translation (Peng and Croce 2016).

The biogenesis of miRNAs involves transcription, maturation, and incorporation into the RNA-induced silencing complex (RISC) (Fig. 1a). miRNAs are produced from long primary transcripts (pri-miRNAs) catalyzed by RNA polymerase II (RNA pol II) forming hairpin structures. Maturation starts when Drosha/DiGeorge syndrome chromosomal region 8 (DGCR8) complex converts pri-miRNA into a pre-miRNA with about 70 nucleotides with a stem-loop structure. Then, exportin-5 forms a complex with GTP-binding nuclear protein Ran (RanGTP) named XPO5 and transports the pre-miRNA to the cytoplasm. Once in this compartment, Dicer cleaves the pre-miRNA to produce mature miRNAs able to form a complex with RISC and regulate mRNAs translation (Wu et al. 2018a).

Sixty percent of all genes in the human genome display at least one conserved site for miRNA binding (Friedman et al. 2009). Accordingly, these molecules play key roles in all biological processes including growth, senescence, cell division, metabolism, stemness, mobility, apoptosis, etc. (Chen et al. 2013; Follert et al. 2014; Wu et al. 2014; Papaioannou et al. 2014; Hodgkinson et al. 2015). Consequently, dysregulation of miRNAs has also been associated with diverse pathologies, including cancer (Lujambio and Lowe 2012).

miRNAs and cancer

Since their first description, miRNAs have been repeatedly described dysregulated in all types of tumors (Peng and Croce 2016). Different mechanisms have been described as causative of their variation, including altered transcriptional control, epigenetic modifications, chromosomal abnormalities, and defective activity of the enzymes responsible for their biogenesis (Acunzo et al. 2015).

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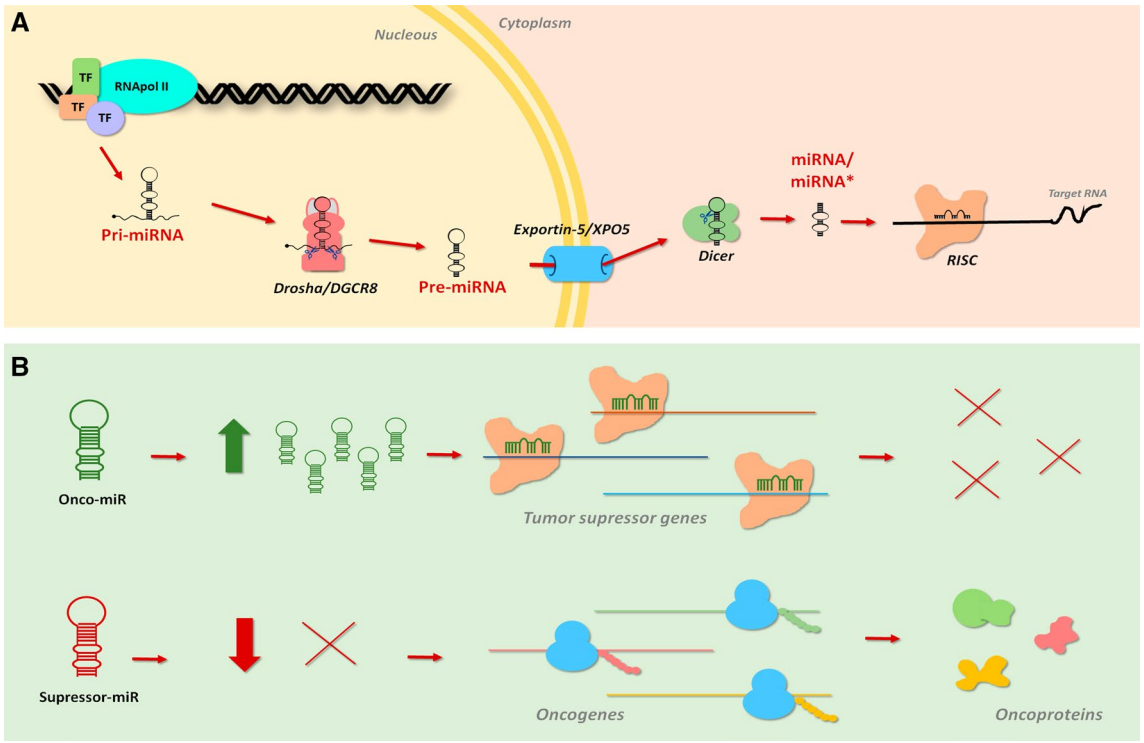

