A Systematic Review of the Role of Runt-Related Transcription Factor 1 (RUNX1) in the Pathogenesis of Hematological Malignancies in Patients With Inherited Bone Marrow Failure Syndromes

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Abstract

Somatic runt-related transcription factor 1 (RUNX1) mutations are the most common mutations in various hematological malignancies, such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Mono-allelic RUNX1 mutations in germine cells may cause familial platelet disorder (FPD), an inherited bone marrow failure syndrome (IBMFS) associated with an increased lifetime risk of AML. It is suspected that additional RUNX1 mutations may play a role in the pathogenesis of hematological malignancies in IBMFS. This review aims to study the role of RUNX1 mutations in the pathogenesis of hematological malignancies in patients with IBMFS. A PubMed database search was conducted using the following medical subject heading (MeSH) terms: “inherited bone marrow failure syndromes,” “hematological neoplasms,” “gene expression regulation, leukemic,” “RUNX1 protein, human,” “RUNX1 protein, mouse,” and “Neutropenia, Severe Congenital, Autosomal recessive.” Three studies published in 2020 were identified as meeting our inclusion and exclusion criteria. Leukemic progression in severe congenital neutropenia was used as a disease model to evaluate the clinical, molecular, and mechanistic basis of RUNX1 mutations identified in hematological malignancies. Studies in mice and genetically reprogrammed or induced pluripotent stem cells (iPSCs) have shown that isolated RUNX1 mutations are weakly leukemogenic and only initiate hyperproduction of immature hematopoietic cells when in combination with granulocyte colony-stimulating factor 3 receptor (GCSF3R) mutations. Despite this, whole-exome sequencing (WES) performed on leukemic transformed cells revealed that all AML cells had an additional mutation in the CXXC finger protein 4 (CXXC4) gene that caused hyperproduction of the ten-eleven translocation (TET2) protein. This protein causes inflammation in cells with RUNX1 mutations. This process is thought to be critical for clonal myeloid malignant transformation (CMMT) of leukemogenic cells. In conclusion, the combinations of GCSF3R and RUNX1 mutations have a prominent effect on myeloid differentiation resulting in the hyperproduction of myeloblasts. In other studies, it has been noted that the mutations in GCSF3R and RUNX1 genes are not sufficient for the full transformation of leukemogenic cells to AML, and an additional clonal mutation in the CXXC4 gene is essential for full transformation to occur. These data have implicitly demonstrated that RUNX1 mutations are critical in the pathogenesis of various hematological malignancies, and further investigations into the role of RUNX1 are paramount for the development of new cancer treatments.

Categories: Pediatrics, Oncology, Hematology
Keywords: mutations and polymorphisms, runx1 gene, pathogenesis, hematological malignancies, inherited bone marrow failure syndromes

Introduction And Background

The runt-related transcription factor 1 (RUNX1) gene is known as a critical regulator of embryogenesis and definitive hematopoiesis in vertebrates, playing a vital role in the generation of hematopoietic stem cells (HSCs) and their differentiation into the myeloid and lymphoid lineage. The discovery of RUNX1 mutations as the cause of familial platelet disorder (FPD) was pivotal to understanding the implications of this gene in hematological malignancies. FPD is an inherited bone marrow failure syndrome (IBMFS) with quantitative and qualitative platelet abnormalities and a high predisposition to acute myeloid leukemia (AML) [1,2]. IBMFS are genetic disorders characterized by cytopenia and hypoproliferation of one or more cell lineages in the bone marrow [1]. The production of blood cells (erythrocytes, granulocytes, and platelets) is compromised because of the mono-allelic gene mutation in one of certain bone marrow genes. Besides FPD, the other most common IBMFSs include Fanconi anemia (FA), Diamond-Blackfan anemia (DBA), Shwachman-Diamond syndrome (SDS), and severe congenital neutropenia ( SCN) [3]. Patients with IBMFSs show a predisposition to developing hematological complications, such as myelodysplastic syndrome (MDS) or AML [3]. MDS is a pre-leukemic state defined by the presence of refractory cytopenia or...
refractory cytopenia with an excess of blasts (5–29%) in the bone marrow. AML is a blood cancer that is characterized by rapid leukemic blast cell growth and the presence of more than 30% myeloid blasts in the bone marrow [2].

