The Clinical, Molecular, and Mechanistic Basis of RUNX1 Mutations Identified in Hematological Malignancies

Asumi Yokota1, Li Huo1,2, Fengli Lan1,3, Jianqiang Wu1, and Gang Huang1,*

1Divisions of Pathology and Experimental Hematology and Cancer Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, USA, 2Jiangsu Institute of Hematology, Key Laboratory of Thrombosis and Hemostasis of Ministry of Health, The First Affiliated Hospital of Soochow University, Suzhou 215006, China, 3Department of Pediatrics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
*Correspondence: Gang.Huang@cchmc.org
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RUNX1 plays an important role in the regulation of normal hematopoiesis. RUNX1 mutations are frequently found and have been intensively studied in hematological malignancies. Germline mutations in RUNX1 cause familial platelet disorder with predisposition to acute myeloid leukemia (FPD/AML). Somatic mutations of RUNX1 are observed in various types of hematological malignancies, such as AML, acute lymphoblastic leukemia (ALL), myelodysplastic syndromes (MDS), myeloproliferative neoplasm (MPN), chronic myelomonocytic leukemia (CMML), and congenital bone marrow failure (CBMF). Here, we systematically review the clinical and molecular characteristics of RUNX1 mutations, the mechanisms of pathogenesis caused by RUNX1 mutations, and potential therapeutic strategies to target RUNX1-mutated cases of hematological malignancies.

Keywords: clinical incidence and prognosis, pathogenesis, RUNX1 mutations, targeted therapy

INTRODUCTION

The RUNX1 transcription factor is a critical regulator of embryogenesis and definitive hematopoiesis in vertebrates. Since the somatic point mutation of RUNX1 was first identified two decades ago, RUNX1 has become known to be one of the most frequently mutated genes in a variety of hematological malignancies (Fig. 1) (Deltcheva and Nimmo, 2017; Hayashi et al., 2017; Osato et al., 1999). Despite the improvement of technology for the detection of mutations and a deeper understanding of the diseases, there are still unanswered questions about the functional consequences of RUNX1 mutations in hematological malignancies, such as (1) the frequency of different RUNX1 mutations in various subgroups of hematological malignancies and their impact on prognosis; (2) the mechanisms of how RUNX1 mutations contribute to pathogenesis; and (3) the potential mechanism-based therapeutic strategies. In this review article, we describe the clinical and molecular characteristics of RUNX1 mutations, the mechanisms of pathogenesis caused by its mutations, and potential therapeutic strategies for those RUNX1-mutated cases.

GERMLINE MUTATION OF RUNX1 AND FPD/AML

Familial platelet disorder with predisposition to acute myeloid leukemia (FPD/AML) is an autosomal dominant disorder characterized by quantitative and qualitative platelet abnor-
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Fig. 1. The discovery procession of RUNX1 gene and its mutations in hematological malignancies.

As one of the frequently mutated genes in MDS, RUNX1 is essential for the development of hematopoietic stem cells (HSCs) in the embryonic stage. In adult hematopoiesis, however, it is dispensable for the maintenance of HSCs but required for megakaryocyte maturation and T lymphocyte-lineage differentiation (Ichikawa et al., 2004; Taniuchi et al., 2002). Loss-of-function or dominant-negative effect caused by mutated RUNX1 leads to the phenotype of FPD/AML (Cavalcante de Andrade Silva et al., 2018; Latger-Cannard et al., 2016; Vormittag-Nocito et al., 2019). FPD/AML is caused by germline mutations of RUNX1, which is located at 21q22 and plays pivotal roles in the regulation of hematopoietic differentiation (Song et al., 1999). RUNX1 is essential for the development of hematopoietic stem cells (HSCs) but required for megakaryocyte maturation and T lymphocyte-lineage differentiation (Ichikawa et al., 2004; Taniuchi et al., 2002). Loss-of-function or dominant-negative effect caused by mutated RUNX1 leads to the phenotype of FPD/AML (Cavalcante de Andrade Silva et al., 2018; Latger-Cannard et al., 2016; Vormittag-Nocito et al., 2019). Most of the mutations were clustered in the runt homology domain (RHD) and the c-terminal transactivation domain (TAD) with a few exceptions (Schlegelberger and Heller, 2017; Sood et al., 2017). FPD/AML was reported to transform to MDS/AML at a median onset age of 33 years old (Churpek et al., 2013). The median incidence rate of transformation is ranged from 35% to 44% in different studies (Godley, 2014; Owen et al., 2008a; 2008b). A few cases transformed to other types of leukemia, such as T-ALL (Nishimoto et al., 2010) or CMMML (Shiba et al., 2012). Compared with loss-of-function mutations, dominant-negative mutations of RUNX1 are more frequently related to higher risk of developing hematological malignancies (Latger-Cannard et al., 2016). However, these RUNX1 mutations by themselves are not sufficient for the development of leukemias. Additional mutations in RUNX1 (a second mutation), CDC25C, epigenetic modifiers, splicing factors, and tumor suppressors were reported to coordinately induce myeloid malignancies (Antony-Debre et al., 2016; Preudhomme et al., 2009; Yoshimi et al., 2014). Mutations in ASXL1, TET2, IDH1, CEBPD, RB1, MLL2, FLT3-ITD, WT1, and SRSF2 have also been detected by next-generation sequencing (Schlegelberger and Heller, 2017).

