The emerging role non-coding RNAs in B cell-related disorders

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Abstract
Long non-coding RNAs and microRNAs have recently attained much attention regarding their role in the development of B cell lineage as well as participation in the lymphomagenesis. These transcripts have a highly cell type specific signature which endows them the potential to be used as biomarkers for clinical situations. Aberrant expression of several non-coding RNAs has been linked with B cell malignancies and immune related disorders such as rheumatoid arthritis, systemic lupus erythematosus, asthma and graft-versus-host disease. Moreover, these transcripts can alter response of immune system to infectious conditions. miR-7, miR-16-1, miR-15a, miR-150, miR-146a, miR-155, miR-212 and miR-132 are among microRNAs whose role in the development of B cell-associated disorders has been investigated. Similarly, SNHG14, MALAT1, CRNDE, AL133346.1, NEAT1, SMAD5-AS1, OR3A4 and some other long non-coding RNAs participate in this process. In the current review, we describe the role of non-coding RNAs in B cell malignancies.

Keywords: B cell, Immune system, IncRNA, miRNA, Expression

Introduction
B cells are a subset of immune cells which contribute in the induction of humoral responses. These cells can be sub-classified to three classes based on their ontogeny and anatomic localization. B1 cells are produced from B1 progenitors. B cell progenitor cells of the bone marrow can produce the marginal zone and follicular B cells. Notably, B1 lymphocytes are originated from B1 progenitor cells which reside in the hepatic tissue during the fetal period. These cells preserve their self-renewal capacity after the neonatal time. B2 cells are developed from transitional 2 B cells originating from bone marrow precursors and have sustained output all through the adulthood period [1]. Abnormal development of B cells can result in human disorders including immune deficiency, autoimmunity, or allergy [2].

B cells are the principal source of antibodies. A typical example of antibodies produced by B1 lymphocytes is the naturally produced antibodies against ABO blood groups [3]. B1 cells can produce IgM antibodies contributing in the maintenance of tissue homeostasis due to their aptitude to bind with reformed self-antigens. These antigens include those produced in the process of cell apoptosis, ischemic damage and oxidative insult in atherosclerosis [7]. Besides, polyreactive IgA antibodies produced by B1 and follicular B cells participate in the mucosal immunity [4].

In addition, B cells also have an immunomodulatory effect through regulation of immune responses via producing cytokines that impede initiation or progression of immune-related disorders [1].

Several non-coding RNAs have been demonstrated to be involved in the regulation of function of different classes of B cells, thus contributing in the pathoetiology of related diseases. In fact, three classes of non-coding
Several miRNAs have been found to affect function of B cells. This process has been mostly evaluated in the context of immune-related disorders and cancers. For instance, miR-7 has been shown to influence expression of PTEN in B cells. Expression of this miRNA has been increased in MRL*lpr/lpr mouse model of lupus. Treatment with miR-7 antagonist has decreased disease manifestations in these animals. miR-7-related inhibition of PTEN/AKT signaling has enhanced differentiation of B cells into plasmablasts/plasma cells. Moreover, miR-7 silencing has reduced spontaneous formation of germinal center and normalized B cell subtype fractions in the spleen. In addition, miR-7 antagonist has decreased phosphorylation of STAT3 and IL-21 synthesis. Taken together, miR-7 has an important role in regulation of PTEN expression and functions of B cells [9].

Tan et al. have assessed miRNA profiles of naïve, germinal center and memory B cells. They have reported elevation of numerous miRNAs in germinal center B cells. miR-17-5p, miR-106a and miR-181b have been among mostly up-regulated miRNAs in these cells. miR-150 has been a miRNA with high expression in all three B-cell subsets. However, its expression has been found to be lower in germinal center B cells compared with naïve and memory B cells. Notably, expressions of miR-17-5p, miR-106a and miR-181b have been gradually decreased from the dark to the light zone of germinal center. Expression of miR-150 has been inversely correlated with c-Myb and Survivin levels in tonsil tissues, implying potential inhibition of these genes by miR-150 [10].

Several other miRNAs have been found to affect pathogenesis of diffuse large B-cell lymphoma (DLBC). A number of miRNAs have been shown to be dysregulated in these patients. For instance, expression of miR-16–1 has been found to be significantly lower in DLBC patients compared to controls in a single study [11]. Another study has shown differential expression of miR-197 in DLBCL versus controls. While expression levels of miR-197 have not been correlated with clinicopathologic parameters such as international prognostic index, down-regulation of this miRNA has been associated with disease progression in patients treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. Down-regulation of miR-197 levels could predict shorter progression-free survival in this subgroup of patients as well as non-germinal center B-like subgroup. Cell line studies have shown that miR-197 can enhance doxorubicin-associated apoptosis in SUDHL9 cells but not in OCI-Ly1 cells [12].

Another study in the context of sepsis has shown up-regulation of miR-19a in B cells. Moreover, in vitro studies have confirmed over-expression of this miRNA in activated B cells. Expression of CD22 has been initially increased but afterwards reduced. Notably, up-regulation of miR-19a has led to activation of BCR signaling, whereas up-regulation of CD22 has resulted in the attenuation of the effects of miR-19a and enhanced its expression. Taken together, miR-19a and CD22 contribute in establishment of a feedback circuit for B cell responses in sepsis, which can be considered as a putative target for re-establishment of immune homeostasis [13].

miR-30a is another miRNA that participates in the activation of B cells. This miRNA can specifically bind the 3'-UTR of Lyn transcript to inhibit its expression. miR-30a expression has been found to be elevated in B cells of patients with systemic lupus erythematosus (SLE) compared with controls. Moreover, its levels have been negatively correlated with Lyn levels in B cells. Up-regulation
of miR-30a has promoted proliferation of B cells and release of IgG antibodies. Thus, up-regulation of miR-30a can reduce Lyn levels in B cells, indicating its role in induction of B cell hyperactivity in SLE [14].

miR-155 is an example of miRNAs whose functions have been evaluated in different contexts such as rheumatoid arthritis [15], DLBC and non-Hodgkin lymphoma [16] as well as chronic psychological stress [17]. In B cell malignancies, higher levels of miR-155 have been correlated with the presence of B symptoms, involvement of extranodal sites, and high ECOG score [16].

Figure 1 depicts the impacts of miRNAs on regulation of their target genes in the context of DLBCL.

**Contribution of IncRNAs in the regulation of B cell functions and related disorders**

Impacts of IncRNAs on B cell functions have been investigated in malignancies, particularly DLBCL. SNHG14 has been shown to be elevated in DLBCL. Its silencing has decreased proliferation, migration and epithelial to mesenchymal transition (EMT) features in these cells. From a mechanistical point of view, SNHG14 could sponge miR-5590-3p and subsequently enhance expression of ZEB1. Moreover, ZEB1 could activate transcriptional of SNHG14 and PD-L1 to increase immune evasion in these cells. Cumulatively, SNHG14/miR-5590-3p/ZEB1 axis can promote progression of DLBCL and immune evasion in a positive feedback loop. This axis can regulate PD-1/PD-L1 checkpoint [90].

Another study has shown up-regulation of MALAT1, PD-L1 and CD8 in DLBCL tissues, parallel with down-regulation of miR-195. Mechanistically, MALAT1 has been shown to sponge miR-195 to influence PD-L1 levels. MALAT1 silencing has enhanced miR-195 levels and reduced PD-L1 levels. Moreover, MALAT1 silencing has suppressed proliferation, migratory potential and immune escape aptitude of DLBCL cells while increasing their apoptosis. MALAT1 silencing has also inhibited EMT features through modulation of Ras/ERK signaling [91].

NEAT1 is another IncRNA whose expression has been enhanced in DLBCL tissues and cell lines parallel with up-regulation of GLI1 and down-regulation of miR-34b-5p. NEAT1 silencing or miR-34b-5p up-regulation could inhibit proliferation and enhance apoptosis of these cells. In fact, NEAT1 acts as a competing endogenous RNA (ceRNA) to regulate expression the miR-34b-5p/GLI1 axis. Besides, MYC has been shown to modulate NEAT1 expression through directly binding to promoter of NEAT1 [92]. Figure 2 shows the interactions between IncRNAs and miRNAs in the context of DLBCL.