Recent studies have shown that RUNX1 germline mutations in patients with IBMFS are like acquired or somatic RUNX1 mutations that were found in myeloid malignancies, particularly in MDS and AML [3]. It has become clear that somatic RUNX1 mutations are more prevalent in MDS/AML that is secondary to IBMFS, such as FA and SCN. Unlike acquired MDS/AML, these forms of secondary MDS/AML are often refractory to treatment, resulting in a poor prognosis. Because the somatic mutation of RUNX1 was first identified in MDS and AML, RUNX1 has become known to be one of the most frequently mutated genes in a variety of hematological malignancies [4].

Despite recent research having demonstrated the strong association of RUNX1 mutations in a variety of hematological malignancies, it is unclear how RUNX1 mutations contribute to the pathogenesis of hematological malignancies in IBMFS. What are the frequencies of different RUNX1 mutations in various subgroups of hematological malignancies, as well as their impact on prognosis? Furthermore, is there any potential for the development of new cancer therapies following recent findings regarding the role of RUNX1 in the malignant transformation [5]?

In this article, we summarize new research on the role of RUNX1 mutations, published in February 2020 by three different groups [6-8]. They performed different experiments in human, mouse, and induced pluripotent stem cell (iPSC) models to decipher the role of the RUNX1 gene in the malignant transformation of IBMFS; the mechanisms of pathogenesis; clinical and molecular characteristics of RUNX1 mutations; and the potential for the treatment of cancers. The mouse and iPSC models suggested that secondary RUNX1 mutations in clones with granulocyte colony-stimulating factor 3 receptor (GCSF3R) mutations are weakly leukemogenic and that an additional clonal mutation in the CXCC finger protein 4 (CXXC4) gene is required for the full transformation to AML [9]. Mutations in the CXXC4 gene lead to the hyperproduction of inflammatory proteins called the ten-eleven translocation (TET2) proteins. This inflammation, in combination with the RUNX1 mutations, drives the development of myeloid malignancies [10]. The other pathogenic mechanisms wherein RUNX1 mutations may initiate tumor cell proliferation 18 are the inhibition of the p53 pathway and hypermethylation of the promoter of Wingless and Int1 (WNT) inhibitor gene called secreted frizzled-related protein 2 (SFRP2) [11,12].

These discoveries may have the potential to aid the development of new therapeutic strategies. Specifically, immunotherapy may be employed for suppression of the excessive immune response to hyperproduction of TET2 proteins. The other potential therapeutics, such as mouse double minute 2 (MDM2) and poly adenosine diphosphate-ribose polymerase (PARP) inhibitors, may be used to inhibit the hyperactivation of the p53 pathway and hypersensitivity to DNA damage resulting from RUNX1 mutations [11]. Because the presence of RUNX1 mutation represents a poor prognostic factor in patients with MDS or AML, the investigation of various biomarkers is critical as they may detect the clones with RUNX1 mutation, in the early stages of leukemic progression [7].

**Review**

**Methodology**

**Search Strategy**

The PubMed online database search was used to select the articles which are included in this review. The findings were reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following medical subject heading (MeSH) parameters were used: "inherited" and "bone marrow" and "failure" and "syndromes." This search resulted in 5,051 articles.

**Selection Criteria**

The identified articles were further filtered. The review selected only articles that met the following criteria: (1) papers published between January and December 2020; (2) free full-text available; (3) papers written in English; and (4) studies conducted on human participants. Among screened articles, only clinical trials, meta-analyses, randomized controlled trials, and systematic reviews were included. Five citations from other sources were not included because they were not relevant to the topic. To further select the articles, we included the following MeSH terms: "hematologic neoplasms," "gene expression regulation, leukemic," "RUNX1 protein, human," and "Neutropenia, Severe Congenital, Autosomal recessive." Any articles that were not relevant to the role of the RUNX1 gene were excluded. These criteria allow comparison between articles; however, it should be noted that differing lab protocols between studies prevents validation of results using the same assessment tool. A systematic search review is reported using the PRISMA 2020 guidelines [13]. The diagram is presented in Figure 1.
Results

The selected articles were used to evaluate the clinical and molecular characteristics of RUNX1 mutation in various types of hematological malignancies, the mechanisms of pathogenesis caused by RUNX1 mutations, and potential therapeutic strategies for hematological malignancies with RUNX1 mutations.

