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Potential Biomarkers for Diagnosis and Prognosis of Acute Myeloid Leukemia

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ABSTRACT: For many years, cancer has affected the global population from an economic, social and political point of view and, in most cases, it is a malignant tumor with serious consequences for patients. The objective of this study is to answer the potential biomarkers for the diagnosis and prognosis of acute myeloid leukemia. Therefore, this is an exploratory, descriptive bibliographic study with a qualitative approach. The data were collected from a bibliometric survey carried out during a study of scientific production on the proposed topic from 2013 to 2023. After searching for articles, 210 articles were found on the PubMed platform, and no results were found for the key suggested by word in other databases. Among the 210 articles, 28 articles were selected for review. In this way, we seek to analyze which biomarkers have been addressed in the last 10 years in the scientific literature, thus aiming to demonstrate possible targets for new research. We divide our research into genes that are promising biomarkers for diagnosis and/or prognosis and the role of miRNAs as biomarkers.

KEYWORDS: Acute myeloid leukemia, biomarkers, diagnosis, neoplasm genes, tumor biomarker, screening.

INTRODUCTION

Over the years, cancer has been affecting the world's population from an economic, social and political point of view, in most cases they are highly malignant neoplasms that generate serious consequences for the patient, putting pressure on the public health system for many years, causing a significant number of deaths. Factors such as high population growth over the years, aging and socioeconomic conditions have contributed to morbidity and mortality levels, resulting in high rates of new cases, reaching 18 million cases, and high mortality rates (9.6 million of deaths). Solid neoplasms can affect various organs, the most common of which are the lung, breast, colon, rectum and prostate. However, liquid neoplasms, such as hematological ones, were responsible, between 2020-2022, for around 5,920 new cases for men and 4,890 new cases for women (Brasil, 2019).

Blood is made up of several cells, including erythrocytes, platelets and leukocytes. If they are within their normal functionality, they perform intrinsic functions of extreme importance for the body, such as transporting oxygen and nutrients, combating infection through the immune system, among others. However, when there is an accumulation of deficient cells located in the bone marrow, there is a dysfunction in the course of the functional normality of the blood, thus leading to defective cells performing essential functions in the functioning of the body. Leukemias are the direct result of the effect of these defective cells performing functions in the blood, depending on their origin, they can be classified as chronic, acute, myeloid and lymphoid, where one of the main ones is Acute Myeloid Leukemia (AML) (Oliveira; Castro; Horner, 2021).

AML consists of a heterogeneous group of leukemias that originate from the clonal transformation of hematopoietic precursors through chromosomal changes derived from diverse mutations (Rubnitz; Gibson; Smith, 2010). AML is based on a clonal disease of cells originating from the myeloid lineage, resulting in a low rate of mature cells in peripheral blood, that is, immature cells end up playing roles within the blood circulation that would only be performed by properly matured cells. Due to this hematopoietic cellular immaturity, the individual may present symptoms such as fever and paleness, and may also be affected by infections, hemorrhages, and leukostasis.

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For a population of 100,000 inhabitants there is a prevalence of 3.6 new cases per year, affecting people aged 66 on average. (Brazil, 2014). Between 2008 and 2017, the mortality rate increased by approximately 23%, thus presenting a variation rate from 1,996 deaths in 2008 to 2,462 deaths in 2017 (Melo, 2020). When it comes to good factors that can be analyzed for diagnosis, biomarkers are among the most promising. According to (Jesus., Oliveira, 2020), substances synthesized from the tumor (or consequence of its presence) that can be measured in biological samples are referred to as "tumor markers", which were initially used for screening and diagnostic strategies for neoplasms, such as example ovary and prostate. Even with their limitations, they still have great importance in the scientific world.

Therefore, this research seeks to answer what are the potential biomarkers for the diagnosis and prognosis of Acute Myeloid Leukemia. We aim to carry out a screening of the main biomarkers for AML over the last 10 years. Considering the malignant neoplastic characteristics of this condition and its importance in the pressure exerted on the Unified Health System, it is extremely important to know mechanisms that reduce costs and assist in diagnosis along with risk categorization so that patients can be managed in the best way possible. . In addition to improving the patient's quality of life.

METHODOLOGY

This was an exploratory-descriptive bibliographic study with a qualitative approach. Data collection took place from a bibliographical survey carried out through research carried out on scientific productions on the proposed theme, from 2013 to 2023. The literature search was carried out in the following databases: Latin American and Latin American Literature Caribbean in Health Sciences (LILACS), and PubMed. It is noteworthy that the LILACS database was consulted through the Virtual Health Library (VHL). The searches were carried out using the Health Sciences Descriptors (DeCS) from the Regional Library of Medicine (Bireme): Neoplasm genes, biomarkers, tumor biomarker, acute myeloid leukemia, diagnosis, screening English and Spanish with the help of the Boolean operators "AND". The inclusion criteria for the selection of content were those published in full according to the theme, documents, regulations, regulations from health entities on the topic, articles published in English and Spanish and articles with free access.

The exclusion criteria were articles that were not relevant to the topic, duplicated, incomplete materials, debates, reviews, summaries, materials unavailable in full and articles that are outside the pre-established time frame. Data analysis proceeded in three stages: first, a floating reading was carried out, where the researcher obtained an overview of the participants' opinions; in the second stage, an exhaustive reading was carried out, that is, thorough and repeated, of all the data collected; and in the third, the construction of categories was carried out for better analysis of the data, observing the methodology and results of the studies found, which aimed to search for answers that that article proposes for the questioning of this study.