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**Fig. 1** The impacts of miRNAs on regulation of their target genes in the context of DLBCL. Detailed information about these miRNAs is presented in Table 1.
| microRNA       | Expression pattern | Disease/ Sample Description                                     | Cell line                  | Interaction | Signaling pathway | Function                                                                 | References |
|---------------|--------------------|-----------------------------------------------------------------|-----------------------------|-------------|-------------------|---------------------------------------------------------------------------|------------|
| miR-16–1      | ↓                  | 40 untreated patients diagnosed with DLBC and 15 healthy controls | CD19(+) and CD20(+) cells  | –           | –                 | –                                                                         | [11]       |
| miR-15a       | no difference      | 40 untreated patients diagnosed with DLBC and 15 healthy controls | CD19(+) and CD20(+) cells  | –           | –                 | –                                                                         |            |
| miR-150       | ↑ (lower in GC B cell than the other two subsets) | chronic tonsillitis children with chronic tonsillitis | Naive B cells, GC B cells and memory B cells | c-Myb, Survivin and Foxp1 | –                 | ↑ miR-150 ↑ the amount of apoptotic/death cells, ↓ c-Myb, Survivin and Foxp1 | [10]       |
| miR-155       | ↑ (abundantly in synovial B cells) | RA 27 patients with ERA and 33 patients with LSRA, 14 patients with osteoarthritis, 9 healthy controls | B cells, CD19+ cells, synovial B cells | PU.1 | –                 | ↑ RA B-cell activation associated with autoantibody production ∆ miR-155: ↓ anti-body synthesis | [15]       |
| viral miR-BHRF1 | ↓                  | EBV-immortalized B lymphoblastic cell malignancy | –                           | Ramos and BJAB, Manassas, VA, B95.8, HEK293 | SMAD3, JUN, and COL1A | TGF-β signaling pathway | LA: ↓ viral miR-BHRF1-1: ↑ adhesion and the growth of EBV-infected B cells | [18]       |
| miR-28        | ↓                  | BL                                                              | –                           | GC B cells, HEK293T cells and B-cell lines | MAD2L1, BAG1, MYC | –                                                                         | ↓ proliferation and clonogenic properties of BL cells, MYC-induced transformation | [19]       |
| miR-19a       | ↑                  | sepsis 64 patients with SIRS and 15 healthy controls            | PBMCs                       | CD22        | BCR signaling     | ↑ BCR signaling                                                          | [13]       |
| miR-30a       | ↑                  | SLE patients with SLE and healthy controls                     | Daudi and Raji B cell lines | Lyn         | –                 | ↑ B cell proliferation and the production of IgG antibodies through inhibiting Lyn | [14]       |
| microRNA | Expression pattern | Disease/ Sample | Cell line | Interaction | Signaling pathway | Function | References |
|----------|--------------------|-----------------|-----------|-------------|------------------|----------|------------|
| miR-194  | ↓                  | PTLD            | PBMC or lymph node from six PTLD patients and 4 healthy blood donors | A5S, J87, JC62, MF4, VB5, ZDB derived from PBMC or lymph node of six PTLD patients and 8 lymphoblastoid cell lines isolated from 4 healthy blood donors | IL-10   | –          | Expression of microRNA-194 was suppressed by EBV microRNA-194 inhibited IL-10 expression, so reduced proliferation and promoted apoptosis of EBV (+) B cell lymphoma lines | [20] |
| miR-125b | ↑                  | –               | –         | murine Bcl1.3B3 B lymphoma and the human U266 multiple myeloma cell lines | BLIMP-1 and IRF-4 | –          | ↓ differentiation of GC centroblasts and myeloma cell survival through inhibiting BLIMP-1 and IRF-4 translation | [21] |
| miR-148b | ↓                  | BCL             | Peripheral blood from 21 patients with BCL and 18 healthy controls, Lymphatic tissue from 30 patients with BCL and 20 healthy controls, male BALB/c nude mice | Raji and SU-DHL-10 human BCL cell lines, HEK-293 T | Bd-w   | –          | ↓ cell viability, colony formation, and ↑ apoptosis in irradiated BCL cells, ↓ growth of tumors in nude mice (↑ radiosensitivity of BCL cells) | [22] |
| miR-197  | ↓                  | DLBCL           | 51 patients with DLBCL | SUDHL9 and OCH-LY1 human DLBCL cell lines | –       | –          | ↑ miR-197, ↑ effects of doxorubicin on reducing cell viability and enhancing apoptosis | [12] |
| miR-124  | ↓                  | DLBCL           | –         | OCH-Ly1 and HBL1 | p65     | –          | ↓ cell proliferation and survival | [23] |
| microRNA      | Expression pattern | Disease/Sample | Cell line | Interaction | Signaling pathway | Function | References |
|---------------|--------------------|----------------|-----------|-------------|-------------------|----------|------------|
| miR-17–92     | ↑                  | B-NHL          | WT, KO and TG lymphoma cells and reactive hyperplasia lymph cells obtained from mice | –           | –                 | ↑ miR-18; ↓ OS | [24]       |
|               |                    |                |           |             |                   | ↑ miR-19 and miR-92a; ↓ OS and EFS |          |
|               |                    |                |           |             |                   | ↑ miR-17–92; ↓ the duration of incubation required for visualization of the xenograft tumor |          |
| miR-155       | –                  | DLBCL          | DEPTOR and c-CBL | BCR signaling | –                 | ∆ mir-155: ↓ expression of NFkB target genes and ↑ sensitivity DLBCL cells to ibrutinib | [25]       |
|               |                    |                |           |             |                   | Low expression of DEPTOR (a target of mir-155) increased the migration of DLBCL cells toward the CXCL12 gradient and modulated cytokine production |          |
| miR-320d      | ↓                  | DLBCL          | CDK6      | –           | –                 | ↓ proliferation in GCB type of DLBCL cells and ↓ CDK6 expression | [26]       |
| miR-195       | ↓                  | DLBCL          | –         | –           | –                 | Expression levels of miR-195 closely correlated with tumor diameter, IPI score and Ann Arbor stage | [27]       |
| microRNA | Expression pattern | Disease/ Sample | Cell line | Interaction | Signaling pathway | Function | References |
|----------|-------------------|-----------------|-----------|-------------|-------------------|----------|------------|
| miR-155 | ↓ in vincristine-resistant DLBCL cell lines | DLBCL | 73 patients with DLBCL, GEO database: data (GSE10846 and GSE31312) | U-DHL-5 and OCI-Ly7 GCB-DLBCL cell lines, RIVA and NU-DHL-1 ABC cell lines | Wee1 (a direct target of miR-155) | – | ↑ sensitivity to vincristine |
|          |                   |                 |           |             |                   |          | Expression level of miR-155 was strongly correlated with superior survival for R-CHOP-treated patients of the GCB subclass | [28] |
| miR-153-3p | ↓ in IM-resistant CML cells | CML | Blood samples obtained from 44 CML patients | human KBMS, K562 and IM-resistant KBMSR, K562R CML cell lines | Bcl-2 (a direct target of miR-153-3p) | – | ↑ miR-153-3p ↑ IM sensitivity and ↓ the survival rate of IM-resistant CML cells ↓ autophagy caused by IM in IM-resistant CML cells | [29] |
| miR-30c | ↑ in patients with PCNSL, SCNSL | PCNSL, SCNSL | 61 CSF samples from patients with PCNSL and 14 samples from SCNSL | – | – | – | miR-30c could act as a biomarker to distinct PCNSL from SCNSL | [30] |
| miR-155 | ↑ | NHL and DLBCL | 84 patients with B-cell NHL and 15 healthy controls | – | – | – | Higher levels of miR-155 were correlated with the presence of B symptoms, involvement of extranodal sites, and high ECOG score in DLBCL; higher levels of miR-155 were correlated with non-germinal B-cell-like type, the presence of B symptoms, involvement of extranodal sites, and higher IPI and ECOG scores | [16] |
| microRNA   | Expression pattern | Disease/ Sample                                                                 | Cell line                                                                 | Interaction | Signaling pathway | Function                                      | References |
|------------|--------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------|------------------|-----------------------------------------------|------------|
| hsa-miR-34a-5p | ↑                  | DLBCL six serum samples from patients with DLBCL and 3 healthy control        | –                                                                         | TP53        | p53 signaling pathway | hsa-miR-34a-5p was involved in 15 pathways such as the p53 signaling pathway | [31]       |
| hsa-miR-323b-3p | ↓                  | DLBCL six serum samples from patients with DLBCL and 3 healthy control        | –                                                                         | –           | –                | hsa-miR-323b-3p was involved in four pathways such as pathways in cancer |           |
| hsa-miR-431-5p | ↓                  | DLBCL six serum samples from patients with DLBCL and 3 healthy control        | –                                                                         | FYN         | –                | regulating FYN                                |           |
| miR-155    | ↑ in EBV-infected B cells | lymphoma six serum samples from patients with DLBCL and 3 healthy control | DG75 cell line originated from an EBV-negative BL, DG75 RBPJ knockout cell line derived from DG75 wt parental cells, IB4 and GM12878 obtained from Coriell Cell Repositories (EBV-immortalized lymphoblastoid cell lines) | EBNA2, IRF4, RBPJ | –                | ↑ the growth of EBV-infected B cells | [32]       |
| miR-3173   | ↓                  | B-ALL GEO database (GSE4732, GSE4475, GSM565540) 135 children with B-ALL and 97 healthy controls plus 430 children with B-ALL and 340 healthy controls | CCRF-SB and SUP-B15 human B-ALL cell lines CRL-2630 PTEN (a direct target of miR-3173) | PTK2        | –                | ↓ proliferation, migration and invasion | [33]       |
| miR-21     | ↑                  | B-ALL 75 children with B-ALL and 50 healthy controls                           | –                                                                         | –           | –                | Lower DFS and OS                              | [34]       |
| miR-21     | ↑                  | DLBCL 36 tissue samples from 26 patients with DLBCL and 10 healthy controls   | CRL-2630                                                                  | PTEN        | –                | higher in stage III/IV patients, ↓ apoptosis (by regulating the expression of PTEN) | [35]       |
| microRNA          | Expression pattern | Disease/ Sample | Cell line                          | Interaction | Signaling pathway | Function                                      | References |
|-------------------|--------------------|-----------------|------------------------------------|-------------|-------------------|-----------------------------------------------|------------|
| miR-222-3p        | ↑                  | DLBCL           | HMy2:CIR human normal B-cell immortalized cell line, DLBCL cell line, germinal central B-cell (GCB)-like OCH-Ly9 and SU-DHL-4, and ABC-like OCH-Ly10 and U2932 | Phosphatase 2 regulatory subunit B alpha (a direct target of miR-222-3p) | –                  | ↑ proliferation, invasion and tumor growth, ↓ apoptosis | [36]       |
| miR-29a           | ↓                  | SLE             | Raji, HMy2:CIR human normal B-cell immortalized cell line, DLBCL cell line, germinal central B-cell (GCB)-like OCH-Ly9 and SU-DHL-4, and ABC-like OCH-Ly10 and U2932 | CRKL (a target gene of miR-29a) | –                  | ↓ the production of IgG (by regulating CRKL) | [37]       |
| hsa-miR-223-3p and hsa-miR-21-5p | ↓ from stage I to stage III of PBC | PBC              | Peripheral B cells from 72 PBC patients and 15 healthy controls | mutual 4 target genes: TGFBR2, MEF2C, FOXP1 and RBPJ | –                  | modulating B cell functions, such as B-cell signal transduction, differentiation, migration, and apoptosis in GO categories | [38]       |
| miR33b, miR96, and miR503 | ↓                  | Lymphoma        | Jeko-1, Pheiffer, SUDHL-2, PDX, and A20 | PRMT5, CYCLIN D1 and c-MYC (target genes of miR33b, miR96 and miR503) | –                  | ↓ lymphoma cell survival | [39]       |
| miR-214           | ↓                  | DLBCL           | OCH-Ly3, SU-DHL-2 and OCH-Ly10 human DLBCL cell lines, a normal B-cell line (NBC) and HEK-293T | PD-L1 | –                  | ↓ viability and invasion, ↑ apoptosis | [40]       |
| miR-107           | ↓                  | ABRM            | B lymphocytes, Daudi, Raji, and HEK-293 | ATG12 | –                  | ↑ miR-107, ↓ formation of autolysosomes in B lymphocytes of recipients, autophagy and secretion of IgG and IgM antibodies | [41]       |
| miR-92a           | ↑ in PMBL than in DLBCL, but not in cHL | PMBL, DLBCL, cHL | Karpas-1106P, SU-DHL-5 | FOXP1 (a target of miR-92a) | –                  | ↓ proliferation, ↑ apoptosis, | [42]       |
| microRNA | Expression pattern | Disease/ Sample | Cell line | Interaction | Signaling pathway | Function | References |
|----------|-------------------|-----------------|-----------|-------------|-------------------|----------|------------|
| miR-21  | ↑                 | DLBCL           | SU-DHL-8, OCH-LY1, and SU-DHL-10 | VHL (a target of miR-21) | –                 | Curcumin decreased the proliferation, migration, and invasion abilities and increased apoptosis by suppressing miR-21 | [43] |
| miR-155 | ↑                 | DLBCL           | DB cells  | –           | –                 | ↑ migration and invasion, ↓ apoptosis | [44] |
| miR-215 | ↓                 | DLBCL           | SU-DHL-4 cells | KDM1B | –                 | ↓ proliferation and ↑ apoptosis Low levels of miR-215 were correlated with shorter 5-year OS | [45] |
| miR-155 | ↑ in tonsillar memory B cells and PBMCs activated with CpG | DS | PBMCs and Tonsils from healthy controls and children with DS | AID (a target of miR-155) | –                 | miR-155 played a role in DS-associated dementia and leukemia | [46] |
| miR-125b | ↑ in tonsillar memory B cells and plasma cells | DS | PBMCs and Tonsils from healthy controls and children with DS | – | – | miR-125b played a role in DS-associated dementia and leukemia | [45] |
| miR-98  | ↑                 | asthma          | PBMCs from healthy controls and patients with asthma | TSP1 | –                 | IL-13 decreased TSP1 expression through up-regulating expression of miR-98 in B cells | [47] |
| miR-28-5p | ↓                | DLBCL           | OCH-LY7 human GCB-type DLBCL cell line and HEK-293 T | BECN1 (a direct target of miR-28-5p) | –                 | Curcumin: ↑ miR-28-5p; ↓ proliferation and autophagy, ↑ apoptosis | [48] |
| miR-21  | ↑                 | DLBCL           | –          | KI-67       | –                 | High expression levels of miR-21 was correlated with poor response to treatment | [49] |
| microRNA | Expression pattern | Disease/ Sample | Cell line | Interaction | Signaling pathway | Function | References |
|----------|--------------------|-----------------|-----------|-------------|------------------|----------|------------|
| miR-10a  | ↓                  | DLBCLs          | OCI-LY7 and OCI-LY3 human DLBCL cell lines and HKB293T | BCL6 (a direct target of miR-10a) | – | ↓ proliferation, ↑ apoptosis | [50] |
| miR-125a | ↓                  | AML             | HL60      | p53, Bcl-2, c-myc | NF-k Pathway | ↑ viability and invasion, ↑ apoptosis | [51] |
| let-7b-5p | ↑                  | ITP             | PBMC from peripheral CD19+ cells | BAFF, BAFF-R, NF-xB2 p100, Bcl-xL | – | ↑ B cell survival, ↑ BAFF-R and BAFF levels, ↑ phosphorylation of NF-xB2 p100 | [52] |
| miR-27a  | ↑                  | KD              | PBMC: from samples, purified CD19+ B cells, CD14+ monocyte cells | IL-10 | – | ↑ monocyte-mediated TNF-α release, ↑ monocyte-mediated inflammatory responses via inhibiting the regulatory function of B10 cells | [53] |
| miR-17–92| –                  | C57BL/6 mice    | 38c13 cells, HEK, CD1 9KO B cells | c-Myc, PTEN (a target of miR-17–92) | PI3K/Akt/Foxo1 pathway | ∆ miR-17–92: ↑ RAGs expression (post-translationally through Foxo1) miR-17–92: ↓ B cell development | [54] |
| miR-4638-5p| ↓ in ERG+DLBCL | DLBCL          | – | ERG | – | More mutations in genes important in cell cycle control; B-cell receptor-mediated signaling and degradation of β-catenin were seen in ERG+ DLBCL more likely harbors | [55] |
Table 1 (continued)