Clinical and Molecular Characteristics of RUNX1 Mutation in Hematological Malignancies

RUNX1 gene has multiple biological functions in the human body. It regulates hematopoiesis, the cell cycle and genome stability, the p55 signaling pathway, apoptosis, and ribosomal biogenesis. During hematopoiesis, this gene controls the development of HSCs and their differentiation in different lineages. The transition from the G1-S to the G2/M phase of the cell cycle is facilitated by RUNX1. This gene controls cellular proliferation and differentiation via direct regulation of transcription, achieved by binding promoters of the genes that are encoding ribosomal RNA/proteins. According to recently published data, somatic mutations of RUNX1 were observed in various types of hematological malignancies. We present the frequency of RUNX1 mutations in various types of hematological malignancies in Table 1 below.
Most frequently, somatic mutations of RUNX1 were associated with the development of myeloproliferative neoplasm (MPN) (10.3-37.5%) and chronic myelomonocytic leukemia (CMML) (32.1-37%). Despite this, the association between RUNX1 somatic mutations and MDS was only 10%.

The Mechanisms of Pathogenesis Caused by RUNX1 Mutations

In the selected studies, the different mechanisms of pathogenesis caused by RUNX1 mutations were characterized. It has been shown that loss of RUNX1 function causes inhibition of differentiation of HSCs. Therefore, in pre-leukemia, we found expansion of HSCs and progenitor cells. RUNX1 mutations may attenuate the G1-S phase and enhance the proliferation of hematopoietic cells that occur during the mitotic phase of the cell cycle (G2/M) [7]. The mutations can also result in genomic instability, leading to increased DNA damage and impaired DNA repair. Some mutations in RUNX1 are associated with alterations of signaling pathways, such as WNT and p53. Hypermethylation of the WNT inhibitor gene promoter, SFRP2, can lead to aberrant activation of the WNT signaling pathway and leukemogenesis in AML. When functioning normally, the RUNX1 gene acts to increase transcriptional activity of the p53 signaling pathway, in response to DNA damage caused by exposure to different agents such as chemicals, radiation, and toxins. Mutations in RUNX1 may lead to defects in p53-mediated apoptosis/DNA repair/cell cycle regulation resulting in tumorigenesis. Furthermore, loss-of-function mutations of RUNX1 may aid tumor-initiating cells in hematological malignancies via inhibition of p53 signaling and apoptosis, among other mechanisms. Such mutations have reduced ribosomal biogenesis in HSCs and directed to malignant proliferative processes in the pre-leukemic stage [6]. In vivo studies, administration of amino acid L-leucine to patients with DBA resulted in loss-of-function mutations in ribosomal protein genes. Research into iPSC confirmed that the introduction of the mutated RUNX1 gene into CD34+CD45+ cells via lentivirus can stimulate receptor which binds the granulocyte colony-stimulating factor 3 receptor (GCSF3R) and initiates the

TABLE 1: The frequency of RUNX1 mutations in various types of hematological malignancies.

| References | Hematological malignancies | Subtypes | Frequency of RUNX1 mutations (%) |
|------------|-----------------------------|----------|---------------------------------|
| Latger-Cannard et al. [14] | FPD/AML | >70 families |
| Sood et al. [5] | FPD/AML | >70 families |
| Vormittag-Nocito et al. [15] | FPD/AML | >70 families |
| Gaidzik et al. [16] | AML | Primary AML | 5.6–17.9 |
| Cazzola et al. [17] | MDS | | 10 |
| Haferlach et al. [18] | MDS | | 10 |
| Steensma et al. [19] | MDS | | 10 |
| Kuo et al. [20] | CMML | | 32.1–37 |
| Tsai et al. [21] | CMML | | 32.1–37 |
| Grossmann et al. [22] | ALL | T-ALL | 15.5–18.3 |
| Zhang et al. [23] | ALL | ETP-ALL | 15.6 |
| Singhal et al. [24] | Radiation t-MDS/AML | | 15.7–39 |
| Cerquozzi et al. [25] | MPN | Ph* MPN | 10.3–37.5 |
| Branford et al. [26] | MPN | Ph* MPN | 12.9–33.3 |
| Baer et al. [27] | MPN | MPN-Eo | 32–71 |
| Strati et al. [28] | MPN | MPN-Eo | 32–71 |
| Chao et al. [29] | CBMF | FA | 20.7–31.3 |
| Quentin et al. [30] | CBMF | FA | 20.7–31.3 |
| Skokowa et al. [31] | CBMF | SCN | 64.5 |