Aiming at this scenario, the articles read were selected and grouped into axes, aiming to better categorize the biomarkers that have been discussed in the last 10 years in the literature, making it possible to highlight which of them are promising for more in-depth research, analyzing their particularities and their functional mechanics. . The articles were separated into the following axes: a) Gene biomarkers that can be used as a diagnostic strategy in AML; b) miRNAs as AML biomarkers.

RESULT AND DISCUSSION

At the end of the search for articles, 210 articles were found, which were found on the PubMed platform, as for the other database, there were no results with the proposed key words. Among the 210 articles, 28 articles were selected to review data on the topic, taking into account some criteria such as: finding answers that could answer the research question; articles that addressed the same genes (even if in different studies) so that there would be more information on the topic.

I. Gene biomarkers that can be used as a diagnostic strategy and prognostic prediction in AML

The genetics that is known and studied today has its origins based on the memories of Gregor Mendel around 1865 in his study of plant hybridization, however the term genetics was only established in 1906, with the aim of designating the new science based in heredity. Around the 1910s, Mendelian genetics was merged with the chromosomal theory of inheritance, giving rise to "classical genetics". Therefore, the gene is defined as a unit of transmission, function, mutation and recombination, however with the discovery of DNA as the basis of inheritance material, in 1950 this concept dissolved, meaning that to this day studies based on them aim to further understand their complexity (Gayon, 2016).

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When we move on to the genetics axis focused on biomarkers, we define this term as essential aspects for development in the medical field, both in terms of diagnosis and therapeutic practice. Recently, biomarkers have been categorized into classes ranging from patient care to the development of new therapies. When we talk about biomarkers for diagnosis, they are defined as those that have the ability to detect or confirm the presence of a disease, a condition of interest or the possibility of identifying subtypes of the disease being researched. Regarding prognosis, a biomarker focused on the area is used to identify the probability of the occurrence of a clinical event, a recurrent disease or even the progression of the patient's condition. Another benefit of prognostic biomarkers is their ability to predict the risk of an unfavorable clinical event related to the disease in the individual, thus being able to act in decision-making that covers the entire medical procedure in the patient (Califf, 2018).

A. ASXL1

Based on the research carried out, in the last 10 years the literature has presented genes that can be used as biomarkers in both diagnosis and prognosis. The ASXL1 gene has several interactions with other genes, such as the TET2 gene, which according to Sasaki et al 2019 is a gene commonly observed in myeloid neoplasms (figure 1). It had been studied and presented by Concepción Prats-Martín et al., 2020 as a gene that could facilitate the diagnosis of AML in patients with myelodysplasia (AML-MRC), targeting patients who present a normal karyotype, and especially in patients who may have a morphological assessment of difficult multilineage dysplasia. MRC-AML is a subtype of leukemia that has a poor prognosis. This study demonstrated that patients who have a mutation in the ASXL1 gene (ASXL1+) express a greater number of leukocytes during the diagnostic process, compared to patients who do not have this mutation. The mutation in this gene, according to the study, is common in patients with AML-MRC, where it brings with it specific aspects such as morphological signs of dysplasia. Regarding the prognostic value of mutations in the ASXL1 gene, it has been demonstrated in some conditions such as myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN) and primary myelofibrosis (FMP).

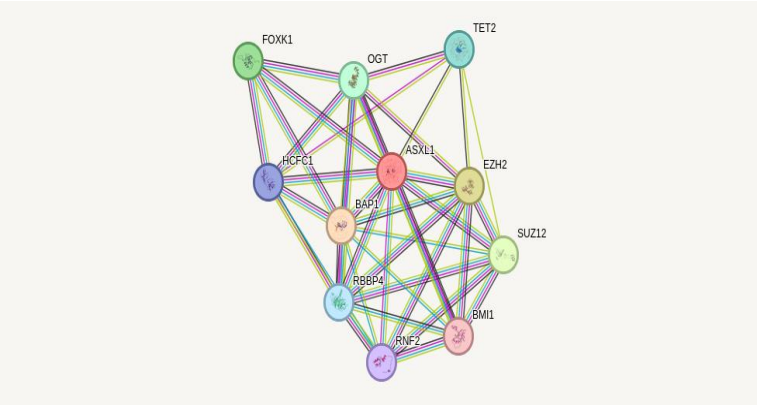

Figure 1: Some connections made by the ASXL1 gene . Demonstration of its interaction with the TET2 gene and other genes. Image made by software © STRING Consortium 2023 version 12.

With regard to AML, these gene mutations are being associated with an adverse outcome. The research by Concepción Prats-Martín et al demonstrates that there is a diversity in the mutations found in ASXL1, mutations such as: *nonsense* type (p.R693* and p.Q965*) and *around 9* different frameshift mutations. According to the research, among the 61 patients analyzed, the most frequent mutation was p.G646fs*12, which was detected in 8 patients. In summary, the study reports that the *nonsense and frameshift* mutations that were observed in exon 14 synthesize a protein truncated in the C-terminal PHD domain, which in turn results in a haploinsufficiency, thus causing a variation in the copy number of a gene resulting in a decrease in gene dosage due to some mutation. The group also points out that the ASXL1 gene has an important role as a marker of worse outcome for patients with this AML condition due to its resulting implications.