| microRNA     | Expression pattern | Disease/ Sample | Cell line | Interaction | Signaling pathway                           | Function                                                                 | References |
|--------------|--------------------|-----------------|-----------|-------------|---------------------------------------------|--------------------------------------------------------------------------|------------|
| miR-518a-5p  | ↓                  | DLBCL            | HMy2.CIR normal B cell line, SU-DHL-2 and SU-DHL-6 DLBCL cell lines | CCR6, (a direct target of miR-518a-5p)                                      | There is a negative regulatory feedback loop between miR-518a-5p and CCR6 in DLBCL ↑ miR-518a-5p: ↓ proliferation and invasion, ↑ apoptosis | [56]       |
| miR-296-5p   | ↑                  | DLBCL            | HMy2.CIR normal B cell line, SU-DHL-2 and SU-DHL-6 DLBCL cell lines | HMy2.CIR normal B cell line, SU-DHL-2 and SU-DHL-6 DLBCL cell lines       | ↓ proliferation and migration, apoptosis did not change                   | [57]       |
| miR-34a      | ↓                  | DLBCL            | HMy2.CIR normal B cell line, SU-DHL-2 and SU-DHL-6 DLBCL cell lines | PIK3CD (a direct target of miR-224)                                       | ↑ miR-224, ↓ proliferation and invasion, ↑ apoptosis                    | [58]       |
| miR-224      | ↓                  | DLBCL            | HMy2.CIR normal B cell line, SU-DHL-2 and SU-DHL-6 DLBCL cell lines | PIK3CD (a direct target of miR-224)                                       | ↑ miR-224, ↓ proliferation and invasion, ↑ apoptosis                    | [59]       |
| miR-451a     | ↓                  | DLBCL            | HMy2.CIR normal B cell line, SU-DHL-2 and SU-DHL-6 DLBCL cell lines | PIK3CD (a direct target of miR-224)                                       | ↑ miR-224, ↓ proliferation and invasion, ↑ apoptosis                    | [60]       |
| miR-152-3p   | ↑                  | SLE              | HMy2.CIR normal B cell line, SU-DHL-2 and SU-DHL-6 DLBCL cell lines | PIK3CD (a direct target of miR-451a), BAFF                               | ↓ self-reactivity of SLE B-cells, and ↓ autoantibody production         | [61]       |
| miR-28       | ↓ in GC-derived neoplasms | Non-Hodgkin lymphoma | HMy2.CIR normal B cell line, SU-DHL-2 and SU-DHL-6 DLBCL cell lines | NAIVE B cells (CD19+GL7−), GC B cells (CD19+GL7+), and post-GC B cells (CD19+GL7−IgA+) from Peyer's patches Ramos and Raji BL GC-derived B-cell lines and MD901 DLBCL cell line | BCR signaling                                                                 | [62]       |
| microRNA    | Expression pattern | Disease/ Sample | Cell line | Interaction | Signaling pathway | Function | References |
|-------------|--------------------|-----------------|-----------|-------------|-------------------|----------|------------|
| miR-98      | ↑                  | heart transplanta-\n| -          | peripheral blood mononuclear cells were isolated from the blood samples | ↓ IL-10 | - | The levels of miR-98 and serum levels of cortisol were increased in peripheral B cells after heart transplantation. Cortisol-suppressed IL-10 expression was mediated by miR-98 |
| miR-21-5p   | ↑ in cHL than GC-B cells | cHL            | L540, KM-H2, L1236, L428 and L591, SUPHD1 CHL cell lines and HEK-293 T | PELI1 | - | \(\Delta\) miR-21-5p ↓ growth, ↑ apoptosis |
| miR-29a     | ↓                  | Arthritis       | -          | miR-29a knockout mice | - | ↑ B-cell activation and germinal center production |
| miR-126     | ↓ in MLL-AF4 ALL   | ALL             | Ebf1 −/− hematopoietic progenitor (Lin −) cells were isolated from the Ebf1 −/− livers of 14 d postcoitum embryos | IRS-1 | - | miR-126 drove B-cell myeloid biphrenotypic leukemia differentiation toward B cells. ↑ B cells |
| miR-212     | ↑                  | Autoimmune dis-\n| C57BL/6 WT and miR-212/132 −/− mice | HEM293T, primary splenic B cells | - | BCR signaling | BCR activation: ↑ miR-212 |
| miR-132     | ↑                  | Autoimmune dis-\n| C57BL/6 WT and miR-212/132 −/− mice | HEM293T, primary splenic B cells | Sox4 | BCR signaling | BCR activation: ↑ miR-132 ↓ early B cell development, ↑ apoptosis in primary bone marrow B cells \(\Delta\) miR-132: B cell recovery after antibody-mediated B cell depletion ↓ B cell leukemia development |
| microRNA          | Expression pattern | Disease/ Sample | Cell line          | Interaction | Signaling pathway | Function                                                                 | References |
|------------------|--------------------|-----------------|--------------------|-------------|------------------|---------------------------------------------------------------------------|------------|
| mir-23a cluster  | –                  | –               | mirn23a / C57BL/6 mice and WT 32Dcl3 | A20 and BML Ebf1, Pax5, Mef2c, Il2rf, FoxO1, Trib3 | –                | Δ mirn23a: ↑ B cells, ↑ B lymphopoiesis, ↑ T1 population of transitional B cells, ↑ CLP population and ↓ myeloid cells, ↓ myelopoiesis, ↓ myeloid progenitor populations | [68]       |
| miR-148a         | ↑                  | Lupus           | gMb-macroself, Gadd45a / –, Bcl2l11 / –, Ptenflfl, Cd19-Cre, Trfslb1b / – mice and CD45.1+ C57BL/6 J mice | HB293T, splenic B cells (CD19+) and BM B cell precursors (CD19+IgM-) from CD45.1+C57BL/6 J mice | Gadd45a, PTEN, Bim | miR-148a was found to be a regulator of B cell tolerance by promoting the survival of immature B cells and accelerating the development of autoimmunity by suppressing the expression of Gadd45a, PTEN, Bim | [69]       |
| microRNA | Expression pattern | Disease/ Sample | Cell line | Interaction | Signaling pathway | Function | References |
|----------|-------------------|-----------------|-----------|-------------|-------------------|----------|------------|
| miR-17–92 | ↑                 | cGVHD           | donor BM-derived cells (Ly5.1+) in peripheral blood and spleen, miR-17–92-deficient B cells, | –           | –                 | miR-17–92 increases the pathogenicity of B cells, promoted GC responses and B-cell function, the development of BO and reduced proteinuria/ascites | [70] |
| miR-125b | Epigenetic silencing of miR-125b is necessary for normal B-cell development | –               | WT and Eμ/miR-125b-Tg mice | HEK293T, bone marrow sinusoidal and parenchymal B cells from Eμ/miR-125b-Tg mice and littermate controls | S1PR1, IRF4 | –          | Expression of miR-125b impaired B-cell egress from the bone marrow to peripheral blood | [71] |
| miR-26a | ↓ in DLBCL cell lines compared to B lymphocytes | DLBCL           | SU-DHL-4, SU-DHL-6, SU-DHL-16 GCB cell lines and SU-DHL-2, SU-DHL-8, and RCK-8 ABC cell lines | CDK5, p35 (a direct target of miR-26a) | –                 | ↓ DLBCL tumor growth, proliferation, cell-cycle progression, and survival | [72] |
| miR-155 | –                 | CD45.1+ congenic mice, SWHEL mice and miR-155-deficient mice (all with the C57BL/6 background) | SWHEL Mir155 +/+ or SWHEL Mir155 −/− donor B cells | –           | –                 | miR-155 regulated the early expansion of B blasts and later on the survival and proliferation of plasmablasts in a B-cell-intrinsic manner | [73] |
| miR-181b | ↑ in neonatal B cells | –               | Neonatal and adult B cells | –           | –                 | ∆ miR-181b, ↑ class-switch recombination | [74] |
| microRNA | Expression pattern | Disease/ Sample | Cell line | Interaction | Signaling pathway | Function | References |
|----------|--------------------|----------------|-----------|-------------|-------------------|----------|------------|
| miR-155 | ↓ | chronic psychological stress | male C57BL/6 mice | In-vitro-induced GC B cells, Naive B cells, Su-DHL4 cells | FBXO11 (a direct target of miR-155), BCL6 | – | Corticosterone treatment: ↓ miR-155, ↓ GC B cell generation and isotope class switching ↑ miR-155; ↓ stress-induced impairment of GC response | [17] |
| miR-221 | – | – | C57BL/6, RAG1−/− (CD45.2, CD45.1) mice | preB cell lines | PTEN (a target of miR221), CXCL12, Bcl2 | PI3K signaling | ↑ precursor B-cell retention in the bone marrow, ↑ CXCR4-PI3K mediated Bcl2 upregulation, ↑ early B-cell adhesion capability via PI3K signaling | [75] |
| miR-92a | ↓ | DM | Adult mice | Min-6 mouse pancreatic bcells | KLF2 (a direct target of miR-92a) | – | ↑ insulin secretion and proliferation, ↓ apoptosis | [76] |
| miR-15a/16–1 | ↓ | Plasma cell and mature B-cell neoplasms | AIDCre/− (wild-type [WT]) control and AID-Cre/−; miR-15a/16–1 fl/fl (knockout [KO]) compound mice with C57BL/6 background | GC B cells from WT and KO mice | – | – | Deletion of the miR-15a/16–1 increased the number of GC B cells, percentage of dark zone B cells, and maturation into plasma cells | [77] |
| miR-146a | – | – | CD21−cre, Cyl−cre, CD4−cre, hCD2−cre, and CD40−deficient mice, B-KO/CD40−/− mice | Naive B cells from unimmunized B-KO mice or WT littermates and GC B cells from corresponding D14 SRBC-immunized mice | – | CD40 signaling pathway | The loss of miR-146a in B cells led to the development of spontaneous autoimmune | [78] |
| microRNA | Expression pattern | Disease/ Sample | Cell line | Interaction | Signaling pathway | Function | References |
|----------|-------------------|-----------------|-----------|-------------|-------------------|----------|------------|
| miR-146a | ↓                 | B-cell oncogenesis | Eμ-Myc, miR-146a −/− mice | 70Z/3 and WEHI-231 | Egr1, Blimp1 and Bcl6 | ↓ miR-146a: ↓ survival, ↑ in peripheral blood CD11b+ myeloid cells, ↑ mature B-cell phenotype, ↑ miR-146a: ↓ cell growth | [79] |
| miR-21   | ↑                 | Lymphoma | NOD-SID mice | OCI-LY3 and Ramos, OCI-LY10, U2932, Raji, Rec-1, Jeko-1, Mave-I and JM11, HB293T | N101, Mxd1 (a target of miR-21), c-Myc | NL101: ↑ miR-21, c-Myc: ↓ miR-21, miR-21: ↑ proliferation and survival, ↓ apoptosis | [80] |
| miR-146a | ↓                 | Immune complex glomerulonephritis | miR-146a −/− mice with C57BL/6 background | B lymphocytes were the spleen, HK-2 | Kim1/Tim1 | Δ miR-146a: ↑ numbers of memory B cells and plasmablasts, ↑ glomerular hypercellularity with age, ↓ Bregs and ↓ Kim1/Tim1 | [81] |
| miR-146a | ↑                 | – | Murine OVA-Induced asthma mice, WT and miR-146a TG mice | purified splenic B cells | Smad4 (a direct target of miR-26a), 14-3-3σ | ↑ class switch and secretion of IgE in B cells | [82] |
| miR-142  | ↑                 | Lymphoma | BMT and transgenic (Eμ/mir142) mice | KHM108B, Raji, KMS12, OCI-Ly8, Hut 78, and Cos7 | – | In splenic B cells, high expression of Mir142 modified LPS-induced phenotypical changes | [83] |
| miR-7    | ↑                 | SLE | Female MRLlpr/lpr lupus mice | Purified splenic B cells obtained from mice | PTEN | Δ miR-7: ↓ nephritis, ↓ lupus manifestations, ↓ immune Abnormalities, ↓ th1-derived IL-21 expression, ↓ Abnormal B cell differentiation, normalizes splenic B cell subtypes | [9] |
| microRNA  | Expression pattern | Disease/Sample | Cell line | Interaction | Signaling pathway | Function | References |
|-----------|--------------------|----------------|-----------|-------------|-------------------|----------|------------|
| miR-98    | ↑                  | Myocarditis    | BALB/c mice immunized with MyHC-α | B cells isolated from the mouse hearts with myocarditis | ↓ IL-10 (a target of miR-98), TNF-α | –         | [84]       |
|           |                    |                |           |             |                   |          |            |
| Let-7     | –                  |                | Lin28a Itg mice, let-7adf cluster KO mice, and let-7bc cluster KO mice | HEK293T | Hk2 (a target gene of Let-7) c-myc (a target gene of Let-7) Slc1a5 and Gls (indirect target genes of Let-7) | –         | ↓ IgM Production ↓ glycolytic capacity and glucose uptake ↓ glutamine uptake and utilization ↓ B Cell Activation | [85] |
| Let-7     | ↑ in thymic B progenitors by in vitro coculture with IL15, Vitamin-D3, and retinoic acid | – | Foxn1 lacZ/lacZ (Z/Z) mice with C57Bl6/J background, Foxn1 nude heterozygous (Foxn1 +/nude) mice with C57Bl6/J background, Foxn1 lacZ/nude (Z/N) mice, Foxn1 +/lacZ (+/Z) mice | thymic progenitor B cells | Lin28a, And3a | – | ↓ B cell production in the thymus ↓ proliferation of intrathymic progenitor B cells | [86] |
| miR-191   | ↑ during B-cell development and differentiation | – | C57Bl/6 J and NOD.Cg-PrkdcscidIl2rgtm1WjJ/SJ (NSG) mice, C57Bl/6 mice and miR-191 −/− mice | Primary cells from wild-type or chimeric mice, preB1 cells, | Foxp1, E2A, and Egr1 | – | Expression levels of miR-191 are required for efficient B-cell development, V(D)J recombination and IL-7-dependent expansion of preB1 cells | [87] |
| miR-15 family | ↓ | – | Female C57Bl/6 Rag1 −/− mice | wk3, 1587, and 1677 pre-B cell lines from total bone marrow of SLP-65 −/− and SLP-65 −/− LAT −/− mice, respectively, and 1676 and 74 pre-B cell lines | ↑ cyclin E1 and D3 | – | The lack of miR-15 family in pre-B cells caused prolonged proliferation, so failed to trigger the transcriptional reprogramming to accompany their differentiation | [88] |
| microRNA       | Expression pattern | Disease/ Sample | Cell line                  | Interaction                                                                 | Signaling pathway                          | Function                                                                 | References |
|---------------|-------------------|----------------|---------------------------|-----------------------------------------------------------------------------|--------------------------------------------|--------------------------------------------------------------------------|------------|
| mirn23a cluster | ↓                 |                | Wildtype and mirn23a/−−/ CS 7BL/6 mice, CD45.1 recipient mice, femurs and tibias of mice | 70Z/3, A20 and 32Dc13 cell lines          | ↑ Ikzf1, Runx1, Satb1, Bach1 and Bach2 that managed the commitment of MPPs to CLPs | PI3K/Akt and BMP/Smad signaling pathways                          | Mirn23a regulated some related transcription factors and signaling pathways to modulate adult hematopoiesis. Mirn23a was inhibited by EBF1 | [89]       |