RUNX1 MUTATION-RELATED AML

RUNX1 mutations are found in approximately 5.6-17.9% of cases in AML (Cancer Genome Atlas Research Network et al., 2013; Gaidzik et al., 2011; 2016; Grossmann et al., 2012; Tang et al., 2009), 3% in childhood AML patients (Migas et al., 2011), and about 27.7% in secondary AML transformed from MDS (Dicker et al., 2010). Besides being associated with older age and male gender (Gaidzik et al., 2016; Tang et al., 2009), the frequency of RUNX1 mutation was reported to be varied in different risk levels of patients and French-American-British (FAB) subtypes. For different risk levels of patient, the highest frequency of RUNX1 mutations was reported in intermediate-risk AML patients (7.2%-32.7%), followed by high-risk patients (9%), while RUNX1 mutations were absent in low-risk patients (Gaidzik et al., 2011; Schnittger et al., 2011; Tang et al., 2009). The incidence of RUNX1 mutations was different in each FAB subtype: M0 (40%), M1 (17.5%), M2 (6.3%), M4 (15.1%), M5 (16%), and M6 (25%) (Tang et al., 2009). In AML patients with normal karyotype or with noncomplex chromosomal imbalances, patients of subtypes M0, M1, M2, and M4 showed even higher incidences: M0 (65.2%), M1 (30.2%), M2 (32.4%), and M4 (20%) (Schnittger et al., 2011). However, RUNX1 mutations were not detected in M3 cases (Gaidzik et al., 2011). In particular M0 cases with RUNX1 mutations, 56.4-88.9% of them presented biallelic RUNX1 mutations (Osato, 2004; Preudhomme et al., 2000). The high incidence of biallelic mutations in this subtype suggests that the loss of RUNX1 activity affects hematopoietic cells at a very early undifferentiated stage.

As one of the frequently mutated genes in MDS, somatic mutations of RUNX1 account for about 10% of the cases (Cazzola et al., 2013; Chen et al., 2007; Haferlach et al., 2014; Steensma et al., 2005; Tsai et al., 2015), while the frequency in childhood MDS is about 15% (Migas et al., 2011). The incidence of RUNX1 mutations in CMMML is even higher at 32.1% to 37% (Kuo et al., 2009; Tsai et al., 2015). As in FPD/AML, most RUNX1 mutations are found in the RHD and the TAD (Kuo et al., 2009). Mutated RUNX1 is frequently accompanied by additional mutations of the genes ASXL1, SRSF2, TET2, SF3B1, and EZH2 in MDS (Stengel et al., 2019). Del(7)/del(7q) also coexists frequently with RUNX1 mutations in MDS patients (Chen et al., 2007; Xu et al., 2017). Notably, RUNX1 mutations are common in high-risk MDS (MDS-MLD/MDS-EB) and are associated with poor clinical outcomes, especially higher risk and shorter latency for progression to secondary AML (Harada and Harada, 2015; Kuo et al., 2009; Steensma et al., 2005; Tsai et al., 2015). Shorter overall survival (OS) was also observed in MDS patients with RUNX1 mutations (Bejar et al., 2012; Chen et al., 2007).