Fig. 1 **a** RNA polymerase II transcribes miRNA genes, generating long primary transcripts (pri-miRNA) which are processed in the nucleus by Drosha yielding hairpin precursors (pre-miRNA) of approximately 70 nt. After being transported to the cytoplasm by exportin-5, Dicer cleaves the pre-miRNA to produce mature miRNAs able to form a complex with RISC and regulate mRNAs; **b** In cancer, miRNAs can act as oncogenes (onco-miRs) favoring cancer progression by the lack of tumor suppressor proteins (upper side); or show tumor suppressor roles inhibiting the synthesis of oncoproteins, decreasing the chance of cancer development/progression (lower side)

Generally, miRNAs have a redundancy of targets and the majority of them can act on multiple mRNAs, from the same or different cellular pathways. Moreover, different miRNAs can inhibit the same mRNA by targeting distinct regions (Tsang et al. 2010).

More than half of all known miRNAs genes are located in genomic regions or in fragile sites related to cancer (Reddy 2015). Moreover, considering that each cell type presents specific mRNA profiles, a particular miRNA can have opposite roles in different cell types. Nonetheless, a plethora of bioinformatic tools currently is available and allows not only the study of the evolutionary conservation of these molecules but also consents the prediction of the interactions between miRNAs and their target mRNAs (Wang et al. 2016).

Experimental models have also been able to confirm the interaction between specific miRNAs and their targets by inducing their overexpression or ablation. As a result, many miRNAs have been described as key gene regulators in all cancer hallmarks and their dysregulation has a great impact on cancer evolution and progression (Berindan-Neagoe et al. 2014). Indeed, miRNAs can be classified according to their function in onco-miRs or tumor suppressors according to their target mRNAs (Fig. 1b). Furthermore, miRNAs have shown diverse roles in all cancer stages, regulating gene expression during initiation, progression, and metastasis. In the view of this, miRNAs have been more recently categorized according to the mechanism they regulate. miRNAs involved in angiogenesis, for example, are known as angiomiRs, while miRNAs described as important during metastases are usually called metastamiRs (Wang and Olson 2009; Hurst et al. 2009; Kim et al. 2018).

Retinoblastoma

Retinoblastoma (RB) is the most common intraocular malignancy in childhood, accounting for 2–4% of all childhood malignancies. Forty-five percent of all RB cases are heritable; 80% are bilateral, 15% unilateral, and 5% bilateral with pineal/midline neuroectodermal tumor (AlAli et al. 2018). This tumor rapidly develops in cells of the retina (Li et al. 2014) with an estimated rate of 1 in 16,000–18,000 live births, and mean age at diagnosis of 27 months for unilateral cases and 15 months for bilateral (Reis et al. 2012; Soliman et al. 2015). Although there are several mutations involved, RB is primarily initiated by inactivation of the *RB1* gene (Martin et al. 2013b), which

plays important roles in cell cycle progression, cell proliferation, survival, and differentiation (Mirakholi et al. 2013). Moreover, patients who carry congenital *RB1* mutations also present predisposition for the development of other types of tumor later in life, including bone, bladder, lung, skin, and brain cancers (Thériault et al. 2014).