T:\ tuberculosis; CTRL, control; BL, Diagnosis; M1, month 1; M6, month 6; GC, germinal center; SLE, systemic lupus erythematosus; DLBCL, diffuse large B-cell lymphoma; RA, rheumatoid arthritis; ERA, early rheumatoid arthritis; LSRA, long standing rheumatoid arthritis; BCR, B cell receptor; CLP, common myeloid progenitor; LA, lactic acid; MLL, myeloid/lymphoid leukemia; ALL, acute lymphoblastic leukemia; BL, Burkitt lymphoma; SLE, systemic lupus erythematosus; PTLD, posttransplant lymphoproliferative disorder; EBV, Epstein-Barr virus; BCL, B-cell lymphoma; cGVHD, Chronic graft-versus-host disease; BO, bronchiolitis obliterans; B NHL, B cell non-Hodgkin's lymphoma; OS, overall survival; DFS, disease-free survival; Wt, wild-type; KD, knockout; TG, overexpression; IM, imatinib; CML, Chronic myeloid leukemia; PCNSL, Primary lymphomas of the central nervous system; SCNSL, secondary spread of systemic lymphoma to the CNS; CSF, cerebrospinal fluid; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; B-ALL, B-cell acute lymphoblastic leukemia; DFS, disease-free survival; PBc, Primary biliary cholangitis; ANCTs, adjacent non-cancerous tissues; BMRT, bone marrow transplantation; ABMR, Antibody-mediated renal allograft rejection; PMBL, Primary mediastinal large B-cell lymphoma; LNH, lymph node reactive hyperplasia; IPL, reactive proliferative lymphadenitis; PBMCs, Human peripheral blood mononuclear cells; DS, Down Syndrome; DM, diabetes mellitus; RLH, reactive lymph node hyperplasia; AML, acute myeloid leukemia; ITP, immune thrombocytopenia; KD, Kawasaki disease; IgAN, immunoglobulin A nephropathy; RLH, reactive lymphoid hyperplasia; LRH, lymph node reactive hyperplasia; cHL, Classical Hodgkin lymphoma
CRNDE has been shown to be up-regulated in the bone marrow of B-cell precursor acute lymphoblastic leukemia patients and related cell lines. CRNDE silencing has decreased cell proliferation and enhanced cell apoptosis in these cells. Functionally, CRNDE could bind with to miR-345-5p and down-regulate its expression, thus affecting expression of CREB. Notably, in vivo studies have shown that CRNDE silencing increases survival of mice models of this type of leukemia [93].