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RUNX1 mutations were detected in 15.5% to 18.3% of patients with T-ALL, 3.8% of patients with B-ALL (Grossmann et al., 2011a; 2013), and in 9.2% of childhood patients with T-ALL. The incidence was higher in patients with early T-cell precursor (ETP) ALL, reaching 15.6%. RUNX1 mutations were reported to be associated with ETP ALL, which is a high-risk subtype of ALL lacking several T cell surface markers and exhibiting aberrant expression of myeloid and stem cell markers (Zhang et al., 2012). Mutated RUNX1 in T-ALL was associated with older age and lower white blood cell count, but not platelet count, hemoglobin levels, gender or karyotype (Grossmann et al., 2011a). Mutated RUNX1 conferred a poor prognosis on early T-ALL patients with inferior OS (Grossmann et al., 2011a; 2013).

RADIATION-ASSOCIATED AND THERAPY-RELATED MDS/AML WITH RUNX1 MUTATIONS

Radiation-associated MDS/AML and therapy-related MDS/AML (t-MDS/t-AML) are well-known complications after treatment with ionizing radiation, alkylating agents, and topoisomerase II inhibitors which can induce chromosome damages and cytogenetic abnormalities. The most common primary diseases are breast cancer and Hodgkin and non-Hodgkin lymphoma (Deitchche and Nimmo, 2017; Ito et al., 2015; Pedersen-Bjergaard et al., 2006; Shih et al., 2013). The frequency of RUNX1 mutations in radiation-associated MDS/AML and t-MDS/t-AML varies from 15.7% to 39% (Christiansen et al., 2004; Harada et al., 2003; 2004; Singhal et al., 2019; Zharylyanova et al., 2008). The RUNX1 mutations in radiation-associated MDS/AML and t-MDS/t-AML includes missense, nonsense, and frameshift mutations, most of which are located in the RHD and the TAD (Christiansen et al., 2004). Besides RUNX1 mutations, additional mutations or cytogenetic abnormalities were found such as del(5)/del(5q), del(7)/del(7q), NRAS, TP53, and FLT3 (Nirui et al., 2006; Pedersen-Bjergaard et al., 2008). The prognosis of RUNX1-mutated cases are poorer than patients without mutations. Additionally, the survival of t-AML is shorter than t-MDS (3.5 vs 13.2 months) (Singhal et al., 2019).

RUNX1 MUTATIONS IN MPN DISEASE TRANSFORMATION

RUNX1 also plays important roles in MPN and its transformation to acute leukemias. Since 2009, RUNX1 mutations have been detected in 10.3% to 37.5% of post-MPN AML patients (Beer et al., 2010; Cerquozzi and Tefferi, 2015; Ding et al., 2009; Klampfl et al., 2011; Thoennissen et al., 2010). RUNX1 mutations also appear in several chronic myeloid leukemia (CML) studies (Branford et al., 2018). Since the first case of CML-AP (accelerated phase) with RUNX1 mutation was reported (Corm et al., 2005), RUNX1 mutations have been found in 12.9% to 33.3% of CML-AP/BC (blast crisis) patients in the follow-up study (Branford et al., 2018; Grossmann et al., 2011b; Roche-Lestienne et al., 2008; Schmidt et al., 2014; Zhao et al., 2012). In 2016, the WHO classification defines myeloid/lymphoid neoplasms associated with eosiophilia (MLN-Eo) with rearrangement of PDGFRα, PDGFRβ, or FGFR1. RUNX1 mutations were positive in 5 out of 7 (71%) patients with FGFR1 rearrangement, and in a subsequent study, 6 out of 19 (32%) patients had RUNX1 mutations in FGFR1+ and PDGFRα-rearranged cases (Baer et al., 2018; Strati et al., 2018). In the MPN group, most of the mutations were detected in the RHD. Accompanied with RUNX1 mutations, the additional chromosome translocations (1q, 3q, 5q, 6p, 7p, 19q, and 22q) and mutations (ASXL1, NRAS, FLT3, TP53, TET2, CBL, etc.) were detected (Beer et al., 2010; Cerquozzi and Tefferi, 2015; Grossmann et al., 2011b; Klampfl et al., 2011). Regardless of the presence of the Ph chromosome or not, the prognosis is poor (Cerquozzi and Tefferi, 2015; Grossmann et al., 2011b).

