Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 4, July 2024
Manuscript ID ZUMJ-2311-2998 (R1)
DOI 10.21608/ZUMJ.2023.247067.2998

Review Article

An Updated Insight about Possible Roles of NF-κB and MicroRNA in Acute Lymphoblastic Leukemia

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Submit Date 07-11-2023
Revise Date 08-11-2023
Accept Date 08-11-2023

ABSTRACT

Background: The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is considered a group of transcription factors that regulate the transcription rates in various biological activities, ranging from inflammation to memory and learning. The currently proposed hypothesis is that normal NF-κB proteins but abnormally activated, not the mutated derivatives, are more likely to show a critical role in the oncogenesis. Small RNA molecules called microRNAs (miRNAs or miRs) influence gene expression after transcription has already taken place. This review summarizes current knowledge on the possible roles of NF-κB and MicroRNA in Acute Lymphoblastic Leukemia (ALL).

Conclusion: An essential switch that prevents cell death among ALL cases and promotes cell growth is NF-B activation, found constitutively in most ALL patients in the form of RelA/p50 complexes. NF-B activity may be regulated, either positively or negatively, by the production of miRNAs, which NF-B can activate. Furthermore, miRNAs induced by other cell signaling pathways may cross-talk to regulate NF-B activation. However, the role of miRNA in leukemia pathogenesis is still unclear, despite the fact that miRNA expression profiles have showed promise as biomarkers for diagnosis, prognosis, and therapy response in leukemia.

Keywords: Updated insight, NF-κB, MicroRNA, Acute Lymphoblastic Leukemia

INTRODUCTION

There is a group of malignant hematological neoplasms known as acute lymphoblastic leukemia (ALL) that is characterized by the accumulation of abnormally proliferating immature lymphoid progenitors in the bone marrow, where they replace the normal hematopoietic cells, or in the peripheral blood and other extramedullary sites, where they damage surrounding tissues [1]. World Health Organization (WHO) classifies ALL into two categories according to predominate cells: B-lymphoblastic or T lymphoblastic leukemia [2].

In children, acute lymphoblastic leukemia is widely and significantly being the most common form of cancer globally, representing 28% of all childhood malignancies and 78% of leukemias, except in some countries in the

Equator region in Africa, where Lymphoma is more common than leukemia [3].

In Egypt, there are four new patients per 100.000 children per year diagnosed with ALL in the National Cancer Institute (NCI), Cairo University [4]. While the incidence of leukemia at Children's Cancer Hospital Egypt (CCHE) was 27.6%, The 5-year overall survival of children with ALL aged 0-18 years at CCHE during the diagnosis period 2007-2017 was 79.1% [5].

About 75% of childhood ALL patients have recurring chromosomal alterations, either aneuploidy or translocations, which can be detected by methods varying from karyotyping, which identifies considerable alterations, to whole genome sequencing, which detects cryptic changes in the entire genome. Identifying these abnormalities is crucial for optimum disease evaluation, risk stratification, and treatment planning [6].

Clinical presentations of ALL are usually nonspecific, representing a challenge for early diagnosis of the disease; the onset of the disease is generally sudden; however, the symptoms might take anywhere from a few days to several months [7].

Pathophysiology of the disease can be explained by being a lymphoproliferative disease, in which immature blasts replace normal hematopoietic cells in the bone marrow and infiltrate extramedullary organs [8].

Medullary involvement can cause the most prevalent clinical signs of ALL, leading to bone marrow failure syndrome. As a result, the patients may develop recurrent infections, pallor, bleeding, petechia, purpura, fatigue, muscle pain, anorexia, and pallor. ALL patients are considered immune compromised regardless of their white blood cell count as neutropenia, which is defined as a decrease in the absolute count of neutrophils below 500 and is familiar even with the presence of high WBCs, leads to infection and febrile illness [9].

From inflammation to memory and learning, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is thought to be a collection of transcription factors that regulates transcription rates.[10]. NF-κB was first defined in 1986 by Ranjan Sen and David Baltimore in B-cell lines in a search for κ light-chain gene activator; since then, thousands of experiments have been carried out studying this factor, which was found to activate hundreds of genes in most cells. Consequently, when triggered, it can fundamentally alter the molecular makeup of cells [11].

Now, it is widely known that NF-κB plays a vital role as an endogenous proinflammatory factor as well as regulates several processes, which could be either physiological or pathological, including cell division, angiogenesis, tumorigenesis, cell death, treatment resistance, inflammation, and immunological responses [12].