B. FLT3

The FLT3 gene consists of a tyrosine kinase receptor, which is activated by a transmembrane ligand that generally tends to be expressed by stem cells of the hematopoietic axis or in progenitor cells, which in turn end up developing relevant functions in

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the initial stages of the myeloid segments. and lymphoid. FLT3 is turned on and activated, thus promoting cell survival, proliferation and differentiation. Signaling pathways are activated in this process, such as PI3K and STAT5, as shown in figure 2.

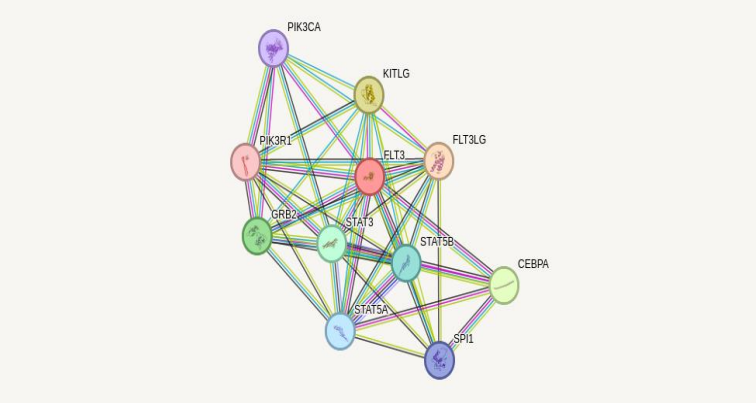

Figure 2: Some connections made by the FLT3 gene. Demonstration of some signaling pathways such as PI3K and STAT5. Photo taken by software © STRING Consortium 2023 version 12.0, software that makes protein-to-protein bonds

In the study carried out by Daver et al., 2019, a mutation called FLT3-ITD (internal tandem duplication) is presented which, according to the authors, consists of a high leukemic load and which can confer a poor prognosis to the patient. Regarding the diagnostic axis, testing for the FLT3-ITD mutation is important both in the first moment and in the relapse of the disease, since in the research it is reported that the initial evidence of this mutation came from comparative studies that observed this mutation in samples of bone marrow, defining it as a driver mutation. The mutations that occur in this gene occur in approximately 30% of newly diagnosed AML cases. The FLT3-ITD mutation occurs in the form of a replicated sequence in the juxtamembrane domain (JM), varying its location and size.

Daver et al., 2019 point out that there is an observation to be taken into consideration, which consists of analyzing the mutations expressed by the FLT3 gene, as it can evolve both in diagnosis and in disease recurrence. At this point, it should be noted that testing for mutations in the FLT3-ITD gene may be necessary during several episodes during the course of the disease. By adopting this strategy, the patient will be able to have better therapeutic guidance. With the use of the FLT3-ITD rapid diagnostic assay, the patient will be able to receive better care, where it will be possible to identify patients with a poor prognosis, thus making the possibility of early therapeutic intervention viable, directing specific therapies.

A study by JIANG et al., 2018, demonstrates the relationship between the Wnt/β-catenin signaling pathway and the FLT3 gene, pointing out that its disruption can offer antileukemic effects. Wnt/β-catenin signaling is proposed to be necessary for the functionality of leukemic stem cells, and when there is a mutation linked to the FLT3 gene there is an increase in the nuclear localization of β-catenin along with transcriptional activity, however Wnt/β signaling -catenin acts in several relevant functions, such as the regulation of cell proliferation, survival and differentiation. When there is a deregulation of this signaling, it is possible to observe the link between the beginning of the process and the progression of AML, given that it is reported that the overexpression of Wnt /β-catenin is attributed to an adverse prognostic factor in AML. Therefore, the study proposes that the inhibition of Wnt/β-catenin signaling may present a promising therapeutic strategy. One study reports the importance of investigating the allelic load of FLT3 as a prognostic factor, as the presence of the mutation represents a poor prognosis in patients with AML (Candoni et al., 2017.

C. WT1

Another gene cited in the literature within the proposed time frame was the Wilms tumor gene (WT1) (figure 3). In 2016 UJJ, et al., points out that the gene has been targeted as a marker of Minimal Residual Disease (MRD), however, the data reported in the literature are not free from controversy and that after the accumulation of data expressed on the molecular functionality of the gene in AML will be more evident the use of the gene as an aspect of extreme relevance, however in 2017, a study carried out by Zhao et al., consisted of analyzing WT1 as a basic biomarker of Minimal Residual Disease (MRD) expressed in AML. The WT1 gene is located on chromosome 11p13 where its functional activity is to encode a DNA-binding protein, which has been identified as an indicator for monitoring MRD. As a result of the study, the authors pointed out that the establishment of WT1 messenger RNA

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(mRNA) is greater than 2.98%, indicating a high risk of recurrence, where it was detected in around 41 patients during the initial diagnosis.