Predictors of overall outcome comprehend tumor size, localization, the presence of sub-retinal fluid, and histopathological features (AlAli et al. 2018). RB is now a highly curable tumor (almost 100%) in developed countries. However, there are still disparities around the globe, and most children with RB in developing or economically disadvantaged countries die as a result of late diagnosis/delayed enucleation and poor treatment amenability, what leads to extraocular dissemination and metastasis to other organs including lymph nodes, lungs, bone, central nervous system, liver among others (Canturk et al. 2010; Levy et al. 2014; Traoré et al. 2018). Thus, the progress of miRNAs analysis opens new avenues in the search for clinically reliable biomarkers for RB diagnosis and management.

Differentially expressed miRNAs in RB

Different studies have focused on the involvement of miRNA dysregulation in RB establishment and progression (Fig. 2). The first microarray profiling identified downregulation of let-7b in three RB tumor samples (Huang et al. 2007). However, in a bigger cohort, this miRNA was found up-regulated (Zhao et al. 2009) and had no success as a biomarker at plasma samples (Liu et al. 2014b). Ongoing research showed that downregulation of let-7b, let-7c, and let-7i might be in part associated with the monoallelic loss of Dicer1, which promotes RB tumor formation (Lambertz et al. 2010; Mitra et al. 2012). Moreover, the hypoexpression of other let-7 family members in RB was later described (Danda et al. 2013; Yang and Mei 2015).

Others have shown that miR-34 functions as a tumor suppressor in RB, since its increased expression leads to growth inhibition and promotes apoptosis (Dalgard et al. 2009). This miRNA can be activated by p53, promoting cell cycle arrest and increasing apoptosis through different targets, including *MDMX* and *Sirt1* (He et al. 2007; Dalgard et al. 2009), and *HMGB1* (high mobility group

