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Systematic review of the potential of MicroRNAs in the management of patients with follicular lymphoma

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ABSTRACT

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma and usually presents as an indolent disease. However, some patients present poor outcomes, and FL can transform into more aggressive lymphomas, such as Diffuse Large B cell lymphoma (DLBCL). MicroRNAs (miRNA) are small RNA molecules that participate in posttranscriptional regulation of gene expression, that are emerging biomarkers in cancer. In this systematic review, we included studies evaluating miRNA expression in tumor tissue as diagnosis, transformation or prognosis biomarkers in FL. We identified several miRNAs, which could be diagnostic biomarkers in FL: miR-155-5p and miR-9-3p as miRNAs of potential utility for diagnosis of FL, and miR-150 and miR-17-92 cluster for differential diagnosis between FL and DLBCL. Prognosis and transformation prediction have not been studied in enough depth to draw solid conclusions. Further research is needed to exploit the potential of this field.

1. Introduction

Follicular lymphoma (FL) is the most common indolent lymphoma accounting for about 35 % of all non-Hodgkin lymphomas in developed countries (Sant et al., 2010)., Although FL is considered an incurable disease (except for limited stage FL), most patients present an indolent course and long-term survival (Horning and Rosenberg, 1984). Differential diagnosis between FL and other lymphomas is often of critical importance due to prognostic and therapeutic implications. In addition, there are two subsets of FL patients that present a more aggressive disease with limited survival and poor response to treatment. Thus, their early identification would be of great interest.

First, FL can undergo histologic transformation to an aggressive lymphoma, usually diffuse large B cell lymphoma (DLBCL) of germinal center subtype, but transformation to other histology is also possible. Transformation happens in around 2–3 % of patients annually. Prognosis of patients with transformed FL is generally poor, presenting median overall survival around one to two years. Besides, transformation can also be difficult to diagnose, as it may occur in small areas relative to the total tumor burden that may not be included in diagnostic biopsy. As DLBCL and FL can coexist in the same patient, a correct diagnosis is of extreme importance in this case, since transformation bears prognostic and therapeutic implications. (Casulo et al., 2015; Ban-Hoefen et al., 2013)

Second, early progression, most commonly defined as progression of disease within 24 months after starting therapy (POD24), occurs in around 20 % of patients treated with standard immuno-chemotherapy and has been associated with a poor outcome (Jurinovic et al., 2016). Up to date, some clinical and biological variables have been linked to the risk of POD24 or transformation, such as Follicular Lymphoma International Prognostic Index (FLIPI), histologic grade, or specific somatic mutations, However, these tools are not precise enough detecting high risk patients to allow for guided risk adapted therapy. Therefore, new biomarkers are needed to improve current prognostic tools.

In this sense, microRNAs (miRNAs) are emerging as novel biomarkers with diagnostic and prognostic potential in hematological

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malignancies, such as lymphoblastic leukemia, multiple myeloma or non-Hodgkin lymphoma (Lopez-Santillan et al., 2018; Larrabeiti-Etxebarria et al., 2019). These miRNAs are small, non-coding RNAs with a role in gene expression regulation at the post-transcriptional level. They bind the 3' untranslated region (UTR) of a target mRNA, resulting in their repression or degradation. More than half of human genes are regulated by miRNAs (Kozomara and Griffiths-Jones, 2014), including genes corresponding to the main pathways involved in cancer (Valencia-Sanchez et al., 2006), and many of them have already been involved in cancer pathogenesis, either as oncogenes or tumor suppressors (Johnson et al., 2005; He et al., 2005; Voorhoeve et al., 2006).

In fact, several miRNAs have been involved in the regulation of pathways central to B cell biology. For example, BCR signaling is regulated at different levels by many miRNAs, including miR-34, miR-150 and miR-17-92 family, which have already been involved in low and high-grade B cell malignancies (Musilova and Mraz, 2015). Furthermore, the underlying mechanisms of FL transformation seem to be, at least, partially related with miRNA and other non-coding RNA regulation (Devan et al., 2018; Kumar et al., 2020; Li et al., 2020a). While research about this topic in FL is sparse in comparison to other lymphomas, such as DLBCL (Lopez-Santillan et al., 2018; Larrabeiti-Etxebarria et al., 2019), some potential miRNAs have already been identified (Fassina et al., 2012; Musilova et al., 2018). Therefore, the aim of this review is to assess the value of miRNA expression in FL tumor samples as diagnostic, prognostic, and transformation prediction biomarkers.