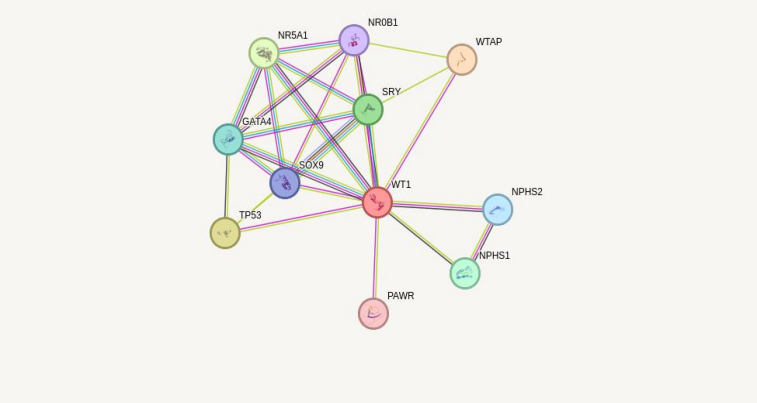

Figure 3: Some connections made by the WT1 gene. Photo taken by software © STRING Consortium 2023 version 12.0, software that makes protein-to-protein bonds

In summary, using the receiver operating characteristic curve (ROC) study by Zhao et al concludes that the level of WT1 mRNA expression can be used as an indicator for monitoring MRD during the remission phase of AML, and when the mRNA level is established as greater than 3.00%, this predicts clinical recurrence of the disease.

Another study (Huang et al., 2019) points out that overexpression of the WT1 gene and PRAME can predict poor outcomes in patients presenting MDS with thrombocytopenia. According to the authors, both WT1 and PRAME are promising candidates for specific immunotherapy. WT1 plays a relevant role in the regulation of myeloid differentiation in hematopoiesis, where when there is an abnormal expression of this gene, there is a delay in proliferation and/or differentiation. cell phone. PRAME has been described as a repressor of retinoic acid signaling, where it inhibits hematopoietic differentiation, apoptosis and the completion of the cell cycle. A priori, its description was pointed out in solid tumors, such as breast, lung and ovarian cancer, acting on their tumor stage. The study points out that there is several evidence that both WT1 and PRAME are overexpressed in several malignancies, including leukemia and MDS. However, the overexpression of WT1 and PRAME was associated by the study with a high percentage of blasts, worse cytogenetics and a higher risk of Revised International Prognostic Scoring System (IPSS-R), being independent factors of poor prognosis for the evolution of AML. Concomitantly, the overexpression of these genes was able to identify patients with MDS who have substantially worse survival.

A recent study carried out by Chen et al., 2021, also reports the overexpression of the WT1 gene, however related to the low expression of diffraction cluster 58 (CD58), pointing out interesting results that demonstrate that the combination of the WT1 gene and CD58 can be potential biomarkers to better categorize patients with cytogenetically normal acute myeloid leukemia (AML-CN), ranking between low, intermediate and high risk, however the study indicates that it is relevant to combine the WT1 gene with other genes to obtain better stratification risk for patients. According to GOEL et al., 2020, monitoring MRD is extremely relevant for preventing future relapses, thus improving Overall Survival, demarcating that the gene can be used as a promising biomarker for evaluating residual blasts. And as previously reported by Zhao et al., 2017, the study also points out that the WT1 gene is a promising target for MRD detection, thus promoting advances in early identification of AML recurrence.

D. TP53

Recently, a study was published by WEN et al., 2021, reporting on the TP53 gene (figure 4) and its prognostic relationship, tumor mutational load and immunological characteristics related to AML, also pointing out that mutation in this gene is a frequent feature in AML. disease, also reaching the immunological context, making this gene a good biomarker for predicting the immune response of AML. The TP53 gene is located on chromosome 17p13.1 where it encodes a phosphoprotein of approximately 393 amino acids and acts as a transcription factor, with the function of tumor suppression. In general, mutations in this gene are observed in several tumors. but when compared with solid tumors, the gene appears more rarely, although it is closely linked to AML. The study found that the TP53 gene was frequently affected by mutations and that they exhibited a certain exclusivity with other common

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mutated genes, also associated with a poor prognosis. The study also addresses that CD8+ T cells demonstrate high infiltration in the TP53 gene mutant group, thus inspiring further studies of immunotherapeutic approaches aimed at T cells in TP53-mutated AML.

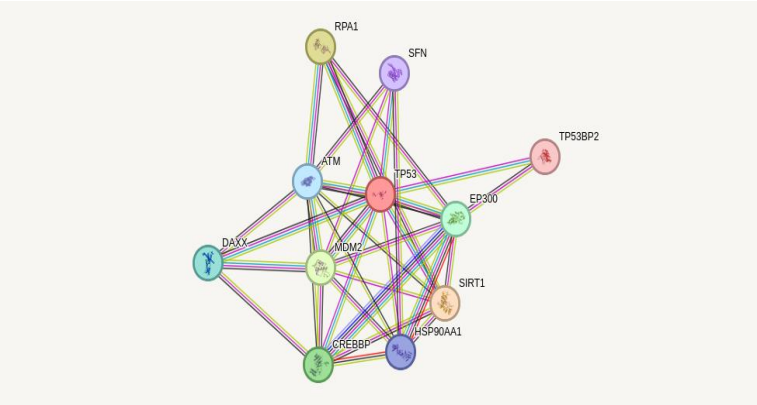

Figure 4: Some connections made by the TP53 gene. Image made by software © STRING Consortium 2023 version 12.0.