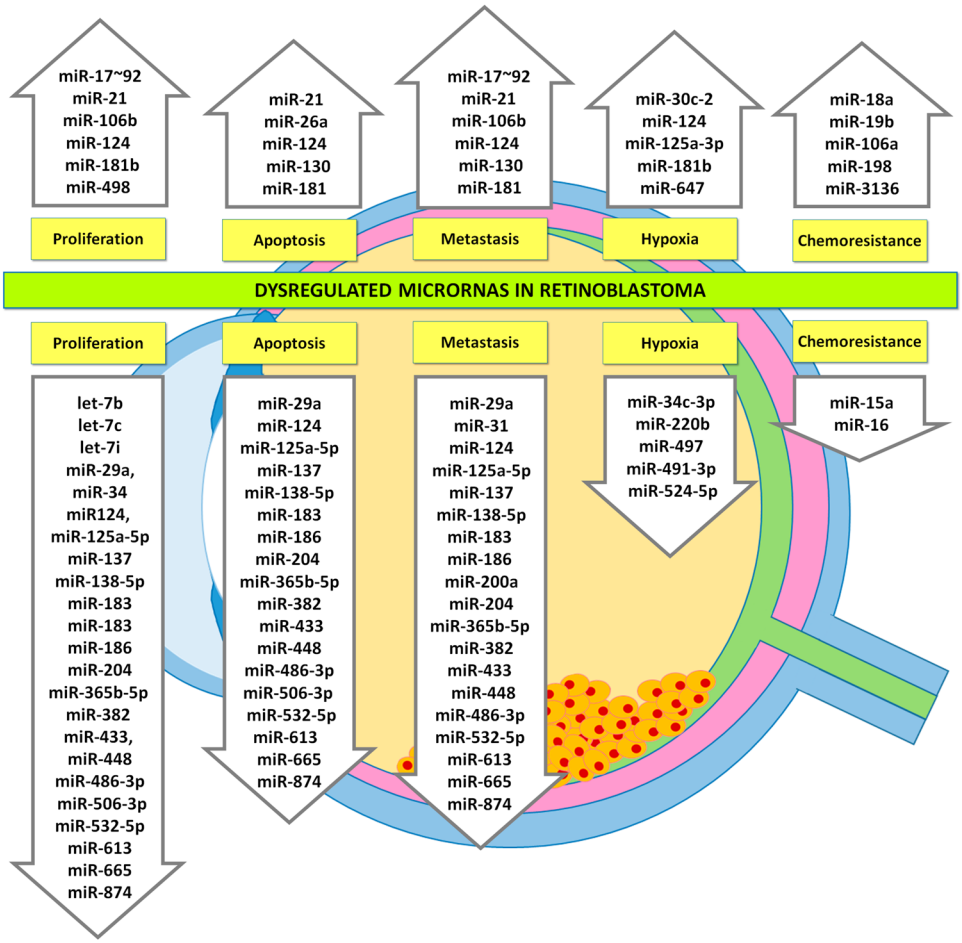

Fig. 2 Dysregulated miRNAS in retinoblastoma according to biological function. Upside and downside arrows designate hyperexpressed and hypoexpressed miRNAs, respectively

box 1), which inhibits autophagy, and consequently, improves chemotherapy response (Liu et al. 2014a). In hereditary RB, a SNP (rs4938723T>C) in mir-34b/c gene could influence risk and may represent a biomarker (Carvalho et al. 2017).

Many other miRNAs also present themselves at low expression levels in RB tumor samples and/or cell lines when compared to normal retina. Martin and colleagues (Martin et al. 2013b) found hypoexpression of miR-129-3p, miR-504, miR-22, miR-139-3p, miR-382 and miR-129-5p in 12 RB tumor samples and in RB cell lines. While Yang and Mei found low levels of miR-125b and miR-181a in three RB samples (Yang and Mei 2015). In addition, expression levels of miR-183, miR-365b-5p, miR-204, miR-433, miR-125a-5p, miR-486-3p, miR-532-5p, miR-124, miR-613, miR-138-5p, miR-186, miR-382, miR-665, miR-29a, miR-874, miR-137, and miR-448 were downregulated in RB, and overexpression of these miRNAs exhibited antitumorigenic effects in RB cell lines, inhibiting tumor growth, migration, and increased apoptosis by targeting different genes and pathways (Wang et al. 2013, 2017; Venkatesan et al. 2015; Li et al. 2016; Zhang et al. 2016, 2017, 2018a, b, c; Song et al. 2017; Liu et al. 2018b; Che et al. 2018; Wu et al. 2018b). Recently it was shown that miR-506-3p is downregulated in RB playing a tumor suppressor role by targeting the mitosis Gene A (NIMA)-related kinase 6 (NEK6) and thus, regulating cell proliferation, cell cycle arrest, and apoptosis (Wu et al. 2018c).

MiR-31 and miR-200a, as well, are significantly reduced, and target genes commonly expressed in RB such as T-cell lymphoma invasion and metastasis 1 (TIAM1), protein kinase C epsilon (PRKCE), and cell-adhesion-Ephrin. Overexpression of these miRNAs inhibited expansion of highly proliferative cell line Y79, but did not restrict the growth of the less aggressive Weri1 cells (Montoya et al. 2015). MiR-145 is likewise downregulated in human RB tissues and cell lines and its restoration suppressed RB cell proliferation and invasion, by targeting ADAM19 (Sun et al. 2015).

On the other hand, the members of the miR-17 ~ 92 cluster (oncomiR-1) (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1 and miR-92a) showed increased expression and synergized with deletions of *Rb* family or loss of p107 leading to tumor promotion, proliferation, and brain metastasis (Conkrite et al. 2011; Busch et al. 2017). Conversely, loss of one miR17~ 92 allele, its knockdown, or the abrogation of its maturation, promotes a delay in RB development, decreasing proliferation and invasion and inducing cell cycle arrest and apoptosis (Kandalam et al. 2012; Nittner et al. 2012; Subramanian et al. 2015). However, miR-17~ 19 members encoded by the same transcript showed heterogeneity in the levels of expression in a more recent study that used an Affymetrix® platform including 2578 mature miRNAs (Castro-Magdonel et al. 2017).