RUNX1 MUTATIONS IN CBMF DISEASE PROGRESSION

Congenital bone marrow failure (CBMF) disorders are rare diseases characterized by peripheral blood cytopenia and hypoproliferation of one or more cell lineages in the BM (Goering et al., 2007; Kutler et al., 2003). Individuals with Fanconi anemia (FA) have a high risk (30%-40%) of developing MDS and AML, yet the secondary somatic mutations leading to hematological malignancies remain to be elucidated (Quentin et al., 2011). RUNX1 mutations were detected in 20.7% to 31.25% of FA-associated MDS or MDS/AML (Chao et al., 2017; Quentin et al., 2011). The frequency of RUNX1 mutations in severe congenital neutropenia (SCN) was up to 64.5% (Skokowa et al., 2014). Mutated RUNX1 was also frequently associated with additional aberrations, such as -7/7q, -5/5q-, and ASXL1, EZH2, KRAS, NRAS, SUZ12, CBL, FLT3-ITD, and TET2 mutations, in this group (Chao et al., 2017; Skokowa et al., 2014). Notably, in SCN-related MDS/AML, the frequency of CSF3R mutations was as high as that...
of RUNX1 mutations (Skokowa et al., 2014).

In the sections above, we briefly introduced and summarized the clinical and molecular characteristics of RUNX1 mutations in each of hematological malignancies (Table 1).

### MECHANISMS

The RUNX1 transcription factor is a key regulator of normal hematopoiesis and its functional disruption by point mutations is one of the major factors for developing hematological malignancies (Deltcheva and Nimmo, 2017). There are two major subtypes of RUNX1 mutations in hematological malignancies: (1) the RHD, in which many mutations have been identified and are involved in residues at the DNA binding interface; (2) the TAD, in which most mutations result in production of the proteins lacking all or part of the TAD. Most of the RUNX1 mutations are mono-allelic, and different mutation types contribute to different biological properties of RUNX1 protein and presumably to disease phenotype as well (Mangan and Speck, 2011). We will describe the mechanisms of pathogenesis caused by RUNX1 mutations according to the biological function of RUNX1.

### RUNX1 mutations on stem cells

RUNX1 is required for the emergence of adult HSCs during embryonic development and for the maturation of different lineages from HSCs in adult BM (Hong et al., 2017). Loss of RUNX1 function is associated with a pre-leukemic state, probably owing to the expansion of HSCs and progenitor cells, as well as differentiation defects. To rescue RUNX1 mutations in HSCs, genome editing technologies such as CRISPR-Cas9 will hopefully accelerate the studies of the mutations, leading to a better understanding of the pathogenesis of leukemia and novel targeted treatments (Sood et al., 2017).

### RUNX1 mutations on cell cycle and genomic instability

RUNX1 mutations on cell cycle and genomic instability

RUNX1 levels are increased at the G1-S phase and decreased during G2/M transition in hematopoietic cells. RUNX1 mutations may cause enhanced proliferation, attenuated mitotic checkpoint, and cell-cycle arrest. RUNX1 mutations can also cause genomic instability including increased DNA damage and impaired DNA repair. The potential therapeutic options for mutated RUNX1-associated abnormalities of cell cycle and genomic instability may come down to checkpoint inhibitors and DNA repair inhibitors, which can bypass cells with DNA damage/impaired DNA repair to M phase (Goyama et al., 2015; Ito et al., 2015).

### RUNX1 mutations on oncogenic signaling pathways

Mutations in RUNX1 are associated with alterations of various signaling pathways, such as WNT, BMP, TGF-β, RAS-ERK, Hippo-YAP1, and Notch, most of which have been described in cases of solid tumors. Notably, the possible involvement of RUNX1 mutations in WNT signaling has been shown in AML. WNT signaling controls cellular proliferation and differentiation and aberrant activation of WNT signaling has been reported in various tumors. RUNX1 mutations were closely associated with hypermethylation of the promoter of one of the WNT inhibitor gene, SFRP2, in AML. It is suggested that the WNT inhibitor hypermethylation might lead to aberrant activation of WNT signaling and interact with genetic alterations in the leukemogenesis (Hou et al., 2011).