The data presented in the study carried out by Knaus et al., 2018, based on CD8+ T cell dysfunction, indicated that the response to chemotherapy is related to the positive regulation of costimulatory and inhibitory T cell signaling pathways, indicative of the restoration of the function of these cells . His research made it possible to demonstrate that AML presents the uniqueness of sculpting CD8+ T cell responses and also its peculiarity in the signatures expressed in the response to chemotherapy, pointing out the relevance of integrating new immunotherapy strategies aimed at increasing antileukemic immunity.

A recent study carried out by XIE et al., 2022, analyzed which transcriptomic deregulation is associated with mutation of the TP53 gene, which may be linked to the poor prognosis of the disease, analyzing microRNAa (mRNAs) and non-coding RNAs (IncRNAs) together with two modules of co-expression that allowed risk stratification and patient survival, indicating that both mRNAs and lncRNA present in the gene mutation could provide a prediction of survival for patients with AML. Another study also points out that mutations associated with TP53 have a very unfavorable effect, it also points out that the activation of the gene protein (p53) can be studied based on its pharmacological activation, being a logical therapeutic strategy aimed at leukemia (Kojima ; Ishizawa; Andreeff, 2016).

E. DNMT3A

According to Chen et al., 2020, mutations in the DNMT3A gene (figure 5) have been widely described in several types of cancer, especially hematological diseases in adults. The gene was associated as a biomarker that promotes prognostic assessment and monitoring of MRD in AML. The study points out that the DNMT3A gene mutation can be a dangerous element for AML, therefore being a new prognostic factor and target for therapeutic processes. The authors carried out research based on bioinformatics, where they pointed out that mutations in the DNMT3A gene may indicate a possible contribution to the progression of the disease together with analysis of the prognosis, as they can influence aspects such as proliferation, differentiation, morphogenesis and cellular hemoptysis in patients affected by AML, also pointing out that signaling pathways such as PI3K-Akt together with transcriptional dysregulation in cancer can influence DNMT3A mutations in AML. An older study developed by Jost et al., 2013, had already pointed out that a large proportion of patients with AML had mutations or epimutations in the DNMT3A gene, thus indicating a high relevance for the development of the disease, making it necessary to increasingly address the issue in greater depth. relevance that this gene together with its mutations have for diagnostic and prognostic strategies in conjunction with risk stratification by individual to better define a therapeutic strategy.

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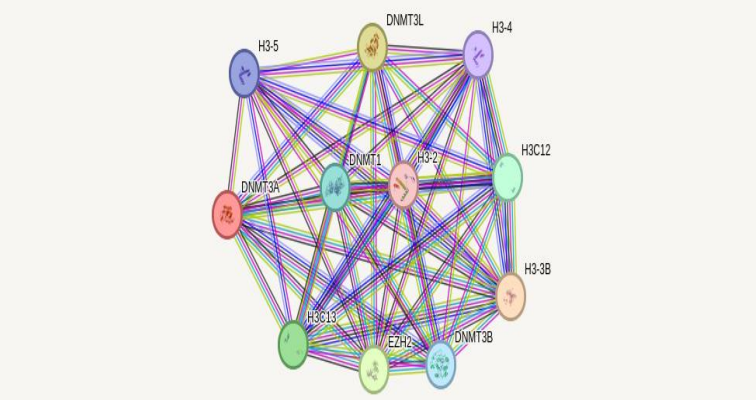

Figure 5: Some connections made by the DNMT3A gene. Image made by software © STRING Consortium 2023 version 12.0.

F. NPM1

Over the last ten years, the literature has continually cited the NPM1 gene (figure 6). JIN et al., 2018 points out that nucleophosmin (NPM1) is one of the most altered genes in patients with acute myeloid leukemia with normal karyotype (AML-NK), reaching high rates of occurrence in adult patients. The study aimed to analyze the relationship between inositol polyphosphate 4-phosphatase type II (INPP4B **)** and phosphoinositide-3 kinase (PI3K) and its clinical relevance in NPM1-mutated AML. Their results demonstrated that INPP4B promotes the survival of leukemia cells through the activation of SGK3, thus being promoted as a promising therapeutic target for NPM1-mutated AML. High levels of INPP4B indicate serious clinical problems in AML, as its overexpression promotes the survival/proliferation of leukemic cells. According to the study, the data they point out indicates a strategic therapeutic path aimed at delving deeper into the mechanism of INPP4B in AML with a mutation in the NPM1 gene.

In 2018, Jin et al., carried out a study indicating a potential biomarker aimed at NPM1, lncRNA XLOC_109948. The study demonstrated that low expression of the lncRNA , in short, could predict the patient's chemotherapy response, also pointing out that further studies on lncRNAs can be of great value for therapeutic strategies for the pathogenicity of AML, determining their molecular mechanisms and therefore using them for better therapeutic decisions in the future.