The NF-κB consists of five genes, which give rise to seven proteins. In the resting state, these proteins are retained in the cytoplasm as homodimers or heterodimers bound to the inhibitors of NF-κB (IκB) family proteins [13]. DNA binding, interaction with IB, and dimerization are all mediated by a similar N-terminal 300-amino-acid Rel homology domain (RHD) in these proteins [14]. The primary regulatory mechanism of NF-κB activity is an interaction between the inhibitors of NF-κB (IκB) and their opponents IκB kinases (IKK). To date, there are seven identified IκB proteins, subclassified into canonical IκB proteins (IκBα, IκBβ, and IκBε) and atypical IκB proteins (IκBζ, IκBδ, IκBη, and BCL3), these proteins characterized by presence of five to seven ankyrin repeats about thirty amino acids in length which interact with NF-κB [15].

Molecular mechanisms of NF-κB activation

Activation of NF-κB is considered to involve many signaling pathways that are initiated by distinct cytokines, growth factors, and tyrosine kinases. There are two proposed molecular processes that activate NF-B: the canonical pathway and the alternate pathway [16].

In the canonical pathway, NF-κB activation is triggered by many ligands such as bacterial lipopolysaccharides (LPS), TNF-α, and IL-1, which stimulate extracellular receptors like

interleukin-1 receptor (IL-1R), tumor necrosis factor receptor (TNFR), as well as toll-like receptors (TLRs) [17]. Identifying intracellular pathogens and direct cell stresses like reactive oxygen species and DNA double-strand breaks are also examples of internal signals that can activate NF-κB.[18].

In response to stimulation, the cytoplasmic domain of the receptors becomes populated with adaptors (such as TRAF), which subsequently recruit the IKK complex and contribute to the phosphorylation and degradation of the IB Inhibitor. NF-κB dimers, composed of Rel-A, c-Rel, Rel-B, and p50, are activated by the canonical pathway [18]. On the other hand, the NF-κB inducing kinase (NIK), which phosphorylates and activates the IKKa complex, is involved in the non-canonical activation that leads to processing and releasing active p52/Rel-B heterodimers by phosphorylating p100 [19].

In both pathways, after IκB is degraded, the released NF-κB is translocated to the nucleus and binds κB sites using the consensus sequence GGGRNNYYCC (N=any base, R=purine, and Y=pyrimidine) found in promoter and enhancer regions of hundreds of target genes [20]. Therefore, it is unsurprising that NF-κB is highly regulated by both positive and negative regulatory factors at various levels. Tight coordination with other signaling pathways when at rest is also present. This complex interaction is essential for transforming the many biological actions of NF-κB into cell-type and context-specific responses [21].

NF-κB and cancer

Cancer is characterized by malignant cells' unique ability to promote tumor development and spread by maintaining proliferative signaling, resisting cell death, having the capacity for replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming energy metabolism, and avoiding immunological devastation. Interestingly, NF-κB is essential in most cellular changes [22]. The currently proposed hypothesis is that normal NF-κB proteins but abnormally activated, not the mutated derivatives, are more likely to play an essential role in the oncogenesis [23]. NF-κB is found to be continuously activated in many human malignancies, either solid tumors (such as Hepatocellular carcinoma (HCC), colorectal cancer, breast cancer, and prostate cancer) or hematological malignancies including leukemias, lymphomas, and multiple myeloma [24].

NF-κB in ALL

Transient activation of several receptors, like antigen receptors, Toll-like receptors (TLRs), and interleukin-1 (IL-1), and TNF receptors, induces NF-κB signaling in lymphocytes, which is crucial for cell survival, proliferation, and the acquisition of effector functions [25]. Aggressive lymphomas in birds and other animals are caused by the viral oncogene product v-Rel, and studies of v-Rel have provided the first evidence linking key components of the NF-kappaB signalling pathway to lymphomagenesis [26]. An essential switch that prevents ALL cell death and promotes cell growth is NF-κB activation, which is found constitutively in most ALL patients in the form of RelA/p50 complexes [27]. As an illustration, the activation of NF-B due to BCR-ABL expression in T-ALL or B-ALL cells is critical to the pathogenicity of Philadelphia-positive (Ph+) leukemias [28].

Also, translocation known as t(14; 19) may be present in certain B-cell lymphocytic leukemias. Bcl-3 is found close to the chromosomal breakpoint of chromosome 19q13, leading to overexpression of Bcl-3, which increases NF-kB activity because it functions as a transcriptional coactivator of p50 or p52 homodimers [16]. In T-ALL, NOTCH1 activating mutation is found in 60% of cases [29]; evidence suggests that Notch-NF-κB crosstalk is a crucial mediator of Notch-driven T-ALL transition through a variety of pathways [30], so inhibition of NF-κB alone or in combination with NOTCH1 inhibitors may be an effective T-ALL therapeutic strategy [31].