MiR-130 and miR-181 families were also found upregulated and the use of antagomirs in vitro decreased cell viability, invasion, and induced apoptosis (Beta et al. 2014). Several other miRNAs are overexpressed in RB tumor samples and/or cell lines when compared to normal retina, including miR-494, miR-513-1 and -2, miR-518c*, miR-129-1 and -2, miR-198, miR-492, miR-498, miR-503, miR-373*, miR-373, miR-19b, miR-26a, miR-195, miR-22, miR-320, miR-21, miR-449a and -b, miR-221/222, and miR-25 (Zhao et al. 2009; Martin et al. 2013a; Shen et al. 2014; Ding et al. 2014; Yang and Mei 2015; Liu et al. 2018a; Wei et al. 2018). MiR-24 also presented overexpression especially in cell lines and RB tumor samples with *Rb1* loss (To et al. 2012). MiR-21, on the contrary, has a controversial behavior. While described as irrelevant for RB (Zhao et al. 2009), a recent study showed that its inhibition suppresses cell viability, migration, and invasion via inhibition of metalloproteinases MMP2 and MMP9, which play crucial roles during tumor migration and invasion. MiR-21 also showed to affect the PTEN/Pl3k/AKT signaling pathway, responsible for modulated tumor cell proliferation, apoptosis, and invasion (Gui et al. 2016).

MiR-498 has also shown higher levels in RB, and when inhibited, induced apoptosis and decreased cell proliferation, by inhibition of cell cycle progression 1 (CCPG1) (Yang et al. 2018). Likewise, suppression of miR-106b also inhibited Y79 RB cell proliferation and migration through changes in Runt-related transcription factor 3 (*Runx3*) expression (Yang et al. 2017). Along the same line, miR-26a was shown to inhibit the anti-apoptotic and pro-autophagy protein: Beclin 1 (Han et al. 2016).

Furthermore, some hypoxia-related miRNAs (HRM) have been characterized in RB. Xu et al. (2011) for instance, described miR-181b, miR-125a-3p, miR-30c-2, and miR-647 as upregulated while miR-497, miR-491-3p, miR-34c-3p, miR-220b, and miR-524-5p were downregulated in tumor samples. Interestingly, inhibition of miR-181b, the most differently expressed HRM, leads to decreased proliferation (Mitra et al. 2012). Furthermore, miR-181b stimulated the ability of capillary formation of endothelial cells and showed activity on the programmed cell death (PCDD10) and GATA binding protein 6 (GATA6) genes (Xu et al. 2015).

MiR-320 is also overexpressed in RB and targets HIF-1α (Zhao et al. 2009; Liang et al. 2017), inhibiting autophagy in WERI-RB1 cells, under hypoxic conditions (Liang et al. 2017). MiR-124 also presents an autophagy suppressing role, by targeting *metastasis-associated lung adenocarcinoma transcript 1* (*MALAT1*) (Huang et al. 2018) which acts as an oncogene, and promotes cancer proliferation and metastasis (Gutschner et al. 2013).

Furthermore, low expression of miR-15a and miR-16 and a higher expression of miR-198, miR-18a, miR-19b, and miR-106a have demonstrated some involvement with RB

chemoresistance (Mitra et al. 2012). Also, stem-like retinoblastoma cells positive for the multidrug resistance ATP-binding cassette (ABC) transporter ABCG2 do not express miR-3136. Overexpression of this miRNA directly inhibits ABCG2, cell proliferation, and accentuates apoptosis under treatment with several drugs including cisplatin, carboplatin, vincristine, doxorubicin, and etoposide (Jia et al. 2016).

RB-associated miRNAs in clinics

Delayed diagnosis in 6 months may increase the mortality of RB by 70% (Dimaras et al. 2012). Then, a biomarker for its early detection/diagnosis may enable treatment prior to exacerbation and improve cure rates.