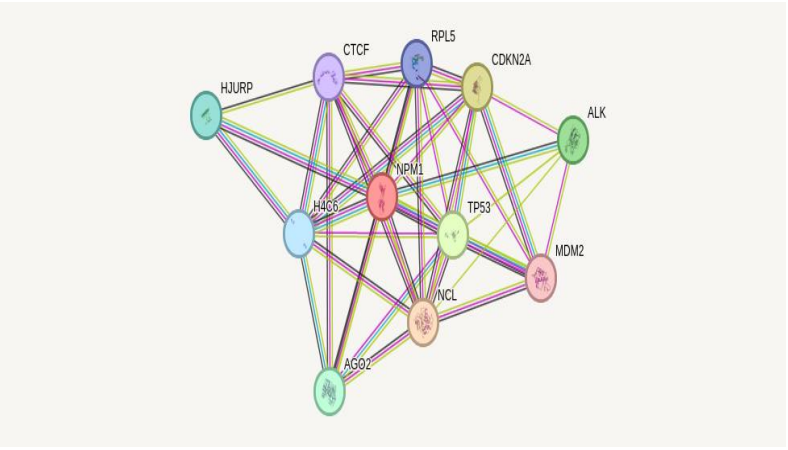

Figure 6: Some connections made by the NPM1 gene. Image made by software © STRING Consortium 2023 version 12.0.

G. SALL4

According to IBRAHEEM et al., 2019, the SALL4 gene (figure 7) is a promising marker for diagnostic prediction and risk stratification, as the gene is a zinc finger transcriptional factor of the SALL gene family and is one of the only ones that makes the connection with self-renewal properties of both embryonic stem cells and normal hematopoietic stem cells and leukemic stem cells, thus promoting risk stratification for patients, helping to categorize individuals into appropriate risk groups. In their study using

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real-time quantitative PCR to analyze the expression of the SALL4 gene in the peripheral blood of 52 adult patients (along with 10 control/healthy patients) where the data showed that the expression of the SALL4 gene is easily detectable by real-time PCR .

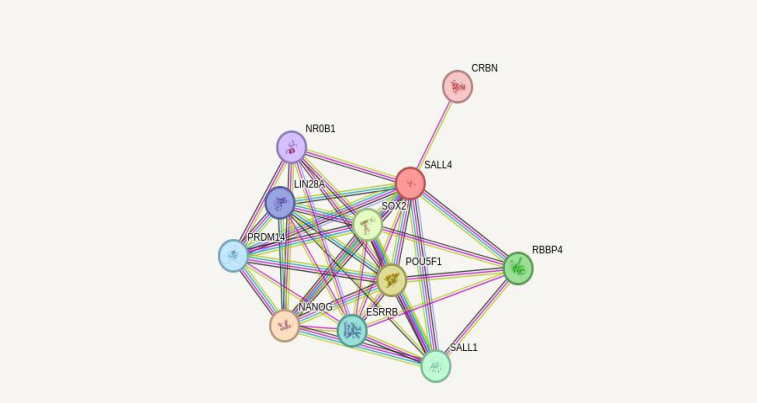

Figure 7: Some connections made by the SALL4 gene. Image made by the software © STRING Consortium 2023 version 12.0

H. SAMHD1

The SAMHD1 gene (figure 8) was mentioned in the study carried out by Oellerich et al., 2019, which pointed to the gene as a predictive biomarker and a therapeutic target for therapeutic procedures based on decitabine (DAC), but the study reported that the gene does not contribute as a biomarker for azacitidine (AZA)-based treatments. Using the SAMHD1 gene as a biomarker makes a contribution to pre-clinical and clinical axes, presenting differences in efficacy along with the initial response expressed by the drugs. The authors point out that decitabine contains a metabolite that could cause the inactivation of the SAMHD1 gene, thus serving as a biomarker for treatment. The authors present DAC and AZA as substances analogous to cytidine nucleosides, which in turn are structurally related. Both DAC and AZA are activated intracellularly by triphosphorylation, however DAC triphosphate (DAC-TP) is incorporated by DNA, while AZA triphosphate (AZA-TP) is incorporated by RNA. According to the study, DAC-TP when derived from DAC and AZA, it can express conditions such as the induction of DNA damage and apoptosis and the suppression of DNA methylation, whereas AZA-TP, expressing unique effects on AZA, can cause interruption of the transcriptional process and protein synthesis. In short, the study reports that several other biomarkers such as DNMT3A, IDH1/2, TET2, ASXL1 and TP53 were proposed as predictions of response to DNA hypomethylating agents (HMAs), but they were sufficiently robust for this purpose. the singular selection of HMA, but they point out that mutations derived from SAMHD1 are not very frequent, therefore it would not be very advisable to analyze this axis as a biomarker as a therapeutic strategy for CAD. According to the article, DAC activity is affected by SAMHD1 triphosphohydrolase in AML cells, thus pointing out crucial points in the mechanism of HMAs, making carrying the gene a promising target for therapeutic use.

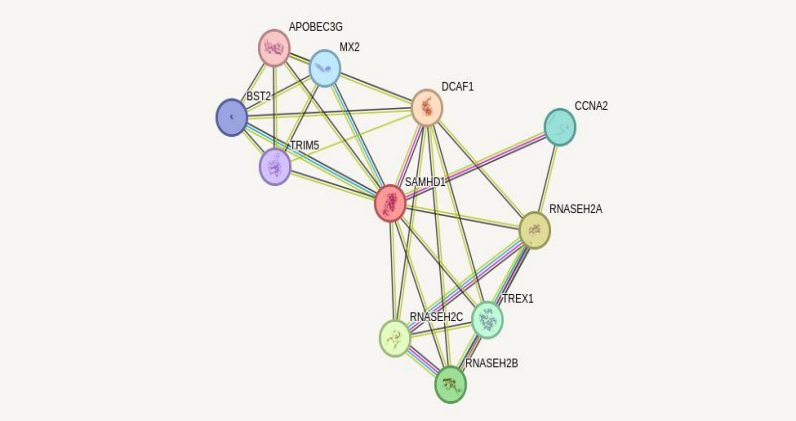

Figure 8: Some connections made by the SAMHD1 gene. Image made by software © STRING Consortium 2023 version 12.0.