In addition to this type of studies, expression patterns of lncRNAs have been compared between cancer cells and non-cancerous controls using high throughput methods. For instance, Cuadros et al. have reported differential expression of 48 lncRNAs between pediatric B-ALL and normal bone marrow specimens. They have recognized AL133346.1/CCN2 as the most relevant lncRNA/mRNA pair in this type of malignancy. Expression of AL133346.1/CCN2 pair has been enhanced in B-ALL specimens [94].

Expression of PTTG3P has been shown to be up-regulated in samples obtained from patients with IgA nephropathy compared with normal samples. Notably, expression of PTTG3P in urine samples has been correlated with expression of PTTG3P in intra-renal samples of IgA nephropathy cases. Up-regulation of PTTG3P has stimulated B cell growth and increased expressions of cyclin D1 and ki-67. In addition, its up-regulation of PTTG3P has led to induction of IL-1β and IL-8 release. PTTG3P up-regulation could suppress expression of miR-383 in B cells. Taken together, PTTG3P could increase B cell growth and IL-1β and IL-8 release through influencing expression of miR-383. Through this effect, PTTG3P contributes in the pathogenesis of IgA nephropathy [95].

Expression of IncRNA RP11-530C5.1 has been shown to be higher in relapsing MS patients, compared to remitting MS patients and healthy subjects, whereas expression of AL928742.12 has been decreased. Notably, expression levels of RP11-530C5.1 and AL928742.12 have been correlated with PAWR and IGH-A2 levels, respectively [96].

Table 2 shows the impact of IncRNAs in B cell functions.