FPD: familial platelet disorder; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia; MPN: myeloproliferative neoplasm; ALL: acute lymphoblastic leukemia; CBMF: congenital bone marrow failure; FA: Fanconi anemia; SCN: severe congenital neutropenia
production of immature cells. The percentage of immature cells was significantly increased when compared to the percentage in empty vector (ev) control studies. The myeloid differentiation of GCSF3R-d715/RUNX1-D171N and GCSF3R-d715/ev cells without RUNX1-D171N lentiviral expression vector or with an ev is presented in Figure 2.

**FIGURE 2: Myeloid differentiation of GCSF3R-d715/RUNX1-D171N cells compared to GCSF3R-d715/ev cells without RUNX1-D171N lentiviral expression vector or with an ev.**

GCSF3R: granulocyte colony-stimulating factor receptor; RUNX1: runt-related transcription factor 1; ev: empty vector

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**Potential Therapeutic Strategies for RUNX1-Mutated Cases of Hematological Malignancies**

Clinical trials demonstrated potential therapeutic strategies for RUNX1 mutated hematologic malignancies. Based on the current RUNX1 roles in human hematopoiesis, various therapeutic options were developed. Thus far, the different DNA repair inhibitors can be useful in the M phase of cell cycle repair or bypassing the cells with damage because RUNX1 mutations lead to DNA damage and impaired DNA repair [32]. In addition, adriamycin as an antineoplastic drug can stimulate the RUNX1-p53 complex which is important in the activation of p53-mediated apoptosis [11]. L-leucine can be used to improve anemia in the genetic DBA mouse models and DBA patients. This agent is a potent stimulator of protein translation that is initialized by the activation of the mammalian target of rapamycin (mTOR) protein kinase. This kinase stimulates protein synthesis [33]. Another agent, clustered regulatory interspaced short palindromic repeats-associated genes (CRISPR-Cas) can be used as a genomic targeted treatment as this agent can edit the RUNX1 gene by cutting pieces of DNA where RUNX1 mutations are, followed by stimulating natural DNA repair [6]. Finally, hypoxia-inducible factor 1α (HIF-1α) inhibitor can potentially treat various hematological malignancies as a modulator of cell metabolism. MDS and other hematological malignancies are in hypoxia-like status and produce their energy through the tricarboxylic acid (TCA) cycle. The use of HIF-1α inhibitor can suppress the TCA cycle and modulate it into an aerobic metabolic pathway called glycolysis through which the normal cells are supplied with energy. The recent studies proposed therapeutic strategies that employed the different pathophysiological mechanisms to correct the RUNX1 mutations, as shown in Figure 3.
The *RUNX1* gene plays essential roles in a wide range of biological processes, including the development of HSCs, cell proliferation, megakaryocyte maturation, T lymphocyte-lineage differentiation, and apoptosis. It is not surprising that *RUNX1* dysfunction is associated with the development of IBMFSs and various hematological malignancies [7,21,34].

Previous studies have shown that *RUNX1* is one of the most frequently mutated genes in hematological malignancies. *RUNX1* mutations account for about 10-15% of all somatic mutations that have been detected in MDS [21,35]. The incidence of *RUNX1* mutations in CMML and chronic myelogenous leukemia (CML) is even higher, ranging from 32.1% to 37%, respectively [36]. *RUNX1* mutations have also been reported in 14% of patients with MPN, 15.6% of patients with acute lymphoblastic leukemia (ALL), and 10.3-37.5% of AML patients. Importantly, these studies have shown that mutated *RUNX1* can be used as an independent prognostic factor for event-free survival (EFS), relapse-free survival (RFS), or overall survival (OS) in hematological malignancies [37]. Therefore, AML patients with *RUNX1* mutations had worse prognosis, resistance to chemotherapy, and inferior EFS, RFS, and OS. Reduced OS was also observed in high-risk MDS patients with *RUNX1* mutations who had poor clinical outcomes and shorter latency for progression to secondary AML [38,39].