Since the first description of circulating miRNAs in lymphoma (Lawrie et al. 2008), their presence in the serum and plasma of patients has been increasingly investigated. Indeed, circulating miRNAs are of paramount importance in the search for specific and reliable biomarkers. These molecules are transported through body fluids in membrane vesicles such as exosomes, and/or associated with ribonucleoprotein particles and act as mediators of intercellular communication in both, paracrine and endocrine manner (Hunter et al. 2008; Stamatopoulos et al. 2015). Since circulating miRNAs are thereby protected from nucleolytic degradation and preserve their integrity in plasma, they are easy to detect and recover, becoming useful non-invasive tools for early detection, diagnosis, monitoring treatment response, and outcome prediction in cancer patients (Lawrie et al. 2008; Jones et al. 2014). Consequently, liquid biopsy has become the least invasive strategy and the less time-consuming to supplement the available diagnostic tools (Heitzer et al. 2015).

So far, only a couple of studies have tested the usefulness of circulating miRNAs as RB biomarkers. The first performed an in silico profiling on 14 pooled sera from children with advanced RB and described 21 upregulated and 24 downregulated miRNAs. From those, the hyperexpression of miR-17, miR-18a, and miR-20a was validated by qRT-PCR (Beta et al. 2013). Later, Liu and co-workers (Liu et al. 2014b) compared the expression patterns of miR-320, let-7e, and miR-2165 in plasma samples from 65 RB affected children with paired controls. Plasma levels of the three miRNAs were downregulated in the patient samples; however, their diagnostic sensitivity and specificity were not considered accurate, what was aggravated by the fact that they had previously been described as hyperexpressed in RB tissue (Beta et al. 2013). Alternatively, the survey for other sources of samples for noninvasive diagnosis has led to consider other fluids from the eye: tears, the vitreous humor, and the aqueous humor (AH) (Tanaka et al. 2014).

Recently, AH samples from the eyes of children with RB have shown to contain elevated levels of various substances, including secreted peptides like survivin and transforming growth factor beta-1 (Shehata et al. 2016). In this regard, Dismuke et al. (2015), though studying samples collected from patients undergoing cataract surgery, described exosomes as a major constituent of AH, identifying ten mature miRNAs through small-RNA sequencing. In the same line, others have been able to successfully profile the miRNA differential expression between glaucoma subtypes in individual AH samples (Drewry et al. 2018). Hence, taking into account its accessibility and independence from other organs, AH has shown to be an attractive font for the study of miRNA secreted by tumor cells (Fig. 3a). Small samples (60–100 µL) can be collected by anterior chamber paracentesis using a small-gauge needle inserted through

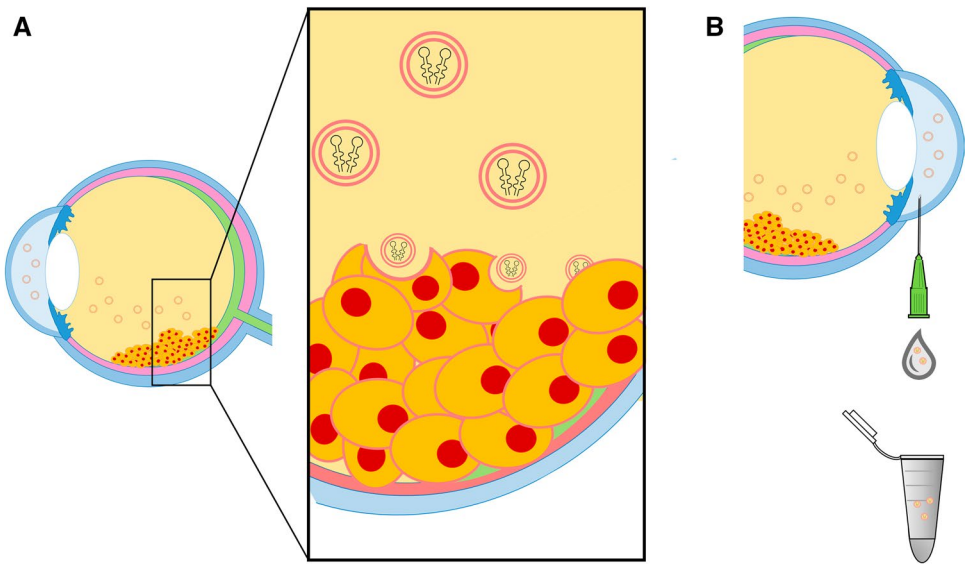

Fig. 3 **a** Tumor-derived exosomes (20–100 nm cellular secreted vesicles) transport miRNAs through body fluids, including those in eye compartments; **b** liquid biopsy can be performed with a small-gauge needle inserted into the anterior chamber and aqueous humor collected by capillarity