2. Methods

We performed a systematic search in PubMed database to identify articles published between January 1960 and March 2020 that analyzed the role of miRNAs in FL using the following search terms: [(microRNA OR miRNA) AND (Follicular Lymphoma)]. Articles were included if they presented original independent data and evaluated the value of miRNA expression in tumor samples as a biomarker for diagnosis, prognosis or transformation risk prediction in human adult patients with FL. We excluded articles not published in English, reviews, case reports, opinion articles, as well as those studies carried out in other animals, cell lines, or other diseases. All the references within the selected studies were also revised in search of additional matches. Two researchers (JAM and ELL) assessed each eligible manuscript independently and disagreements were resolved by consensus. The following information was extracted from each study: publication date, sample source, patients' characteristics, miRNAs studied, methods used for the analysis of miRNA expression, and the list of differentially expressed miRNAs. MiRNAs were named according to current mirBase nomenclature (Kozomara and Griffiths-Jones (2014)).

3. Results

A total of 55 records were initially identified. Among them, 24 were excluded after abstract revision because they did not meet the inclusion criteria; and the remaining 19 articles were included for further analysis. After full text review, we included 12 articles (Fassina et al., 2012; Musilova et al., 2018; Hezaveh et al., 2016; Lawrie et al., 2009, 2007; Malpeli et al., 2018a, b; Pan et al., 2016; Roehle et al., 2008; Takei et al., 2014; Thompson et al., 2016; Wang et al., 2012) and we classified them into the following four non-exclusive groups, depending on their design: 1) FL diagnosis, 2) differential diagnosis between FL and other type of lymphoma, 3) prognosis and treatment response prediction, and 4) transformation prediction (Fig. 1). Characteristics of the studies were summarized in Table 1.