Little is known about the role of the *RUNX1* gene in the development of secondary somatic mutations in patients with IBMFSs and how these mutations lead to hematological malignancies. The data have shown that individuals with IBMFSs, such as FPD and FA, have a high lifetime risk (30-44%) of developing MDS and AML [29,30]. Among FA-associated MDS or MDS/AML patients, *RUNX1* mutations were detected in the range from 20.7% to 31.25%, respectively. In SCN-MDS/AML patients, *RUNX1* mutations were seen at the highest rate of up to 64.5% which revealed that these types of mutations are the most frequent somatic secondary mutations in SCN-MDS/AML [31,40,41]. Given that the patients with SCN are more prone to develop somatic *RUNX1* mutations, SCN/AML has been recognized as an important model to further investigate the role of secondary *RUNX1* mutations in the molecular pathogenesis of hematological malignancies. SCN is an IBMFS classified by severe neutropenia and life-threatening infections such as fungal infections or bacterial sepsis [40]. The most frequent mutated gene is encoding neutrophil elastase (ELANE). The treatment consists of lifelong administration of GCSF that successfully alleviates the neutrophil counts [42]. As is common with other forms of IBMFSs, SCN patients have a high risk of developing MDS or AML. The incidence of developing MDS or AML directly correlates to the number of years on GCSF. Therefore, after 15 years on GCSF, the incidence of developing MDS or AML is 21% [31]. The majority of SCN patients with leukemic progression develop hematopoietic clones with somatic mutations in GCSF3R, resulting in a truncated form of GCSF3R [42]. It is important to note that these clones can persist for several months or years before MDS or AML becomes symptomatic, raising the question of how these GCSF3R mutants contribute to the malignant transformation of SCN [31,41]. Given this, a mouse model was used to study the role of *RUNX1*. In this study, a truncated GCSF3R (GCSF3R-D715) identical to the mutant GCSF3R form in SCN patients was expressed in mice [43]. In addition, a lentiviral expression vector was used to express *RUNX1*-mutant D171N in conjunction with an enhanced green fluorescent protein (eGFP) [8]. The mouse bone marrow (BM) cells with expressed GCSF3R-D715 mutation were subsequently serially transplanted into wild-type recipients. Before transplantation, the recipients were treated either three times per week with GCSF or with peripheral blood solvent (PBS) control. Primary recipients who were treated with GCSF and transplanted with GCSF3R-*RUNX1*-mutant BM cells developed myeloblasts in peripheral blood (PB) that were sustained...
for at least 30 weeks. None of these mice developed symptoms of AML, suggesting that the elevated
myeloblasts in the PB reflected a pre-leukemic state rather than a fully transformed state. However, upon
transplantation in secondary and tertiary recipients, mice developed GCSF3R-RUNX1-mutant AML. Whole-
exome sequencing (WES) was performed on lin-c-kit (LK) cells and revealed that AML cells from the
secondary and tertiary recipients had seven-fold higher expressions of CXXC4 mutations than the cells from
the primary recipient. Recently, CXXC4 mutations have also been detected in human AML cases [9]. It seems
that CXXC4 mutations enhance the production of TET2 protein which is known to be an inflammatory factor
and has a similar role to interferon-gamma, interleukin-6, and others. Interferon-gamma and interleukin-6
are cytokines that are produced in response to infections and tissue damage, with pro- and anti-
inflammatory effects. Hyperproduction of TET2 leads to inflammatory processes that may play an important
role in the development of myeloid malignancy involving RUNX1 mutations [10]. In conclusion, isolated
RUNX1-Runt homology domain (RHD) mutations are only weakly leukemogenic and an additional clonal
mutation that reduces levels of TET2 is what drives the full transformation to AML [8,32]. The data suggest
the need for further investigation into the somatic RUNX1 mutations in HSPCs that already harbour a
GCSF3R nonsense mutation. To achieve this, a CRISPR/Cas9-based strategy was used to introduce a patient-
derived GCSF3R nonsense mutation into iPSC. CRISPR-Cas9 is a technology used for removing, adding, or
altering sections of the DNA. After culturing iPSC, CD34+CD45+ cells were transduced using a lentivirus to
express the RUNX1-RHD D171N mutant. The experiments confirm that the combinations of GCSF3R and
RUNX1 mutations have a moderate effect on myeloid differentiation and result in an increasing number
of myeloblasts. These findings corroborate the findings in the mouse model and suggest that secondary RUNX1
mutations in clones with GCSF3R mutations are not sufficient to fully transform to AML.