MicroRNA

Most of the human genome is composed of non-coding RNAs (ncRNAs). For a long time, ncRNAs were assumed to be inert molecules, but the fact that eukaryotic cells express more

ncRNAs than mRNAs that code for proteins makes this assumption too far away to be valid. New research shows that ncRNAs serve an important regulatory role, leading to abnormal expression, which in turn causes a wide variety of human disorders. According to their length, ncRNAs are divided into two groups: long ncRNAs (>200 nucleotides) and short ncRNAs (<200 nucleotides). The latter includes microRNA (miRNA), short interfering RNAs (siRNA), piwi-interacting RNA (piRNA), and small nucleolar RNA (snRNA) [32].

Small RNA molecules called microRNAs (miRNAs or miRs) influence gene expression after transcription has already taken place. MiRNAs serve crucial roles in most cellular functions, from development to homeostasis, and as a result, they are connected to several disorders, including cancer. Numerous studies on the function of miRNAs in disease have been conducted since the first microRNA (miRNA) was discovered in 1993. According to Airbase (http://mirbase.org), there are now 1917 known human miRNA genes scattered among chromosomes, most of which have distinctive biological characteristics and gene targets [33].

NF-κB and miRNAs

MiRNA expression is a very dynamic process that is based on cellular elements that control transcription. However, the connection between miRNA and some transcription factors, such as NF-κB, is bidirectional [34]. A positive or negative feedback loop involving miRNA expression and NF-B activity is possible. Furthermore, NF-B activity may be cross-regulated by miRNAs that are activated by other cell signaling pathways. Many miRNA genes have sites in their promotors that have been approved as NF-κB targets, such as miR-146, whose promoter has two NF-κB binding sites. Other examples of miRNAs are controlled with NF-κB miR-155, miR-132, miR-9, miR-21, miR-147, and miR-301a [35].

On the other hand, about 29 miRNAs have been identified to have the potential to decrease NF-κB activity either targeting NF-κB activating kinases or other NF-κB signaling components, for instance, miR-146, let-7b, miR-124a, miR-155, miR-125b, miR-220, miR-199b, and miR-301a [35].

MiRNAs in cancers

Numerous human diseases, including autoimmune, cardiac, schizophrenia, and cancer, have been linked to changes in miRNAs. Some miRNAs have been reported to act as oncogenic miRNA (OncomiR), which is elevated in tumors, while others are tumor suppressive miRNA (TS-miR), which is downregulated in malignancies [36].

Causes of abnormal miRNA expression

Chromosomal alteration

Half of all miRNA genes are found in either highly unstable regions of the genome or regions associated with cancer. It is possible that these sections are shared breakpoints, a minimal area of loss of heterozygosity that contains a tumor suppressor gene, and an amplified minimal part that has oncogenes. For example, the 5q33 region that includes miR-143 and miR-145 is commonly deleted in lung cancer, leading to down-regulation of both miRNAs 8/17/2024 11:20:00 AM, in contrast, elevated levels of miR-17-92 in B-cell lymphomas, lung cancer, and T-cell acute lymphoblastic leukemia as a result of amplification of the miR-17-92 cluster gene [37].

Single nucleotide polymorphisms (SNPs**)**

SNPs are the most common type of genetic variation in the human genome. There are about 10 million identified SNPs until now, which occur in both coding and noncoding regions. SNPs in the coding areas have gained the most attention as they may result in changes in amino acids, but there is growing evidence that SNPs in non-coding regions are not less significant. The presence of SNPs inside the miRNA sequence or miRNA binding site is known as miR-SNP and can impact how miRNAs interact with their target. According to location, miRNA genomic variation has several effects in tumors, such as a single change in the miRNA precursor sequence might cause the splicing enzymes' mis-localization. More critically, SNP in mature miRNA sequences, especially seed sequences, can potentially reduce their

inhibitory impact or change the mRNAs they target [37].