**Contribution of circRNAs in the regulation of B cell-related disorders**

The impact of circRNAs on B cell functions has been mostly assessed in the context of DLBCL. For instance, circ_OTUD7A expression has been found to be increased in DLBCL. Its silencing has suppressed proliferation and metastasis of DLBCL, induce cell cycle arrest and enhance their apoptosis. Mechanistically, circ_OTUD7A
| IncRNA       | Expression pattern | Disease | Sample                                                                 | Cell line                                                                 | Interaction                  | Signaling pathway                  | Function                                                                 | References |
|-------------|--------------------|---------|------------------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------|------------------------------------|--------------------------------------------------------------------------|------------|
| SNHG14      | ↑                  | DLBCL   | 38 pairs of B cell lymphoma tissues and ANCTs, BALB/c mice             | GM12878, 293 T, A20, OCL-LY7, DB, U2932, and FARAGE                    | ↓ mIR-5590-3p, ↑ ZEB1, PD-1/PD-L1 | ∆ SNHG14: ↓ proliferation, migration, and EMT process, There is a positive feedback loop between SNHG14 and ZEB1 to promote DLBCL | [90]        |
| MALAT1      | ↑                  | DLBCL   | 37 patients with DLBCL                                                 | OCL-LY10 human DLBCL cell line, CD8 + T cells                          | ↓ mIR-195, ↑ PD-L1 and CD8    | Ras/ERK signaling pathway         | ∆ MALAT1: ↓ proliferation, migration and immune escape ability, BMT-like process, ↑ apoptosis | [91]        |
| CRNDE       | ↑                  | BCP-ALL | BM biopsies from 26 patients with BCP-ALL and BM biopsies from 15 patients with unexplained thrombocytosis or anemia as controls | NALM-6, RS4;11 CEMO-1, CCRF-SB, and SUP-B15 BCP-ALL cell lines          | ↓ mIR-345-5p, ↑ CREB          | ∆ CRNDE: ↓ proliferation, ↑ apoptosis |                                                          | [93]        |
| AL133346.1  | ↑                  | B-ALL   | GEO dataset: GSE128254                                                | –                                                                         | ↑ CCN2                       | It was found that either AL133346.1 regulates CCN2 expression in cis; or AL133346.1 and CCN2 are regulated by the same regulatory elements | [94]        |
| NEAT1       | ↑                  | DLBCL   | 30 patients with DLBCL and 30 healthy controls                        | OCL-Ly1, OCL-Ly8, OCL-Ly10 and SUDHL-4 DLBCL cell lines                | ↓ mIR-34b-5p, ↑ GLI1        | ∆ NEAT1: ↓ proliferation, ↑ apoptosis |                                                          | [92]        |
| SMAD5-AS1   | ↓                  | DLBCL   | 11 patients with DLBCL and 11 healthy controls, BALB/c-nude mice      | TMD8, U2932, GM12878, HEK-293, OCL-Ly3, WSU-FSCCL, Jeko-1, L428, and Raji | ↑ mIR-135b-5p, ↓ APC         | ↑ Wnt/β-catenin pathway           | ∆ SMAD5-AS1: ↓ proliferation, ↑ apoptosis                              | [97]        |
| OR3A4       | ↑                  | DLBCL   | 58 patients with DLBCL and healthy controls                           | 2932, SU-DHL-6, SU-DHL-4, OCL-LY-7, OCL-LY-10 DLBCL cell lines and WIL2 human B lymphocyte | ↑ FOXM1                      | ↑ Wnt/β-catenin signaling pathway | ∆ OR3A4: ↓ proliferation and ↑ apoptosis OR3A4 is upregulated by FOXM1 | [98]        |
| lncRNA   | Expression pattern | Disease                  | Sample                                                                 | Cell line                                                                 | Interaction | Signaling pathway                          | Function                                                                 | References |
|----------|--------------------|--------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------|--------------------------------------------|--------------------------------------------------------------------------|------------|
| FIRRE    | ↑                  | DLBCL                    | 70 pairs of DLBCL patient samples and healthy controls                 | 2932, SU-DHL-6, SU-DHL-4, OCL-LY-7, OCL-LY-10 human DLBCL cell lines and WIL2S one normal B-cell line | MYC         | ↑ Wnt/β-catenin signaling pathway          | ↑ proliferation and ↓ apoptosis                                           | [99]       |
| RP11-513G11.1 | ↑              | DLBCL                    | 93 patients with DLBCL and 62 healthy controls                        | –                                                                         | –           | –                                         | Patients with high expression levels of RP11-513G11.1 showed shorter PFS and OS | [100]      |
| Inc-290  | ↑ in B cells stimulated by LPS | inflammation and tissue damage | female C57Bl/6 mice                                                   | GFP+ cells                                                                | CD69/CD86, LPS/TLR signaling pathway | NF-κB/ERK pathways           | Δ Inc-290: ↓ growth of B cells, ↓ cell differentiation and ↓ immunoglobulin production, ↓ B cell activation by blocking the LPS/TLR4 signaling pathway | [101]      |
| LINC01857 | ↑                | DLBCL                    | TCGA and GTEx databases, GEO databases                                | HCC1 395, CYP6D, OCI-Ly3, and Raji                                         | ↓ miR-141-3p, ↑ MAP4K4 | PI3K/mTOR pathway           | ↑ proliferation, ↑ EMT process and ↑ cell cycle progression, ↓ apoptosis | [102]      |
| TEX41    | ↑ in B-ALL        | B-ALL                    | 79 patients with B-ALL, 25 patients with T-ALL, and 38 acute myeloid leukemia | RS4;11 cells, p53 and p21                                                 | –           | –                                         | ↑ proliferation, ↑ cell growth and ↑ cell cycle progression            | [103]      |
| AFAP1-AS1 | ↑                | GCB-DLBCL                | 48 patients with DLBCL                                                | OCI-Ly1 and OCI-Ly19 GCB-DLBCL cell lines                                  | SFPQ, NONO, SRSF2, SRSF6, and KHSPR | BCR and TNF signaling pathways | Δ AFAP1-AS1: ↓ proliferation, ↑ GO/G1 arrest and ↑ apoptosis      | [104]      |
| PTTG3P   | ↑                  | IgAN                     | patients with IgAN and healthy controls                              | B cells                                                                   | ↓ miR-383, cyclin D1 and ki-67, IL-1β and IL-8                           | –                                      | ↑ PTTG3P: ↑ B cell growth and ↑ cyclin D1 and ki-67 expression, ↑ IL-1β and IL-8 production | [95]       |
| lncRNA     | Expression pattern | Disease | Sample                                                                 | Cell line                                                                                     | Interaction          | Signaling pathway | Function                                      | References |
|------------|--------------------|---------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|----------------------|-------------------|-----------------------------------------------|------------|
| SNHG8      | ↑                  | DLBCL   | –                                                                      | GM12878 human B lymphocytes and OCI-Ly10, OCI-Ly7, OCI-Ly8, and U2932 human DLBCL cell lines | ↓ miR-335-5p         | –                 | Δ SNHG8: ↓ proliferation, ↓ colony formation and ↑ apoptosis | [105]      |
| PCAT1      | ↑                  | DLBCL   | 48 pairs of DLBCL tissues and ANCTs                                   | OCH-LY-7, OCH-LY-7, TMD8 and U2932 DLBCL cell lines, IM-9 human peripheral blood B-lymphocyte | ↓ miR-508-3p, ↑ NFIB | –                 | ↑ PCAT1: ↑ proliferation, ↑ migration and ↑ invasion | [106]      |
| SBF2-AS1   | ↑                  | DLBCL   | 50 patients with DLBCL                                                | OCH-LY-3, OCH-LY-7, OCI-LY-10, SU-DHL-4 and SU-DHL-6 and HEK293 cells                      | ↓ miR-494-3p, ↑ FGFR2 | –                 | Δ SBF2-AS1: ↓ viability and ↓ growth            | [107]      |
| SNHG14     | ↑                  | DLBCL   | 21 patients with DLBCL and 21 healthy controls                        | GM12878, OCH-LY-7, ABC, OCI-LY-3 and RCK-8                                                   | ↓ miR-152-3p         | –                 | ↑ growth, migration, and EMT-like processes, ↓ apoptosis | [108]      |
| LINC00908  | ↑                  | DLBCL   | 28 pairs of DLBCL tissues and ANCTs, female BALB/c nude mice          | GM12878 human lymphoblastoid B cell and OCI-LY7, DB, U2932, and FARAGE human DLBCL cells     | miR-671-5p           | –                 | Δ LINC00908: ↓ proliferation and invasion, tumor growth | [109]      |
| TCONS_00022357-XLOC_010919 | ↑     | GD      | Peripheral blood from 34 patients with GD, and 34 healthy controls   | CD19+ B cells from 21 healthy individuals and 24 GD patients, PBMCs                           | TCL1A                | –                 | TCONS_00022357-XLOC_010919 regulated TCL1A, and TCL1A is involved in B-cell proliferation | [110]      |
| n335641    | ↑                  | GD      | Peripheral blood from 34 patients with GD, and 34 healthy controls   | CD19+ B cells from 21 healthy individuals and 24 GD patients, PBMCs                           | TCL1A                | –                 | n335641 regulates TCL1A, and TCL1A is involved in B-cell proliferation |            |
| n337845    | ↓                  | GD      | Peripheral blood from 34 patients with GD, and 34 healthy controls   | CD19+ B cells from 21 healthy individuals and 24 GD patients, PBMCs                           | SH2D1A               | –                 | n337845 regulates SH2D1A, and SH2D1A is involved in B-cell proliferation |            |
| LncRNA   | Expression pattern | Disease          | Sample                                                                 | Cell line                          | Interaction | Signaling pathway           | Function                                                                                     | References |
|---------|--------------------|------------------|------------------------------------------------------------------------|------------------------------------|-------------|-----------------------------|--------------------------------------------------------------------------------------------|------------|
| ZEB1-AS1| ↑                  | B-ALL            | 30 with B-ALL and 30 healthy controls                                  | hBMSC-TERT                         | –           | IL-11/STAT3 pathway         | 
|         |                    |                  |                                                                        |                                    |             | Δ ZEB1-AS1: ↓ proliferation and IL-11 production | High expression levels of ZEB1-AS1 showed poor prognosis of B-ALL patients ZEB1-AS1 promoted IL-11 stability | [111]      |
| UCA1    | ↑                  | DLBCL            | 38 patients with DLBCL and 38 healthy controls                         | GM12878, JeKo-1, TMD8, U2932, OCI-Ly-10 and OCI-Ly-7 cell lines and U2932 | ↓ miR-331-3p | –                           | Δ UCA1: ↓ proliferation, viability, migration and invasion | [112]      |
| LAMP5-AS1| ↑ in MLL leukemia patients than that in the MLL-wt leukemia | MLL leukemia | 58 patients with MLL leukemia and 163 MLL-wt leukemia, NOD-SCID mice | MOLM13, THP1, MV4-11, RS4-11, and HEK293T human MLL leukemia cells | DOT1L       | –                           | Δ LAMP5-AS1: ↓ colony formation and ↑ differentiation of primary MLL leukemia CD34+ cells Patients with high levels of LAMP5-AS1 showed a reduced 5-year leukemia-free survival LAMP5-AS1 increased the methyltransferase activity of DOT1L | [113]      |
| LINCO00152| ↑                | Gastric cancer  | 30 pairs of GC tissues and ANCTs, male BALB/c nude mice               | RGM-1 human epithelial cells of gastric mucosa, and human BGC-823 GC cell | Bcl-2       | –                           | ↑ migration and invasion, ↓ apoptosis | [114]      |
| HCP5    | ↑                  | DLBCL            | 48 patients with DLBCL and 14 RLH samples                              | OCI-LY7 and OCI-LY3 human DLBCL cell lines | ↓ miR-27b-3p, ↑ MET | –                           | Δ HCP5: ↓ proliferation, ↑ apoptosis Geniposide treatment: Δ HCP5 | [115]      |
| PEG10   | ↑                  | DLBCL            | 25 patients with DLBCL and 25 healthy controls                        | SU-DHL8 and OCI-LY-8 DLBCL cell lines | ↓ miR-101-3p, ↑ KIF2A | –                           | Δ HCP5: ↓ proliferation, migration and invasion, ↑ apoptosis | [116]      |
Table 2 (continued)