the peripheral cornea (Fig. 3b) and easily recover analyzable amounts of RNA (Tanaka et al. 2014; Wecker et al. 2016).

Remarkably, Berry et al. (2017) recently demonstrated the prospect of analyzing AH samples in RB. The small samples (0.1 mL) obtained after primary enucleation and before intravitreous injection of melphalan yielded measurable concentrations of cell-free DNA, RNA, and miRNA. DNA was also obtained in samples collected before enucleating the eye and was likewise useful to confirm the presence of somatic chromosomal alterations through copy number variation profiling. Thus, even though the authors did not confirm their results in plasma from the patients, these findings expand the panorama for the establishment of a noninvasive method for early detection of RB and the identification of specific genetic changes at diagnosis or during treatment.

Thereafter, considering that miRNAs are highly resistant to degradation and their expression levels can be obtained in a few hours with little biological sample (Kong et al. 2012), their examination in AH holds promise for rapid diagnosis and creates hope for personalized RB treatment by molecular modulation.

RB management consists mainly of chemotherapy with typical drugs (carboplatin, vincristine, cyclophosphamide, and doxorubicin) and enucleation (Chintagumpala et al. 2007). However, much evidence shows that only very small portions of systemically administered drugs reach the ocular tissue because the blood–retina barrier limits their entry (Urtti 2006; Short 2008). Other administration routes such as intravitreal injections are being tested for different ocular tumors (Nair et al. 2008), including RB (Shields et al. 2014). Nonetheless, drug delivery through this route may lead to damaging side effects, such as retinal detachment and endophthalmitis. To reduce such complications, several nanotechnology-based manipulations are being investigated (Nair et al. 2008; Joseph and Venkatraman 2017).

MiRNA-based therapy is still preliminary and its applicability is often hindered by inefficient delivery (Nguyen et al. 2008). For systemic administration, some strategies like encapsulation in lipidic or polymer nanoparticles and other formulations have shown promising results in mice models (Tivnan et al. 2012; Janssen et al. 2013, Hsu et al. 2013; Gill et al. 2014; Wang et al. 2015; Liu et al. 2015). Alternatively, the direct injection of RNAs into the vitreous humor engenders great optimism because this compartment presents low endonuclease activity (de Fougerolles et al. 2007) and allows the local uptake from target cells.

The direct intravitreal injection of miR-126, miR-200a or miR-200b mimics prevented the expression of VEGF in the retina of rats and non-human primates (McArthur et al. 2011; Bai et al. 2011; Chung et al. 2016). Another proof-of-concept was observed with the intravitreal injection of a miR-195 antagomir to ameliorate the levels of SIRT1 in animal models with diabetic retinopathy (Mortuza et al. 2014).

Following the same line, some RNAi therapeutics for the treatment of age-related macular degeneration like Bevasiranib (Garba and Mousa 2010) and PF-04523655 (Nguyen et al. 2012) have already entered clinical trials giving promise for the extrapolation of this kind of treatment strategy to other eye diseases, including RB.

Concluding remarks

The potential use of miRNA as diagnostic and prognostic markers in RB has been pointed out by many studies during the past decade. miRNAs with tumor suppressor, oncomir, and treatment resistance roles have been related. Moreover, circulating miRNA have also been explored as biomarkers in RB. In the near future, miRNA-based interventions may become efficient options to improve diagnosis, monitoring disease progression, decide treatment options, and to predict prognosis.

Compliance with ethical standards

Conflict of interest Authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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