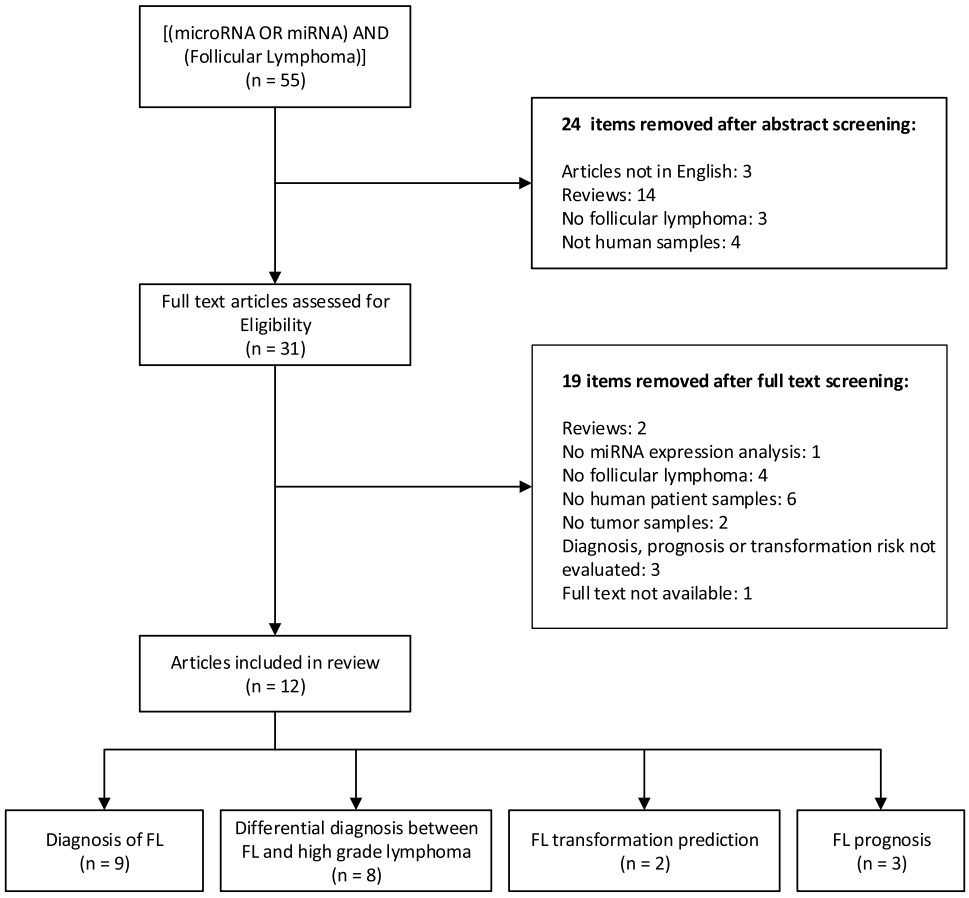

Fig. 1. Flow-chart diagram of study selection. N = Number of records.

Table 1
Summary of included studies.

Study	N	Sample	RNA extraction	Expression analysis	Studied miRNA
Lawrie et al. 2007	49 DLBCL, 27 F L, 6 normal B cell samples	FFPE and fresh frozen tissue	Trizol	qPCR	3 (miR-21, miR-221 and miR-155)
Roehle et al. 2008	58 DLBCL, 46 F L, 7 normal LNs (controls)	FFPE tissue	Recoverall kit (Ambion)	qPCR	134
Lawrie et al. 2009	16 DLBCL transformed from FL, 64 DLBCL, 18 F L.	FFPE tissue	Recoverall kit (Ambion)	Microarray	464
Fassina et al. 2012	36 DLBCL-CG, 18 F L G3. 5 normal LNs (controls)	FFPE tissue	Recoverall kit (Ambion)	qPCR	8 (miR-19b, miR-20a, miR-92, miR-18b, miR-93, miR-106a, miR-150 and miR-210)
Wang et al. 2012	18 F L. 7 Tonsils (controls)	Fresh frozen tissue	miRNeasy Mini Kit (Qiagen)	Microarray, qPCR validation	851
Raju et al. 2016	15 FL, 26 normal B-cell samples from tonsils or blood	Fresh frozen tissue	*Not stated*	Microarray	11
Hezaveh et al., 2016	16 Burkitt Lymphoma, 21 F L, 19 DLBCL	Fresh frozen tissue	mirVana PARIS (Life Technologies)	miRnome sequencing	miRnome
Pan et al. 2016	3 FL, 3 reactive LNs (controls)	FFPE tissue	Trizol	microarray, qPCR validation	miRnome
Thomspson et al. 2018	13 DLBCL (9 transformed), 13 F L,3 reactive LN (controls)	FFPE tissue	Recoverall kit (Ambion)	qPCR	6 (miR-31, miR-99a, miR-95, let-7c, miR-501, and miR-17-5p)
Malpeli et al. 2018a	12 BL, 13 DLBCL, 8PMBL, 17 MCL, 26 F L, 11 reactive LN	Fresh frozen tissue	Trizol	Microarray, qPCR validation	353
Malpeli et al. 2018b	26 F L, 12 reactive LNs (controls)	Fresh frozen tissue	Trizol	Microarray, qPCR validation	353
Musilova et al., 2018	8 FL and 8 DLBCL (transformed FL) paired samples. 18 transformed FLs, 66 non-transformed FL and 41 *de novo* DLBCLs for miR-150 studies	FFPE or fresh LN	High Pure miRNA Isolation Kit (Roche)	qPCR array, miR-150 validated by qPCR	377 (only miR-150 for prognosis studies)

DLBCL: diffuse large B cell lymphoma; LN: lymph nodes; FFPE: Formalin-Fixed Paraffin-Embedded; qPCR quantitative polymerase chain reaction.