Epigenetic modifications

The term "epigenetics" refers to heritable variations in gene activity that take place without changes in the DNA sequence. The essential epigenetic modifications are DNA methylation and histone modifications. DNA methylation is a chemical alteration of DNA that involves attaching methyl groups to the cytosine 5th carbon by DNA methyltransferases. The most common DNA methylation patterns seen in cancer cells are an increase in CpG island methylation at gene promoters and a reduction in overall DNA methylation patterns. There is a crosstalk between DNA methylation and miRNAs. DNA hypermethylation or hypomethylation resulted in the downregulation or overexpression of several miRNAs, respectively. For instance, miR-127's upregulation was correlated with its DNA methylation status. Additionally, CpG island hypermethylation has been linked to the transcriptional inactivation of the miR-124a, miR-34, and miR-9 families of miRNAs in human tumors. On the other hand, miRNAs can affect the expression of DNA methylation level by changing the level of DNA methylase or their supporting proteins; for instance, it is known that the miR-29 family targets DNA methylases. Because of their proximity to DNA and their ability to undergo post-translational modifications including acetylation, phosphorylation, and methylation, histones are also regarded as an important epigenetic regulator. Therefore, several studies investigate the effect of histone modification on miRNA expression in cancers, as the significant change in miRNA levels occurs after histone deacetylase inhibitor in cancers such as breast cancer and urinary bladder cancer [38].

MiRNA in ALL

The disruption of the miRNAs, which are crucial for controlling healthy hematopoiesis, may lead to leukemogenesis. Since ALL is well-known for its biological heterogeneity and diverse lineage origins, profiling studies have shown that ALL is also variable regarding miRNA expression. This has led some researchers to speculate that miRNA expression profiles could be biomarkers for leukemia diagnosis, prognosis, and treatment response. ETV6-RUNX1 patients have elevated levels of several miRNAs, including miR-100, miR-125b, miR-99a, miR-126, and let-7c, but miR-181a was shown to be significantly downregulated in this subtype as demonstrated in Figure 1. MiRNAs provide an entirely new world of possibilities for our knowledge of the progression and treatment of cancer-based on the aberrant miRNA expression patterns found in human malignancies [39,40].

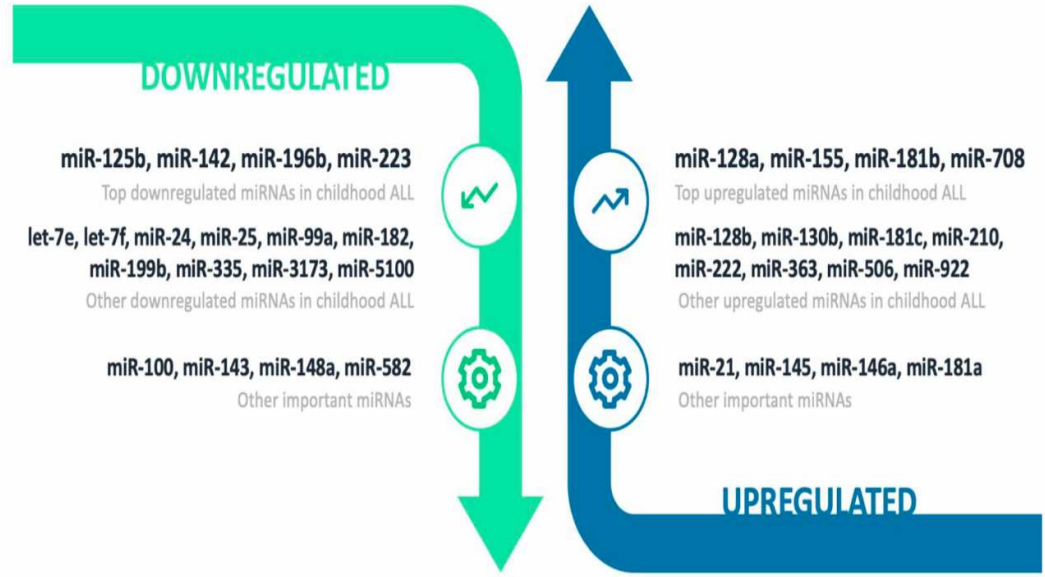

Figure (1): Schematic representation of significantly differentially expressed miRNAs in childhood ALL diagnosis compared to controls

CONCLUSION

An essential switch that prevents cell death among ALL cases and promotes cell growth is NF-κB
activation, found constitutively in most ALL patients in the form of RelA/p50 complexes. NF-κB activity may be regulated, either positively or negatively, by the production of miRNAs, which NF-κB can activate. Furthermore, miRNAs induced by other cell signaling pathways may cross-talk to regulate NF-κB activation. However, the role of miRNA in leukemia pathogenesis is still unclear, despite the fact that miRNA expression profiles have showed promise as biomarkers for diagnosis, prognosis, and therapy response in leukemia.

Declaration of interest

The authors report no conflicts of interest.

Funding information

None declared

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Citation ;

Fawzy, A., Rezk, N., Zakaria, m., Sameh, h. An Updated Insight about Possible Roles of NF-kB and MicroRNA in Acute Lymphoblastic leukemia. Zagazig University Medical Journal, 2040 ; (2332-2344): -. Doi: 10. 21608 /zumj.2023.247067.2998