### RUNX1 mutations on p53 signaling and cell apoptosis

In response to the DNA damaging agent adriamycin, the RUNX1-p53 complex is recruited to the p53 target genes

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**Table 1.** The frequency of RUNX1 mutations in various types of hematological malignancies

| Hematological malignancies | Subtypes | Frequency of RUNX1 mutations (%) | References |
|----------------------------|----------|----------------------------------|------------|
| FPD/AML                    | T-ALL    | > 70 families                    | (Latger-Cannard et al., 2016; Sood et al., 2017; Vormittag-Nocito et al., 2019) |
| AML                        | Primary AML | 5.6-17.9                        | (Cancer Genome Atlas Research Network et al., 2013; Gaidzik et al., 2011; 2016; Grossmann et al., 2012; Tang et al., 2009) |
| MDS                        | Secondary AML | 27.7                             | (Dicker et al., 2010) |
| CMML (MDS/MPN)             | T-ALL    | 32.1-37                          | (Cazzola et al., 2013; Chen et al., 2007; Haferlach et al., 2014; Steensma et al., 2005; Tsai et al., 2015) |
| ALL                        | B-ALL    | 15.5-18.3                        | (Hong et al., 2017) |
|                            | ETP-ALL  | 3.8                               | (Zhang et al., 2012) |
| CMML (MDS/MPN)             | Ph+ MPN  | 12.9-33.3                        | (Christiansen et al., 2004; Harada et al., 2003; 2004; Singhal et al., 2019; Zharlyganova et al., 2008) |
| Radiation t-MDS/AML        | Ph+ MPN  | 15.7-39                          | (Beer et al., 2010; Cerquozzi and Tefferi, 2015; Ding et al., 2009; Klampfl et al., 2011; Thoenissen et al., 2010) |
| MPN transformation         | MN-Eo    | 15.7-39                          | (Branford et al., 2018; Grossmann et al., 2011b; Roche-Lestienne et al., 2008; Zhao et al., 2012) |
| CBMF transformation        | FA       | 28.7-31.3                         | (Baer et al., 2018; Strati et al., 2018) |
|                            | SCN      | 64.5                               | (Chao et al., 2017; Quentin et al., 2011) |
|                            |          |                                   | (Skokowa et al., 2014) |
RUNX1 increases the transcriptional activity of p53, probably by increasing p300-mediated acetylation of p53, and RUNX1 depletion attenuates p53-mediated apoptosis (Wu et al., 2013). Thus, abrogated function of mutated RUNX1 might lead to defects in p53-mediated apoptosis pathway/DNA repair/cell cycle regulation, resulting in tumorigenesis. Furthermore, it was shown that oncogenic Nras induces Runx1, which is required for induction of apoptosis and senescence, and Runx1 deficiency and oncogenic Nras cooperatively contribute to the clonal maintenance of leukemia-initiating cells (Ito et al., 2015; Motoda et al., 2007). Thus, loss-of-function mutations of RUNX1 may support the emergence of tumor-initiating cells in hematological malignancies partly by inhibiting p53 signaling and apoptosis.

**RUNX1 mutation in ribosomal biogenesis**

Loss-of-function mutations of RUNX1 were found to exhibit reduced ribosomal biogenesis in HSCs. RUNX1 directly binds to promoters of the genes encoding ribosomal RNA/proteins and regulates their transcription. Thus, RUNX1 mutations may cause low biosynthetic activity and confer stress resistance on HSCs, which provides a proliferative advantage to HSCs at the preleukemic stage (Cai et al., 2015; Delcheva and Nimmo, 2017). In clinical trials, L-leucine is administrated to patients with Diamond-Blackfan anemia (DBA), which is caused by loss-of-function mutations in ribosomal protein genes. It has been shown that the treatment can improve anemia in the genetic DBA mouse models as well as DBA patients, possibly through mTOR activation, resulting in stimulation of protein translation (Ruggero and Shimamura, 2014). Thus, L-leucine might be a possible therapeutic option for RUNX1-mutated cases as well.