Most of the RUNX1 mutations are mono-allelic, such as in FPD, an IBMFS resulting in a predisposition to
leukemia [1,2]. Germline RUNX1 mutations are dominant-negative mutations and correlate to a higher risk
of developing hematological malignancies compared to RUNX1 loss-of-function mutations [5-8]. It is
important to note, however, that such germline mutations alone are not sufficient for the development of
leukemia and additional mutations in RUNX1 (bi-allelic mutations) or epigenetic modifiers, splicing factors,
or tumor suppressors are required to induce myeloid malignancies [1,4].

It has been observed that mutations in RUNX1 are associated with alterations of p53 and other signaling
pathways, such as WNT, bone morphogenetic proteins (BMP), transforming growth factor-beta (TGF-β), rat
sarcoma-the extracelluar signal-regulated kinase (RAS-ERK), Hippo-yes-1-associated protein (YAP1), and
Notch. Unlike mono-allelic mutations, loss-of-function mutations of RUNX1 are responsible for initiating
tumor cell proliferation by inhibiting the p53 signaling pathway and apoptosis. The p53 pathway is activated
in DNA damage and is responsible for DNA repair. RUNX1 increases the transcriptional activity of p53,
potentially via up-regulation of p300-mediated acetylation of p53. RUNX1 mutations lead to a reduction of
p53-mediated apoptosis [11]. The WNT pathway is important for cellular proliferation and differentiation,
with aberrant activation of this pathway being reported in various tumors. RUNX1 mutations were closely
associated with hypermethylation of the promoter of one of the WNT inhibitor genes (SFRP2) in AML. It was
suggested that the WNT inhibitor hypermethylation might lead to aberrant activation of the WNT signaling
pathway. It is suggested that mutation in the RUNX1 gene can interact with the SFRP2 gene which is known
as an inhibitor gene responsible for the suppression of the WNT signaling pathway. Due to interaction with
genetic alterations, the hypermethylation of SFRP2 gene promoter is initiated and leads to leukemogenesis
where cellular proliferation and differentiation are uncontrolled [12].

Strengths and limitations
This review has highlighted the importance of studying the role of somatic RUNX1 mutations in the
pathogenesis of hematological malignancies and the potential implications in the development of
oncological therapies. This review does, however, had some limitations. First, the results presented in this
review were collected from only three articles that were published over the limited time frame of one year. In
addition, we included only articles that were available in the PubMed database and in both free text format
and English language. This review did not apply the same assessment tools such as the lab protocols for
conducting experiments. Variations between lab protocols did not allow the comparison of study results. In
all the articles included, the scope of the study was the role of RUNX1 mutations in animal and human
disease models, including only SCN and FA as the IBMFS representatives without knowing if RUNX1
mutations may contribute to the development of malignancies in other IBMFS. A broader literature search
and greater inclusion of studies about RUNX1 mutations in the pathogenesis of other IBMFS may better
represent and validate the inferences from this review.

Conclusions
RUNX1 plays important role in responding to cellular stress, maintaining genomic stability, and ensuring
cellular quality control. Dysregulation of RUNX1 expression contributes to the pathophysiology of IBMFS
and cancer predisposition. This review revealed important clinical implications of RUNX1. Mutations in the
GCSF3R factor are associated with granulocyte colony-stimulating factor treatment and may lead to cancer
predisposition in patients with SCN. Combinations of GCSF3R and RUNX1 mutations can activate the p53
signaling pathway and lead to the accumulation of immature cells. Studies in mice have shown that RUNX1
and GCSF3R mutations found in combination do not lead to leukemic progression without additional
inflammation. These discoveries may be utilized in the development of new therapeutic strategies. The use of immunotherapy or different inhibitors (MDM2, PARP) has shown promise in preventing p53 pathway activation and hypersensitivity to DNA damage of cells containing somatic RUNX1 mutations. Further research may lead to the discovery of biomarkers for early detection of leukemic progression, promoting a deeper understanding of molecular mechanisms by which RUNX1 mutations contribute to hematological malignancies and the development of new therapeutic interventions.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Antony-Debré I, Duployez N, Bucci M, et al.: Somatic mutations associated with leukemic progression of familial platelet disorder with predisposition to acute myeloid leukemia. Leukemia. 2016, 30:999-1002. 10.1038/leu.2015.236