| lncRNA | Expression pattern | Disease | Sample | Cell line | Interaction | Signaling pathway | Function | References |
|--------|--------------------|---------|--------|-----------|-------------|-------------------|----------|------------|
| GAS5   | ↓                  | DLBCL   | –      | OCH-Ly3 and TMD8 cells | ↑ miR-18a-5p, ↓ RUNX1 | –       | Δ GAS5: ↓ proliferation, ↓ G1 arrest, ↑ apoptosis | [117]     |
| TUG1   | ↑                  | DLBCL   | 15 tumor tissues and venous blood from DLBCL patients, 15 patients with RLH as controls, female BALB/c athymic nude mice | OCH-Ly7, and OCH-Ly3 human DLBCL cell lines, IM-9 normal B lymphocyte | ↑ MET | – | Δ TUG1: ↓ proliferation and tumor growth | [118]     |
| SNHG12 | ↑                  | DLBCL   | 80 patients with activated B-cell like DLBCL, 80 patients with RLH as controls, male BALB/c nude mice | OCH-Ly7, and OCH-Ly3 human DLBCL cell lines, IM-9 normal B lymphocyte | ↓ miR-195 | – | Δ SNHG12: ↓ cell growth, ↓ migration, and ↓ invasion | [119]     |
| PANDA  | ↓                  | DLBCL   | 114 patients with DLBCL and 114 healthy controls | U2932, SUDHL-6, SUDHL-3, OCH-Ly3, and OCI-Ly8 human DLBCL cell lines and WI.25 normal B-cell line | p53 and MAPK/ERK signaling pathway | ↑ G0/G1 cell cycle arrest and ↓ proliferation through silencing MAPK/ERK signaling pathway. Low levels of PANDA were associated with poorer clinical outcome and lower OS in DLBCL patients | [120]     |
| GAS5   | ↓                  | B lymphocytic leukemia | 30 patients with human B lymphocytic leukemia, 30 healthy controls | RAMOS, ST486, Raji, and Farage human B lymphocytic leukemia cell lines and IM-9 normal B lymphocytic cell line | miR-222 | – | Δ GAS5: ↓ proliferation, and ↓ invasion, ↑ apoptosis and ↑ G1 phase arrest | [121]     |
| DBH-AS1| ↑                  | DLBCL   | 26 patients with DLBCL | RCK-8, OCH-LY-3, OCH-LY-7, and OCH-LY-10 human DLBCL cell lines and IM-9 human peripheral blood B-lymphocyte | BUD13, FN1 | – | Δ DBH-AS1: ↓ proliferation, ↓ invasion, and ↓ migration. DBH-AS1 regulated FN1 expression by recruiting BUD13 | [122]     |
| IncRNA          | Expression pattern | Disease          | Sample                                                                 | Cell line                                                                 | Interaction                                                                 | Signaling pathway                                                                 | Function                                                                                     | References |
|-----------------|--------------------|------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------|------------|
| ROR1-AS1        | ↑                  | MCL              | 5 patients with MCL and 5 healthy controls                          | Mino, Granta, JVM2 and Z138 MCL cell lines, HEB-293 T cell line           | ↓ P16, and SOX11, EZH2 and SUZ12 of polycomb repressive complex-2          | –                                                                            | ↑ ROR1-AS1: ↑ cell growth and ↓ sensitivity to the treatment with drugs ibrutinib and dexamethasone. ROR1-AS1 is involved in epigenetic regulation of gene transcription through EZH2/PRC2 complex. | [123]      |
| LHFPL3-AS1      | ↑                  | Melanoma         | 461 tumor tissues and 558 normal tissues, BALB/c nude mice          | Melanoma stem cells and non-stem cells from MDA-MB-435 cells              | ↑ PTBP1, ↓ miR-181a-5p, ↑ Bcl-2                                             | –                                                                            | Δ LHFPL3-AS1: ↓ proliferation, ↑ apoptosis of melanoma stem cells | [124]      |
| NONHSAG026900  | ↓                  | DLBCL            | GEO dataset GSE12453 including 11 patients with DLBCL and 25 healthy controls and GSE56315, GSE11318, GSE23501, GSE53786, GSE10846, and GSE31312 | –                                                                        | –                                                                            | –                                                                            | ↓ proliferation and cell cycle progression                   | [125]      |
| SNHG16          | ↑                  | DLBCL            | DLBCL tissues (21 GCB and 27 non-GCB) and 14 RLH tissues as controls: male NOD/SCID mice | OCI-LY7 and OCI-LY3                                                       | ↓ miR-497-5p, ↑ PIM1                                                       | –                                                                            | Δ SNHG16: ↓ proliferation, growth, and cell cycle progression, ↑ apoptosis | [126]      |
| NEAT1-1         | ↑ in DLBCL tissues | DLBCL            | 64 patients with DLBCL and 15 patients with lymph-noditis            | OCI-Ly1 and SUDHL-4 DLBCL cell lines                                      | –                                                                            | –                                                                            | Δ NEAT1-1: ↓ viability and migration, ↑ apoptosis High levels of NEAT1-1 were correlated with stage, IPI, extranodal site involvement and drug response | [127]      |
| lncRNA          | Expression pattern | Disease | Sample                                                                 | Cell line                              | Interaction          | Signaling pathway               | Function                                                                                           | References |
|-----------------|--------------------|---------|-----------------------------------------------------------------------|----------------------------------------|----------------------|--------------------------------|---------------------------------------------------------------------------------------------|------------|
| TUC338          | ↑                  | DLBCL   | 102 pairs of DLBCL and normal tissues, serum specimens of 35 patients with DLBCL and 35 healthy controls, BALB/c nude mice | U2932 and OCI-Ly3 DLBCL cell lines    | ↓ miR-28-5p, ↑ EGFR | PI3K/AKT signaling               | TUC338: ↓ proliferation and chemotherapy resistance to Adriamycin, ↑ apoptosis Patients with high TUC338 showed shorter survival time | [128]      |
| LINC00857       | ↑                  | DLBCL   | 87 pairs of DLBCL tissues and ANCTs                                   | HMy2CIR lymphoblast cell line, SU-DHL-6, SU-DHL-4 and SU-DHL-10 DLBCL cell lines | ↓ miR-370-3p, ↑ CBX3 | –                               | LINC00857: ↑ proliferation and cycle progression, ↓ apoptosis TUC338: ↓ proliferation and ↑ apoptosis | [129]      |
| Lnc-IRF2-3 and Lnc-ZNF667-AS1 | ↑                  | B-CLL   | 135 patients with B-CLL and 30 healthy controls                     | –                                      | –                    | –                               | Patients with high levels of Lnc-IRF2-3 had a significant decrease in OS and PFS High levels of Lnc-IRF2-3 and Lnc-ZNF667-AS1 were associated with poor survival | [130]      |
| LINC00963       | ↓                  | DLBCL   | GTEx and TCGA databases (normal N = 337, tumor T = 48), nude mice    | SUDHL4, OCI-Ly1, HBL1 and OCI-Ly3 DLBCL cell lines and GM12878 Non-cancerous human B lymphocytes | ↑ miR-320a, ↓ XBPI    | –                               | LINC00963: ↓ proliferation, and tumor growth, ↑ apoptosis and autophagy                       | [131]      |
| LEF1-AS1        | ↑                  | CLL     | –                                                                    | primary CLL cells and normal B cells  | ↑ LEF1                | –                               | LEF1-AS1: ↑ proliferation and ↓ apoptosis                                                                                     | [132]      |
| PVT1            | ↑                  | MM      | 137 patients with MM and 62 patients with MGUS, and 21 control patients with lymphoma | KMS11, KMS12PE, KMS12BM, KMS26, KM1M1, OPM2, RPMI8226 | ↑ MYC, BRD4          | –                               | High levels of PVT1 were positively correlated with disease progression JQ1 (BRD4 inhibitor): ↓ proliferation and ↓ expression levels of MYC and PVT1                                      | [133]      |
| lncRNA   | Expression pattern | Disease | Sample | Cell line | Interaction | Signaling pathway | Function                                                                 | References |
|----------|--------------------|---------|--------|-----------|-------------|-----------------|---------------------------------------------------------------------------|------------|
| BALR-2   | ↑                  | B-ALL   | 160 patients with B-ALL | RS4;11 and MVA;11, Reh, 697, Nalm-6, and 70Z/3 murine pre-B-cell leukemic cell line, and HEK 293 T cell line | –           | Glucocorticoid response pathway | ∆ BALR-2: ↓ proliferation, ↑ apoptosis and sensitivity to prednisolone treatment; prednisolone treatment: ↓ BALR-2 expression | [134]      |
| FAS-AS1  | ↓                  | Lymphoma | –      | Granta-519 cells and Peripheral blood B-lymphocytes from healthy donors' blood | ↑ sFas, RBM5, ↑ EZH2, | –           | FAS-AS1 could regulate alternative splicing of Fas in lymphomas; Expression of FAS-AS1 could repress by EZH2 | [135]      |
| LUNAR1   | ↑                  | DLBCL   | 87 patients with DLBCL and 28 samples with reactive lymph nodes as controls | OCI-LY-3, OCI-LY-7, OCI-LY-10, SU-DHL-4, SU-DHL-6 and RCK-8 DLBCL cell lines | –           | –           | ∆ LUNAR1: ↓ proliferation; LUNAR1 expression was found to serve as an independent predictor for OS and PFS | [136]      |
| HOTAIR   | ↑                  | DLBCL   | 50 lymph node samples from patients with DLBCL and 20 samples with reactive lymph nodes as controls | RCK-8, OCI-LY-10, OCI-LY-7, SU-DHL-6 and SU-DHL-4 DLBCL cell lines | –           | PI3K/AKT/NF-κB signaling pathway | ∆ HOTAIR: ↓ growth, cell cycle progression, ↑ apoptosis | [137]      |
| RP11-530C5.1 | ↑             | MS      | GEO database and GSE21942, 50 MS patients and 25 controls | –           | PAWR       | –           | –                                                                 | [96]       |
| AL928742.12 | ↓              | MS      | GEO database and GSE21942, 50 patients with MS and 25 controls | –           | IGHA2      | –           | –                                                                 | –          |
| PEG10    | ↑                  | DLBCL   | 107 patients with DLBCL and 46 samples with reactive lymph nodes as controls | OCI-LY-3, OCI-LY-7, OCI-LY-10, RCK-8, SU-DHL-4 and SU-DHL-6 DLBCL cell lines | –           | –           | ∆ PEG10: ↓ growth, ↑ apoptosis; PEG10 levels were significantly associated with B symptoms, IPI score, CHOP-like treatment and rituximab | [138]      |
| lncRNA          | Expression pattern | Disease | Sample                                                                 | Cell line                                                                 | Interaction | Signaling pathway | Function                                                                                       | References |
|-----------------|--------------------|---------|------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------|-------------------|-----------------------------------------------------------------------------------------------|------------|
| HULC            | ↑                  | DLBCL   | 142 patients with DLBCL and 60 samples with reactive lymph nodes as controls | OCI-LY-3, OCI-LY-7, OCI-LY-10, SU-DHL-4, SU-DHL-6 and RCK-8 human DLBCL cell lines | –           | –                 | Δ HULC: ↓ proliferation, ↑ apoptosis HULC was strongly associated with Ann Arbor stages, B symptoms, CHOP-like treatment, rituximab and IPI | [139]      |
| lincRNA-p21     | ↓                  | DLBCL   | 105 patients with DLBCL                                               | SU-DHL-2, OCI-LY-3, OCI-LY-10, SU-DHL-4 and OCI-LY-7 human DLBCL cell lines | –           | –                 | ↑ lincRNA-p21: ↓ proliferation and cycle progression Patients with high expression levels of lincRNA-p21 showed a favorable OS and PFS | [140]      |
| BALR-6          | ↑                  | B-ALL   | Post bone marrow transplant, blood, bone marrow, thymus and spleen were collected from the mice | RS4;11 and MV, Reh, 697, Nalim-6, 702/3 murine pre B-cell leukemic cell line, and the HEK 293 T cell line | SP1, CREB1  | –                 | Δ BALR-6: ↓ proliferation, ↑ apoptosis ↑ BALR-6: ↑ survival, proliferation and expansion of hematopoietic progenitor populations in vivo | [141]      |
| RP11-301G19.1   | ↑                  | MM      | Female BALB/c nude mice                                               | U266, RPMI8226, OPM-2, MM-15, NO-H929 MM cell lines and 293T normal plasma cells | ↓ miR-582-5p, ↑ HMGB2 | PI3K/AKT signaling pathway | Δ RP11-301G19.1: ↓ proliferation and cell cycle progression, ↑ apoptosis | [142]      |
| HULC            | ↑                  | DLBCL   | Male BALB/C mice                                                      | SU-DHL-8, SU-DHL-10 human DLBCL cell lines                                 | –           | –                 | ↑ HULC: ↓ apoptosis                                                                             | [143]      |
| Inc00492        | ↑                  | –       | Inc00492+/− and Inc00492 +/- mice                                     | B220+B cells, MZ B-cells                                                  | ↓ CTBP1     | Notch2 signaling pathway | Lnc00492 is necessary for marginal zone B-cell development                                          | [144]      |
| IncRNA | Expression pattern | Disease | Sample | Cell line | Interaction | Signaling pathway | Function | References |
|--------|--------------------|---------|--------|-----------|-------------|------------------|----------|------------|
| MALAT-1 | ↑ | DLBCL | Female BALB/c-nc/nu/nu nude mice | IM-9 cells, B lymphocytes IM-9, from healthy people and Farage, Pfeiffer, Raji, Daud, Ly1, Ly3, Ly8, and Ly10 from patients with DLBCL | ↓ LC3-II/LC3-I, ↑ p62 | BAFF IFN-I signaling | Δ U MALAT-1: ↓ migration, survival rate, the proportion of cells in S and G2/M phase, and tumor volume and weight, ↑ the proportion of cells in G0/G1 phase | [145] |
| NEAT1 | ↑ | SLE | Lupus-prone MRL/lpr mice | PBMCs, B220+ B cells, G-MDSCs or M-MDSCs from MRL/lpr mice | BAFF | IFN-I signaling | ↑ promotion of G-MDSCs Δ NEAT1: ↓ lupus symptoms and inhibits IFN-I signaling activation | [146] |
**Table 3** CircRNAs and B cells functions