3.1. miRNA expression as biomarker for diagnosis in FL

Nine studies analyzed the expression of miRNAs in FL compared to healthy controls (Fassina et al., 2012; Lawrie et al., 2007; Malpeli et al., 2018a, b; Pan et al., 2016; Roehle et al., 2008; Thompson et al., 2016; Wang et al., 2012; Raju et al., 2016). These nine studies provided 82 miRNAs differentially expressed in FL patients. While many miRNAs were reported to be differently expressed in FL compared to controls in only one study, ten miRNAs were concordantly deregulated in two or more studies (Table 2). Remarkably, two miRNAs were repeatedly reported to be up-regulated in FL patients in more than three studies (miR-155-5p and miR-9-3p (Lawrie et al., 2009; Malpeli et al., 2018a, b; Roehle et al., 2008; Wang et al., 2012)).

Table 2
miRNA differently expressed in FL vs normal controls.

miRNA	UP	DOWN	NS	References
miR-155-5p	4	0	0	(Lawrie et al., 2007; Malpeli et al., 2018a, b; Roehle et al., 2008)
miR-9-3p	4	0	0	(Malpeli et al., 2018a, b; Roehle et al., 2008; Wang et al., 2010)
miR-9-5p	3	0	0	(Malpeli et al., 2018a; Roehle et al., 2008; Wang et al., 2012)
miR-21-5p	3	0	0	(Lawrie et al., 2007; Malpeli et al., 2018a, b)
miR-29a-3p	2	0	0	(Malpeli et al., 2018a, b)
miR-210-3p	2	0	0	(Fassina et al., 2012; Roehle et al., 2008)
miR-195-5p	2	0	0	(Malpeli et al., 2018a; Wang et al., 2012)
miR-374a-5p	2	0	0	(Malpeli et al., 2018a; Wang et al., 2010)
miR-20a-5p	2	0	1	(Fassina et al., 2012; Pan et al., 2016; Wang et al., 2012)
miR-320	0	2	0	(Malpeli et al., 2018b; Roehle et al., 2008)

FL: Follicular lymphoma. DOWN: number of studies in which each miRNA is downregulated in FL compared to normal controls. UP number of studies in which each miRNA is upregulated in FL compared to normal controls. NS: number of studies in which each miRNA is not significantly dysregulated in FL compared to normal controls. Normal control source is described in Table 1.

3.2. miRNA expression as biomarker for differential diagnosis between FL and DLBCL

Eight studies analyzed miRNA expression in low grade FL compared to aggressive lymphoma (*de novo* DLBCL (Fassina et al., 2012; Hezaveh et al., 2016; Lawrie et al., 2009; Roehle et al., 2008; Raju et al., 2016), DLBCL transformed from previous FL (Musilova et al., 2018) or both (Lawrie et al., 2007; Thompson et al., 2016)). 57 miRNAs were found to be differently expressed; among them, ten miRNAs were concordantly reported in two or more studies (Table 3). From these consistently upregulated miRNAs in aggressive lymphoma, seven are members of the miR-17-92 family.

3.3. miRNA expression as biomarker for transformation prediction in FL

Two studies explored miRNA expression in FL cases that later transformed into high-grade lymphoma in comparison with those that did not. In the first study, using an array, six miRNAs were differentially expressed in FL that would transform (let-7b, let-7i, miR-221-3p and miR-222-3p were up-regulated in FL cases that later transformed, while miR-223-3p and miR-217-5p were down-regulated) (Lawrie et al., 2009). The other study only analyzed miR-150-5p expression and did not find any difference between FL cases that later develop transformation and those that did not transform (Musilova et al., 2018).

3.4. miRNA expression as prognostic biomarker in FL

Three studies assessed the putative prognostic value of miRNA expression in FL (Musilova et al., 2018; Malpeli et al., 2018b; Wang et al., 2012). The first of them, using an array, identified several miRNAs (miR-664a-5p, miR-194-5p, miR-502-3p, miR-532-3p, miR-1260a, miR-9-5p, miR-9-3p, miR-96-5p, miR-374a-5p, miR-374b, miR-195-5p, miR-221-5p, miR-7-1-3p, miR-454-3p, miR-98-5p, miR-451a, miR-30b-5p, miR-20a-5p and miR-20b-5p) overexpressed in patients

Table 3
miRNA differently expressed in FL vs DLBCL.