2. Godley LA: Inherited predisposition to acute myeloid leukemia. Semin Hematol. 2014, 51:306-21. 10.1055/s.0034-1378001

3. Harada Y, Harada H: Molecular mechanisms that produce secondary MDS/AML by RUNX1/AML1 point mutations. J Cell Biochem. 2011, 112:425-52. 10.1002/jcb.22974

4. Göhring G, Karow A, Steinemann D, et al.: Chromosomal aberrations in congenital bone marrow failure disorders—an early indicator for leukemogenesis?. Ann Hematol. 2007, 86:753-9. 10.1007/s00277-007-0357-z

5. Sood R, Kamikubo Y, Liu P: Role of RUNX1 in hematological malignancies. Blood. 2017, 129:2070-82. 10.1182/blood-2016-10-68830

6. Samarzaklody AS, Shin NY, Cantor AB: Role of RUNX family transcription factors in DNA damage response. Mol Cells. 2020, 45:99-106. 10.14548/molcells.2019.0304

7. Yokota A, Hsu L, Fan F, Wu J, Huang G: The clinical, molecular, and mechanistic basis of RUNX1 mutations identified in hematological malignancies. Mol Cells. 2020, 45:145-52. 10.14548/molcells.2019.0252

8. Oloosen PA, Touw IP: RUNX1 mutations in the leukemic progression of severe congenital neutropenia. Mol Cells. 2020, 45:139-44. 10.14548/molcells.2020.0010

9. Oloosen PA, Patrai S, van Strien PM, et al.: Malignant transformation involving CXXC4 mutations identified in a leukemic progression model of severe congenital neutropenia. Cell Rep Med. 2020, 1:100074. 10.1016/j.xcrm.2020.100074

10. Ko M, An J, Bandukwala HS, et al.: Modulation of TET2 expression and 5-methylcytidine oxidation by the CXXC domain protein IDAX. Nature. 2015, 497:122-6. 10.1038/nature12052

11. Wu D, Ozaki T, Yoshihara Y, Kubo N, Nakagawara A: Runt–related transcription factor 1 (RUNX1) stimulates tumor suppressor p53 protein in response to DNA damage through complex formation and acetylation. J Biol Chem. 2015, 288:1553-64. 10.1074/jbc.M114.202194

12. Hou HA, Kuo YY, Liu CY, et al.: Distinct association between aberrant methylation of Wnt inhibitors and genetic alterations in acute myeloid leukemia. Br J Cancer. 2011, 105:1927-33. 10.1038/bjc.2011.471

13. Page MJ, McKenzie JE, Bossuyt PM, et al.: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. PLoS Med. 2021, 18:e1003583. 10.1371/journal.pmed.1003583

14. Latger–Cannard V, Philippe C, Bouquet A, et al.: Haematological spectrum and genotype-phenotype correlations in nine unrelated families with RUNX1 mutations from the French network on inherited platelet disorders. Orphanet J Rare Dis. 2016, 11:49. 10.1186/s13023-016-0432-0

15. Vormittag-Nocito E, Ni H, Schmidt ML, Lindgren V: Thrombocytopenia and predisposition to acute myeloid leukemia due to mosaic ring 21 with loss of RUNX1: cytogentic and molecular characterization. Mol Syndromol. 2019, 9:506-11. 10.1159/000494645

16. Gaidzik VI, Leleu V, Papaemmanuil E, et al.: RUNX1 mutations in acute myeloid leukemia are associated with distinct clinico-pathologic and genetic features. Leukemia. 2016, 30:2282. 10.1038/leu.2016.207

17. Cazzola M, Della Porta MG, Malcovati L: The genetic basis of myelodysplasia and its clinical relevance. Blood. 2013, 122:4201-54. 10.1182/blood-2013-09-381665