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I. DDIT4

CHENG et al., 2019 pointed out in their study that the positive regulation of DNA damage-inducible transcript 4 (DDIT4) (Figure 9) presents itself as a biomarker of poor prognosis in AML, which has already been associated as a co-participant of the tumorigenesis process, also affecting patient survival. Conditions such as cellular, endoplasmic reticulum and oxidative stress together with hypoxia, heat shock and starvation are factors that tend to induce the DDIT4 gene, in addition, the gene inhibits the activity of a relevant complex in mammals, rapamycin complex 1 (mTORC1) , an element that plays a role in cell growth, proliferation and survival.

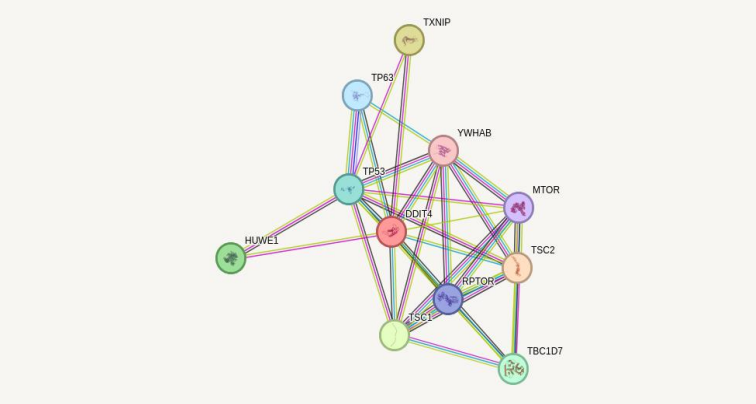

Figure 9: Some connections made by the DDIT4 gene. Image made by software © STRING Consortium 2023 version 12.0.

J. Mirnas as AML Biomarkers

The field of molecular genetics has become a very extensive and detailed axis over the years, with new discoveries human beings have been able to increasingly unravel the small details of the vast genetic world. And just like genes, miRNAs are always being explored by research in order to use them as factors that will contribute in some way to science and health. In AML, miRNAs also present their peculiarities and their collaboration with regard to the disease mechanism. and with this in mind, we researched which miRNAs have not been mentioned in the last 10 years, and what their uses are in AML.

According to Trino et al., 2018, miRNAs are short-length, non-coding single-stranded RNAs that are evolutionarily conserved (presenting around 19 to 22 nucleotides). MiRNAs have crucial functional responsibilities, such as cell growth, proliferation, differentiation and apoptosis, and can also be used as participants in oncogenic processes and/or tumor suppression. MiRNAs also have the ability to regulate several mRNA targets, making their modulation a potential therapeutic target in leukemic progenitors. Trino et al., 2018 also points out that miRNAs are often deregulated in AML due to various mechanisms, such as copy and epigenetic changes, among others. Given these statements, the literature has highlighted some miRNAs that have promising capacity to be used as biomarkers in AML.

Elhamamsy et al., 2017 pointed out three miRNAs that can serve as potential biomarkers for clinical detection of AML. Based on the results of the study, the authors reported that miRNAs not only have the ability to detect AML, but can also serve as prognostic biomarkers monitoring treatment response, as it was possible to detect miRNAs in the plasma and serum of patients, meaning that this condition expressed in plasma and serum may reflect the expression of miRNAs in tumor tissues. miR-92a, miR-143 and miR-342 were chosen by the authors as the focus of their research, pointing to their use as non-invasive biomarkers for malignant hematological processes. The research reports that miR-92a, miR-143 and miR-342 were negatively expressed in patients' plasma (when compared to healthy patients), pointing to the tumor suppressor function expressed by miRNAs. In general, the study states that miR-92a has already been reported in several types of tumors (such as non-Hodgkin's lymphoma), suggesting that miRNAs are conditioned within exosomes, which in turn will be secreted by cells to be taken to other cells to exercise into tissues or organ. The low expression of this miRNA is due to the fact that exosomes with miR-92a are absorbed by the blasts, consequently causing their low expression. Addressing miR-143, it was negatively correlated with the mRNA of the DNMT3A gene, performing crucial functions such as proliferation and apoptosis of leukemic cells, and possibly caused by the silencing of the DNMT3A gene. And finally, miR-342 was identified as a potential biomarker used as a diagnostic strategy, presenting good sensitivity and

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specificity. In summary, the study indicated that the combination of the three miRNAs can serve as a potential diagnostic screening test for AML.