miRNA	UP in DLBCL	UP in FL	NS	References
miR-92a-3p*	3	0	1	(Fassina et al., 2012; Musilova et al., 2018; Lawrie et al., 2009; Roehle et al., 2008)
miR-20a-3p*	3	0	1	(Fassina et al., 2012; Musilova et al., 2018; Hezaveh et al., 2016; Lawrie et al., 2009)
miR-106a-5p*	2	0	1	(Fassina et al., 2012; Musilova et al., 2018; Lawrie et al., 2009)
miR-17-5p*	2	0	2	(Musilova et al., 2018; Lawrie et al., 2009; Roehle et al., 2008; Thompson et al., 2016)
miR-19b-3p*	2	0	1	(Fassina et al., 2012; Musilova et al., 2018; Lawrie et al., 2009)
miR-18b-5p*	2	0	0	(Fassina et al., 2012; Lawrie et al., 2009)
miR-200c-3p	2	0	1	(Musilova et al., 2018; Hezaveh et al., 2016; Lawrie et al., 2009)
miR-93-5p*	3	0	1	(Fassina et al., 2012; Musilova et al., 2018; Lawrie et al., 2009; Raju et al., 2016)
miR-150-5p	0	4	1	(Fassina et al., 2012; Musilova et al., 2018; Hezaveh et al., 2016; Lawrie et al., 2009; Roehle et al., 2008)
miR-31-5p	0	2	0	(Musilova et al., 2018; Thompson et al., 2016)

FL: Follicular lymphoma. DLBCL: Diffuse large B cell lymphoma. UP in FL: number of studies in which miRNA is upregulated in FL compared to DLBCL. UP in DLBCL: number of studies in which miRNA is upregulated in DLBCL compared to FL. NS: number of studies in which each miRNA is not significantly dysregulated in DLBCL compared FL. * miRNA members of the miR-17-92 family.

responding to chemotherapy, compared to non-responding patients (Wang et al., 2012). The second study compared samples from patients that relapsed with those who did not, and found that miR-376c-3p, miR-450a-2-3p, miR-431-5p, miR-1-3p, miR-382-5p, miR-19b-3p, miR-522-3p, miR-181a-3p, miR-101-3p, miR-320a-3p, miR-526a-5p, miR-196a-5p, miR-383-5p, miR-144-3p, miR-184 were upregulated and miR-325, miR-302c-5p, miR-330-3p, miR-376b-3p, miR-194-5p, miR-106b-5p, miR-31-5p, miR-410-3p, miR-491-5p were downregulated in patients who relapsed (Malpeli et al., 2018a). In these two studies, patients were treated before the introduction of modern rituximab based immune-chemotherapy protocols. The other study analyzed only one miRNA and showed that low miR-150-5p expression was associated with lower overall survival (Musilova et al., 2018). None of the miRNAs identified was replicated among studies.

4. Discussion

In this systematic review, we present a deep analysis of the current literature regarding miRNA expression in FL as a biomarker for diagnosis, transformation prediction, and prognosis.

4.1. miRNA expression as biomarker for diagnosis in FL

Regarding the suitability of miRNAs as diagnostic biomarkers, nine studies compared miRNA expression between FL and normal controls, providing nine consistently deregulated miRNAs. Two of them (miR-155-5p and miR-9-3p), were shown to be upregulated in more than three studies (Table 2).

These upregulated miRNAs could have a role in lymphomagenesis in FL by silencing tumor suppressors and promoting oncogenic pathways (Table 4). For instance, miR-155-5p is an essential molecule in the control of several aspects of hematopoiesis including B and T lymphopoiesis. In B lineage, this miRNA regulates differentiation of mature B cells into germinal center B cells, a critical step in the pathogenesis of FL (Johanson et al., 2014; Küppers and Stevenson, 2018). It enhances BCR signaling by inhibiting *SHIP1*, an inhibitor of PI3K/ATK pathway. (Cui et al., 2014) Second, it promotes the expression of PD-L1 through directly binding to its 3′-UTR region (Sontheimer and Carthew, 2005; Zheng et al., 2019). This molecule interacts with PD-1 in the membrane of CD8+ cytotoxic lymphocytes, inhibiting their immune response, and may lead to immune escape.