| circRNA       | Expression pattern | Disease | Sample                                                                 | Cell line                                                                 | Interaction | Signaling pathway                                                                 | Function                                                                                           | References |
|---------------|--------------------|---------|------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|------------|
| Circ_OTUD7A   | ↑                  | DLBCL   | 50 pairs of DLBCL tissues and ANCTs                                    | U2932, TMD8 and OCI-Ly3 LBCL cell lines and GM1287 normal human B lymphocytes | ↓ miR-431-5p, ↑ FOXP1 | –                                                                               | ΔCirc_OTUD7A: ↓ proliferation, metastasis, ↑ cell cycle arrest and apoptosis                          | [147]      |
| circ APC     | ↓                  | DLBCL   | 80 pairs of DLBCL and para-cancerous tissues, plasma samples from 27 DLBCL patients and 16 healthy controls, nude mice | SUDDLHL-3, U2932, TMD8, OCI-Ly3 and L428 human DLBCL cell lines and GM1287 normal human B lymphocytes | miR-888, APC, DNA demethylase TET1 | Wnt/β-catenin signaling pathway                                                  | ΔCircCFL1: ↑ proliferation and tumor growth                                                        | [149]      |
| circBCL11B   | ↑                  | AML     | 61 patients with AML and 16 healthy samples, GEO dataset: GSE137851     | –                                                                         | –           | –                                                                               | ΔcircBCL11B: ↓ proliferation, ↑ apoptosis                                                            | [151]      |
| circ CDYL    | ↑                  | MCL     | 18 patients with MCL and 17 healthy controls                          | HEK293T cells and Z138 human MCL cell line                               | five miRNAs (hsa-miR-129-5p, hsa-miR-3163, hsa-miR-4662a-5p, hsa-miR-101-3p, and hsa-miR-186-5p), three lncRNAs (MALAT1, NEAT1, and XIST), and five mRNAs (NOTCH1, FMR1, ABCB1, TWIST1, and VEGFA) | –                                                                               | ΔcircCDYL: ↓ proliferation                                                                               | [152]      |
| circ_013266  | ↓                  | CLL     | 30 patients with CLL and 30 healthy controls                          | MEC-1, JVM-3 and HEK-293 T                                               | ↑ miR-337-3p, ↓ PML          | –                                                                               | ↑ circ_013266: ↓ proliferation                                                                        | [150]      |
| circ_0005774 | ↑                  | AML     | 20 patients with AML and 20 healthy controls                          | HL-60 and NB4 cells                                                      | ↓ miR-192-5p, ↑ ULK1        | –                                                                               | Δcirc_0005774: ↓ proliferation and viability, ↑ apoptosis                                           | [153]      |
| circ Smad5    | ↓                  | DLBCL   | –                                                                     | JB6 and 293T T cell lines                                               | –                           | Wnt/β-catenin/Lef1 signaling pathway                                           | Δcirc-Smad5: ↑ cell cycle progression and activated Wnt/β-catenin/Lef1 signaling pathway           | [154]      |
| circ_009910  | ↑                  | AML     | 35 patients with AML and 35 healthy controls                          | HL-60 and MOLM-13                                                       | ↓ miR-5195-3p and ↑ GRB10   | –                                                                               | Δcirc_009910: ↓ proliferation and cell cycle progression, ↑ apoptosis                              | [155]      |
| circ CBFB     | ↑                  | CLL     | 47 patients with CLL and 21 healthy controls                          | HEK293T and MEC-1 human CLL cell line                                   | ↓ miR-607, ↑ FZD3           | ↑ Wnt/β-catenin pathway                                                       | Δcirc-CBFB: ↓ proliferation and cell cycle progression, ↑ apoptosis                              | [156]      |
| circ CFL1    | ↑                  | DLBCL   | female BALB/c nude mice                                              | OGI-Ly7 and OCH-Ly3 human DLBCL cell lines                              | ↓ miR-107, ↑ HMGB1         | –                                                                               | ↑CircCFL1, ↑ proliferation, migration, tumor volume and weight                                     | [148]      |

ANCTs, adjacent non-cancerous tissues; AML, acute myeloid leukemia; HSPC, hematopoietic stem and progenitor cell; MCL, Mantle cell lymphomas; CLL, chronic lymphocytic leukemia
acts as a sponge for miR-431-5p and miR-431-5p to further regulate expression of FOXP1 [147].

Another study has shown that up-regulation of circ-CFL1 in DLBCL cells leads to reduction of miR-107 levels and subsequent up-regulation of HMGB1 in these cells. Functional studies have revealed that circ-CFL1 could directly bind with miR-107 and release HMGB1 from inhibitory effects of this miRNA. Up-regulation of circ-CFL1 increases migration and proliferation of DLBCL cells [148].

Circ-APC is another circRNA which is produced from APC and suppress proliferation of DLBCL cells through decreasing activity of Wnt/β-catenin pathway. This effect is exerted through its interaction with TET1 and miR-888 [149].

The impact of circRNAs has also been investigated on progression of leukemia. For instance, circ_0132266 has been shown to be down-regulated in chronic lymphocytic leukemia. This down-regulation has lead to enhancement of viability of these cells via influencing activity of miR-337-3p/PML axis [150]. Table 3 shows the effects of circRNAs in the pathogenesis of B cell-related disorders.

Discussion
Accumulating evidence suggest the role of non-coding RNAs in the development of normal B cells as well as lymphomagenesis. Since they are have a highly cell type specific signature, these transcripts have been suggested as potential biomarkers for diverse clinical situations [157].

LncRNAs particularly those related with p53 or MYC pathways have also applications as therapeutic targets [157]. These transcripts could act as sponges for miRNAs, thus influencing expressions of their target genes. SNHG14/miR-5590-3p, MALAT1/miR-195, CRNDE/miR-345-5p, NEAT1/miR-34b-5p, SMAD5-AS1/miR-135b-5p, PTTG3P/miR-383, SNHG8/miR-335-5p, PCAT1/miR-508-3p, SBF2-AS1/miR-494-3p, SNHG14/miR-152-3p and LINCO00908/miR-671-5p are among lncRNA/miRNA axes which are involved in the regulation of B cells. Ras/ERK, Wnt/β-catenin pathway, NF-κB/ERK, PI3K/mTOR, BCR, TNE, IL-11/STAT3, IFN-I, Notch2, MAPK/ERK, PI3K/akt and glucocorticoid response pathways are among pathways that are regulated by lncRNAs in this context.

CircRNAs that regulate function of B cells are mostly associated with Wnt/β-catenin signaling pathway. They can also serve as sponges for miRNA. For instance, circ_OTUD7A/miR-431-5p, circCFL1/miR-107, circ-APC/miR-888, circ_0132266/miR-337-3p, circ_0005774/miR-192-5p, circ_0009910/miR-5195-3p and circ-CBFB/miR-607 are among important circRNA/miRNA axes in regulation of proliferation of B cells.

Finally, miRNAs that are involved in the pathogenesis of B cell-related disorders can modulate NF-κB, TGF-β, BCR, TAK1/IKKα-IKKβ/IκBα and MAPK/p65 signaling pathways.

Cumulatively, different classes of non-coding RNAs interact with each other to modulate function of B cells. Notably, non-coding RNAs have also interactions with immune check point proteins in the context of B cell disorders.

Conclusion
The observed interaction between non-coding RNAs and immune check point proteins suggests the importance of these transcripts as targets for immunotherapeutic approaches. Moreover, several lncRNAs, circRNAs and miRNAs have been found to affect proliferation of B cells, thus being involved in the pathogenesis of B cell-related disorders, particularly malignant disorders. The observed correlations between expression levels of these transcripts and clinic-pathological parameters further emphasize their role in the carcinogenic processes.

Understanding the impact of non-coding RNAs in B cell-related malignancies would provide new avenues for targeted therapies.

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Authors’ contributions
SGF wrote the manuscript and revised it. MT and EJ supervised and designed the study. TK and BMH collected the data and designed the figures and tables. All authors read and approved the final manuscript.

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Availability of data and materials
The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences. All methods were performed in accordance with the relevant guidelines and regulations.
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