The miRNAs miR-106a-3p and miR-106a-5p were detected and evaluated in pediatric patients with AML in the study carried out by Lim et al., 2017. The miRNAs were expressed abundantly in resistance to treatment, being associated with overall survival and poor event-free survival (EFS). The study presented results that consisted of demonstrating that miR-106a-363 was abundantly expressed in relapsed and refractory samples, and several candidate targets of miR-106a-5p were included in the oxidative phosphorylation process. Research shows that the frequent expression of miR-106a with its genes associated with oxidative phosphorylation results in therapeutic resistance on the part of cell lines, consequently causing cellular quiescence, that is, quiescent cells end up escaping selective therapies for dividing cells and proliferate quickly, therefore the study suggests that miR-106a-363 expression could contribute to resistance to treatment by repressing oxidative phosphorylation.

Aiming to identify biomarker miRNAs in a bioinformatics approach in pediatric patients affected by AML, Yan et al., 2015 proposed that miRNAs can act both in oncogenesis and as tumor suppressors, acting with their main regulatory function. In this focus, their study pointed out that miR-196b, miR-155 and miR-25 as putative diagnostic biomarkers for pediatric AML, presenting miR-155 with overexpression in AML samples and overexpressed peculiarly in M4-M5 subtypes of the AML system. French-American-British (FAB) classification of AML (in vitro via qRT-PCR). Both miR-196b and miR-25 did not show differential expression, but miR-196b, in particular, had aberrant expression in AML in adults, particularly in AML with mutations in the FLT3 and NPM1 genes. The group developed a system called *Pipeline of Outlier MicroRNA Analysis* (POMA) which consists of analyzing genes targeted especially by certain miRNAs, thus being able to measure the independent regulatory capacity of individual miRNAs, thus evaluating the importance of miRNAs in certain diseases. In short, their study presented data that state that miR-155 was overexpressed in pediatric patients affected by AML, while miR-196b was overexpressed in AML subtypes M4-M5, that is, the data express that miR-155 is a potential diagnostic biomarker for all types of AML while miR-196b specifically targets M4-M5 subgroups.

According to ZHOU et al., 2019, *miR-335* was identified as a significant miRNA associated with cancer, epigenetically silenced, the miRNA acted as a tumor suppressor gene in several solid tumors. Bringing it to the AML axis, miR-335 was identified as overexpressing in both adult and pediatric AML. The study carried out by the authors showed that miR-335 was significantly elevated and negatively associated with low ID4 expression in AML. The aberrant expression of miR-335 / ID4 had an effect on the response to chemotherapy and also affected the survival of patients affected by AML. The data presented by the study demonstrated that miR-335 expressed collaboration in leukogenesis through the PI3k/Akt signaling pathway, a pathway that plays an important role in physiological processes, such as cell proliferation, progression, apoptosis and cell survival, in addition to acting in differentiation, angiogenesis and drug resistance. The authors stated that miR-335 is transcribed from chromosome 7q32.2, expressed aberrantly in several types of cancer, including hematological malignancies, playing a crucial role in the origin and progression of cancer. Regarding tumor proliferation, apoptosis, migration and invasion, metastasis, miR-335 was identified in the involvement of these processes. In addition to the association of miR-335 with AML, the study discovered that ID4 suffered a decrease in its expression, presenting a considerable consequence since it acts as a tumor suppressor, in addition, miR-335 expressed pro-proliferative and anti-apoptotic effects. focusing on ID4. In summary, the data indicated that the aberrant expression of miR-335/ID4 served as a prognostic biomarker in AML, as its expression enabled leukemogenesis through the activation of the PI3K/Akt signaling pathway.

Mir-29a-3p and mir-92a-3p were reported as antitumor molecules presenting themselves as potential diagnostic biomarkers of non-invasive factors in AML, and also being used as a future option for therapeutic intervention by Gado et al., 2019 . From bone marrow and peripheral blood samples, the study authors extracted and quantified the miRNAs through RT-PCR using exclusive mir29a-3p and mir92a-3p primers. When analyzing the data, it was possible to observe a relevant negative expression in both marrow aspirate and plasma from patients recently diagnosed with AML. The study points out that the negative regulation of miR-29a is attributed to its function, where it is relevant in inducing cell apoptosis. With this negative regulation, miR-29a is led to an overexpression of the MCL1 gene. In addition to acting in the pathogenicity of AML, MCL1 is also associated with drug resistance and AML relapse. In short, the article points to circulating levels of both mir-29a-3p and mir-92a-3p, also negatively correlating with the transcription of the MCL1 gene, and can thus be used as potential diagnostic biomarkers.

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CONCLUSION

In this review we seek to analyze which biomarkers have been addressed in the last 10 years in the scientific literature, thus aiming to demonstrate the possible targets for new research. We divided our research into genes that are promising biomarkers for diagnosis and/or prognosis and the role of miRNAs as biomarkers in AML, thus facilitating the choice to delve deeper into each axis. However, based on the articles analyzed, we concluded that there is still a need for better elucidation of how biomarkers, both genes and myrnas, can contribute to diagnostic and prognostic factors, enabling more and more patients to benefit from new discoveries regarding biomarkers. , thus carrying out early diagnoses and better guidance on therapeutic practices. Since each gene or myrna has a vast interaction in the human organism, therefore, for more promising results to be put into practice in medical routine, it will be extremely important that future research is focused and in-depth on one of the biomarkers presented here, detailing its relations and cooperation through the LMA.

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