Table 4
pathways and biological effects related to miRNA deregulated in FL.

miRNA	Significance	Targets	Effects in B cells
miR-9-3p	UP in FL	*RCOR1, ITGB1, GNAI1*	Unclear
miR-155-5p	UP in FL	*SHIP-1 C/EBPB, SMAD5, PU.1, AID, PD-L1*	BCR signaling activation. Resistance to growth inhibitory signals. Immune evasion.
miR-150-5p	UP in tFL and DLBCL	*FOXP1, GAB1, CXCR4, MYB*	BCR signaling activation. Increased cell migration.
miR-17-92 family	UP in tFL and DLBCL	*PTEN, BIM, P21, CDKN2A, CD22, FCGR2B*	Reduced apoptosis. PI3K/TK pathway activation. BCR signaling activation. MYC overexpression (miR-92a-3p)

FL: Follicular lymphoma. DLBCL: Diffuse large B cell lymphoma.

In addition, miR-9 is highly expressed in germinal center B lymphocytes and contributes to the regulation of the maturation form GC to plasma cell by enhancing *PDRM1* expression (Zhang et al., 2009). Its role in FL is not well known, but it may be related to impaired maturation and *BCL6* enhancing (Lin et al., 2011).

It is worth noting that these miRNAs are not specific to FL, as some were previously shown to be deregulated in other malignancies. For example, miR-155-5p is upregulated in both FL and DLBCL (Larrabeiti-Etxebarria et al., 2019), and has also been linked to solid malignancies such as breast cancer (Li et al., 2020b). Also, these miRNAs were overexpressed only in one of the three studies that used reactive lymph nodes as controls instead of normal lymph nodes or B cells (Malpeli et al., 2018b). Reactive lymph nodes are a common clinical problem that requires differential diagnosis with low-grade lymphomas (Slack, 2016), thus, whether a miRNA signature could facilitate FL diagnosis in this setting requires further research.

4.2. miRNA expression as biomarker for differential diagnosis between FL and DLBCL

Differential diagnosis between FL and DLBCL is of critical importance as it has prognostic and therapeutic implications. Usually, this can be achieved by morphologic and immunophenotypic studies. However, FL can coexist with DLBCL making diagnosis difficult in some instances. We found eight studies that compared miRNA expression between FL and DLBCL (*de novo* or transformed from FL). Interestingly, among the ten miRNAs with consistent differential expression between FL and DLBCL, seven are members of the miR-17-92 cluster, which has been previously shown to be overexpressed in DLCBL (Fassina et al., 2012; Musilova et al., 2018; Hezaveh et al., 2016; Lawrie et al., 2009; Thompson et al., 2016). MiR-17-92 cluster is formed by three highly conserved miRNA genes that encode a total of 15 miRNAs (Concepcion et al., 2012). This family of miRNAs is upregulated by MYC, a transcription factor that is frequently overexpressed in high-grade lymphomas. This could explain the differences in miR-17-92 found between FL and DLBCL (de novo and transformed from FL). Overexpression of miR-17-92 promotes biological effects that are frequent in DLBCL (Table 4). For instance, members of this miRNA family activate PI3K/ATK pathway by downregulating *PHLLP2* and BCR signaling by inhibiting *CD22*, *FCGR2B*, *PTROT* and *PP2A* (Filip and Mraz, 2020; Jablonska et al., 2017; Psathas et al., 2013), it also inhibits *P21*, which results in increased proliferation and protection from apoptosis. (He

et al., 2005; Jackstadt and Hermeking, 2015; Wang et al., 2010; Zhao et al., 2012). This miR-17-92 family also has a role enhancing *MYC* expression, as miR-92a-3p (a member of this family) promotes MYC activity through inhibiting *FBW7*, which is the substrate recognition component of the SFC complex ubiquitin ligase that marks MYC for degradation. (Olive et al., 2013; Welcker and Clurman, 2008).

It is also worth noting that TP53 deficiency, by mutation or deletion, which is a common alteration in transformed FL, may enhance the oncogenic effect of miR-17-92 family. While miR-92a-3p overexpression results in *MYC* upregulation, it also promotes TP53 dependent apoptosis (Olive et al., 2013). Thus, TP53 deficiency compensates the pro-apoptotic effects of excessive *MYC* transcription, supporting a positive feedback between *MYC* and miR-17-92.