18. Haferlach T, Nagata Y, Grossmann V, et al.: Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia. 2014, 28:241-7. 10.1038/leu.2015.336

19. Steenman DP, List AF: Genetic testing in the myelodysplastic syndromes: molecular insights into hematologic diversity. Mayo Clin Proc. 2005, 80:681-98. 10.4065/80.5.681

20. Kuo MC, Liang DC, Huang CF, Shih YS, Wu JH, Lin TL, Shih LY: RUNX1 mutations are frequent in chronic myelomonocytic leukemia and mutations at the C-terminal region might predict acute myeloid leukemia transformation. Leukemia. 2009, 25:1426-31. 10.1038/leu.2009.48

21. Tsai SC, Shih LY, Liang ST, et al.: Biological activities of RUNX1 mutants predict secondary acute leukemia transformation from chronic myelomonocytic leukemia and myelodysplastic syndromes. Clin Cancer Res. 2015, 21:5341-51. 10.1158/1078-0432.CCR-14-2205

22. Grossmann V, Kern W, Hartich S, et al.: Prognostic relevance of RUNX1 mutations in T-cell acute lymphoblastic leukemia. Haematologica. 2011, 96:1874-7. 10.3324/haematol.2011.03919

23. Zhang Y, Gao Y, Zhang H, et al.: PDGFRB mutation and tyrosine kinase inhibitor resistance in Ph-like acute
lymphoblastic leukemia. Blood. 2018, 131:2256-61. 10.1182/blood-2017-11-817510

24. Singhal D, Wee LY, Kutyna MM, et al.: The mutational burden of therapy-related myeloid neoplasms is similar to primary myelodysplastic syndrome but has a distinctive distribution. Leukemia. 2019, 33:2842-53. 10.1038/s41375-019-0417-9

25. Cerquozzi S, Telfer A: Blast transformation and fibrotic progression in polycythemia vera and essential thrombocythemia: a literature review of incidence and risk factors. Blood Cancer J. 2015, 5:e366. 10.1038/bcj.2015.95

26. Branford S, Wang P, Yeung DT, et al.: Integrative genomic analysis reveals cancer-associated mutations at diagnosis of CML in patients with high-risk disease. Blood. 2018, 132:948-61. 10.1182/blood-2018-02-832253

27. Baer C, Pohlkamp C, Haferlach C, Kern W, Haferlach T: Molecular patterns in cytopenia patients with or without evidence of myeloid neoplasm—a comparison of 756 cases. Leukemia. 2018, 32:2295-8. 10.1038/s41375-018-0119-8

28. Strati P, Tang G, Duose DY, et al.: Myeloid/myeloid neoplasms with FGFR1 rearrangement. Leuk Lymphoma. 2018, 59:1672-6. 10.1080/10428194.2017.1397663

29. Mangan JK, Speck NA: RUNX1 mutations in clonal myeloid disorders: from conventional cytogenetics to next generation sequencing, a story 40 years in the making. Crit Rev Oncog. 2011, 16:77-91. 10.1615/critrevoncog.v16.i1-2.80

30. Mendler JH, Maharry K, Radmacher MD, et al.: RUNX1 mutations are associated with poor outcome in younger and older patients with cytogenetically normal acute myeloid leukemia and with distinct gene and MicroRNA expression signatures. J Clin Oncol. 2012, 30:3109-18. 10.1200/JCO.2011.40.6652

31. Harada H, Harada Y: Recent advances in myelodysplastic syndromes: molecular pathogenesis and its implications for targeted therapies. Cancer Sci. 2015, 106:329-36. 10.1111/cas.12514

40. Skokowa J, Dale DC, Touw IP, Zeidler C, Welte K: Severe congenital neutropenias. Nat Rev Dis Primers. 2017, 3:17032. 10.1038/nrdp.2017.32

41. Rosen PS, Zeidler C, Bolyard AA, et al.: Stable long-term risk of leukaemia in patients with severe congenital neutropenia maintained on G-CSF therapy. Br J Haematol. 2010, 150:196-9. 10.1111/j.1365-2141.2010.08216.x

42. Touw IP: Game of clones: the genomic evolution of severe congenital neutropenia. Hematology Am Soc Hematol Educat Program. 2015, 2015:1-7. 10.1182/asheducation-2015.1.1