Another interesting miRNA in this regard is miR-150-5p, which is downregulated in *de novo* and transformed DLBCL compared to FL. The expression of this miRNA is also lower in higher grade FL (Grade 3 vs 1–2), suggesting that progressive downregulation of miR-150-5p may be a milestone of FL transformation (Musilova et al., 2018). miR-150-5p expression is also downregulated by MYC, which, as said above, is frequently overexpressed in DLBCL (Musilova et al., 2018), thus, this miR-150-5p downregulation may be reflecting the effects of progressive *MYC* overexpression during transformation. Among the targets of miR-150-5p, *FOXP1* and *GAB1* are positive regulators of BCR signaling. GAB1 recruits PI3K to the membrane, upregulating PI3K/ATR signaling, and FOXP1 activates many genes involved in downstream BCR signaling (Cerna et al., 2019; Mraz et al., 2014). Moreover, *FOXP1* overexpression has other roles in DLBCL biology; for instance, it silences *S1OPR2* expression leading to reduced apoptotic activity, and also enhances NF-kB and Wnt pathways (van Keimpema et al., 2014; Gascoyne and Banham, 2017). All these effects of FOXP1 contribute to greater survival and proliferation, which could explain its role in FL transformation to DLBCL. In fact, FOXP1 has already been linked to high-grade transformation in MALT lymphoma, other low-grade NHL (Craig et al., 2011).

Both miR-17-92 family upregulation and miR-150-5p downregulation in DLBCL when compared to FL have been associated with molecular targets involved in biological effects that could partly explain the more aggressive clinical course in DLBCL and biological differences between these two entities, which make them an interesting source of potential biomarkers and therapeutic targets.

4.3. miRNA expression as biomarker for transformation prediction in FL

While many studies evaluated differential miRNA expression between FL and DLBCL, only two studied the value of miRNA expression as a predictive biomarker for transformation risk assessment, by comparing miRNA expression in samples of FL that later transformed into DLBCL and those that did not transform (Musilova et al., 2018; Lawrie et al., 2009). Transformed FL probably originates from a common progenitor cell that carries driver genetic lesions, such as t(14;18) or mutations in *CREBBP*. These progenitors, over time, produce different sub clones of varied clinical behavior, by acquiring secondary mutations, some of which have been associated with high-grade phenotype and histologic transformation. Frequent genetic alterations in transformed FL include overexpression of genes involved in cell cycle (*MYC*, *FOXO1*, *CARD11*), alterations in epigenetic regulators (*KMT2D*, *CREBBP* and *EZH2*) and damaged response to DNA damage (loss of *TP53*). (Devan et al., 2018; Kumar et al., 2020; Filip and Mraz, 2020; Kridel et al., 2017) It is worth noting, that, as mentioned above, some of this pathways affect miRNA expression. (e.g., MYC downregulates miR-150, which is a suppressor of *FOXP1;* epigenetic alterations can lead to a de-regulated miRnome; and *TP53* defects enhance the effects of oncogenic miRNA (Musilova and Mraz, 2015; Li et al., 2020a).

Accordingly, Lawrie et al. found six transformation-predicting miRNAs: let-7b, let-7i, miR-221-3p and miR-222-3p (both members of miR-221 family) were upregulated in FL that would transform, whereas miR-223-3p and miR-217 were downregulated. Using this six miRNAs, authors could predict nearly 90 % of transformation cases in their retrospective series (Lawrie et al., 2009). While interesting, this finding needs to be validated in further studies. On the other hand, Musilova et al. found that, while miRNA-150 expression is lower in DLBCL as mentioned above, there was no difference in miR-150-5p levels between FL that later develop transformation and those that did not transform. This finding suggests that miR-150-5p is only down-modulated during or after the transformation to DLBCL and, thus, it may be useful as a transformation detection biomarker but not to predict which patients are at higher risk of a future transformation.

4.4. miRNA expression as prognostic biomarker in FL

Three studies evaluated miRNAs as prognostic biomarkers in FL, identifying 46 miRNAs that may have prognostic significance. However, none of these results was validated and further studies would be required. Indeed, two of the studies evaluated tumor samples acquired before the introduction of rituximab in first line treatment of FL, so these results may not be applicable to patients treated with modern immunochemotherapy regimens (Malpeli et al., 2018a; Wang et al., 2010). The last study associated miR-150-5p downregulation with poorer overall survival (Musilova et al., 2018). This finding is consistent with the effects of miR-150 downregulation in BCR activation, a discussed above, and also with the fact that downregulation of miR-150-5p was related to higher grade FL (grade 3 vs 1–2), and transformation to DLBCL (Musilova et al., 2018). It would be interesting to further validate this finding in independent studies.

4.5. Limitations

Several limitations were faced while performing this systematic review, as literature about this topic was scarce and available studies were very heterogeneous in scope and methods. First, methodological variability in sample sources, types of controls and expression analysis could be a source of confounding factors, which may limit comparison of results among studies. Formalin fixed paraffin embedded (FFPE) samples are considered an acceptable source of miRNA, however, expression of miRNA has been shown to be different between FFPE and fresh frozen samples (Vojtechova et al., 2017). Extraction method can also bias miRNA expression analysis, but the methods used in these studies are acceptable for miRNA extraction (Brown et al., 2018; Doleshal et al., 2008). It also is worth noting that results from techniques such as miRNA expression arrays or miRnome sequencing, which test a wide group of miRNA simultaneously, require validation to avoid false positives, preferably by techniques that are more specific and in independent cohorts. However, the most consistently dysregulated miRNAs, such as miR-155-5p for diagnosis and miR-92a-3p for differential diagnosis between FL and DLBCL, are significantly dysregulated in studies using diverse methods (qPCR, expression microarray, qPCR array) (Fassina et al., 2012; Musilova et al., 2018; Lawrie et al., 2007; Malpeli et al., 2018b; Roehle et al., 2008).

Second, many of them studied NHL as a whole, and FL represented a subgroup of the included lymphoma histology, which contributed to a low number of FL samples and hindered FL specific data extraction. In addition, several studies analyzed a limited number of miRNAs. These factors may explain the low replication rate (no miRNA was significantly differentially expressed in more than four studies).

4.6. Conclusion and future directions

MiRNA expression in lymphoma is a growing field of study, in which most research focused on high-grade lymphoma. Nevertheless, in this review we have identified miRNAs with diagnostic potential in FL. The most promising biomarkers are miR-155-5p, miR-21-5p, miR-9-5p and miR-9-3p that can differentiate normal lymphoid tissue from FL and

members of miR-17-92 cluster and miR-150-5p which can differentiate between FL and DLBCL (transformed and *de novo*), and whose aberrant expression may have a central role in transformation to higher-grade lymphoma. The prognostic value of miRNAs in non-transforming FL has not yet been thoroughly researched, but miR-150-5p is an interesting biomarker for future research. The identification of FL patients at high risk of transformation or treatment failure is still an unmet clinical need.

Finally, it is worth noting that miRNAs have been shown to be dysregulated in serum or plasma of patients with multiple cancers, including B-cell malignancies such as DLBCL (Lopez-Santillan et al., 2018), and have been proposed as biomarkers. The identification of such biomarkers allows the study of the malignancies in a non-invasive way, which could be of great interest in FL. However, the expression of miRNAs in tumor samples and serum or plasma is not necessarily correlated, and, since specific studies in serum or plasma of FL patients have not been carried out, such studies are needed. The differential expression of miRNAs in the serum of patients with FL compared with other lymphoma and healthy individuals should be studied, and the prognostic significance of miRNAs should be studied in large cohorts of patients treated with modern therapeutic regimes. While miRnome studies produce large amounts of information and they are adequate for hypothesis generation, in this setting, a more focused approach, studying miRNA that are known to be related to mayor pathways involved in lymphoma, could reduce the risk of bias and false positives. In this review, we have identified some miRNAs that would be interesting for further study in serum or plasma, for example, members of the miR-17-92 family, could serve as non-invasive biomarkers of transformation if they were overexpressed in serum as they are in tumor samples.

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Declaration of Competing Interest

None.

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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.critrevonc.2021.103247.

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