**Hypoxic microenvironment**

It has been reported that RUNX1 suppresses transactivation activity of hypoxia-inducible factor 1α (HIF-1α), while HIF-1α increases the activity of RUNX1 (Peng et al., 2008). HIF-1α is critical for cellular response to hypoxia and facilitates glycolysis but suppresses the TCA cycle. As most of the RUNX1 mutations cause loss of its function, RUNX1-mutated HSCs may have more activated HIF-1α pathway and glycolysis-biased metabolism. Metabolic rewiring to a hypoxia-like status is a hallmark of cancer as well as MDS and maintains stemness of tumor initiating cells (Hayashi et al., 2019). Thus, HIF-1α inhibitors or metabolic pathway modulators could be potential therapeutic strategies.

In conclusion, we summarized the mechanisms of pathogenesis caused by RUNX1 mutations and potential therapeutic strategies for RUNX1-mutated cases (Fig. 2).

**CONCLUSIONS AND PERSPECTIVES**

In this review, we briefly described the impact of RUNX1 mutations on clinical disease phenotypes and prognosis in hematological malignancies and the mechanisms of how RUNX1 mutations contribute to pathophysiology. RUNX1 mutations are frequently observed in various types of hematological malignancies and contribute to poor prognosis. RUNX1 is one of the most extensively studied molecules in hematopoiesis and leukemogenesis, and it functions in a variety of biological processes including cell differentiation, proliferation, cell cycle, DNA repair, apoptosis, ribosomal biogenesis, and metabolism. There are still many unknowns, such as how mutations affect this diverse function of RUNX1 and their clinical outcomes. Further elucidation is needed for a deeper understanding of RUNX1-associated hematological malignancies and for the development of better therapeutic strategies.

**Disclosure**

The authors have no potential conflicts of interest to disclose.

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ORCID

Asumi Yokota https://orcid.org/0000-0003-4128-062X
Li Huo https://orcid.org/0000-0002-8831-2505
Fengli Lan https://orcid.org/0000-0001-6443-843X
Jianqiang Wu https://orcid.org/0000-0002-4239-5659
Gang Huang https://orcid.org/0000-0002-5457-5358

REFERENCES

Antony-Debre, I., Duployez, N., Buccii, M., Geoffroy, S., Micel, J.B., Renneville, A., Boissel, N., Dhejain, N., Rea, D., Nelken, B., et al. (2016). Somatic mutations associated with leukemic progression of familial platelet disorder with predisposition to acute myeloid leukemia. Leukemia 30, 999-1002.

Baer, C., Muehlbacher, V., Kern, W., Haferlach, C., and Haferlach, T. (2018). Molecular genetic characterization of myeloid/lymphoid neoplasms associated with eosinophilia and rearrangement of PDGFRα, PDGFRβ, FGFR1 or PC1-MAK2. Haematologica 103, e348-e350.

Beer, P.A., Delhommeau, F., LeCouedic, J.P., Dawson, M.A., Chen, E., Barefrod, D., Kusec, R., McMullin, M.F., Harrison, C.N., Vannucchi, A.M., et al. (2010). Two routes to leukemic transformation after a JAK2 mutation-positive myeloproliferative neoplasm. Blood 215, 2891-2900.

Bejar, R., Stevenson, K.E., Caughey, B.A., Abdel-Wahab, O., Steensma, D.P., Galli, N., Raza, A., Kantarjian, H., Levine, R.L., Neuberg, D., et al. (2012). Validation of a prognostic model and the impact of mutations in patients with lower-risk myelodysplastic syndromes. J. Clin. Oncol. 30, 3376-3382.

Branford, S., Wang, P., Yeung, D.T., Thomson, D., Purins, A., Wadham, C., Shahin, N.H., Marum, J.E., Nataren, N., Parker, W.T., et al. (2018). Integrative genomic analysis reveals cancer-associated mutations at diagnosis of CML in patients with high-risk disease. Blood 132, 948-961.

Bullinger, L., Dohner, K., and Dohner, H. (2017). Genomics of acute myeloid leukemia diagnosis and pathways. J. Clin. Oncol. 35, 934-946.

Cai, X., Gao, L., Teng, L., Ge, J., Oo, Z.M., Kumar, A.R., Gilliland, D.G., Mason, P.W., et al. (2018). Integrative genomic analysis of CML patients with familial myelodysplastic syndrome/acute leukemia predisposition. Mol. Cells 2020; 43(2): 145-152.

Cazzola, M., Della Porta, M.G., and Malcovati, L. (2013). The genetic basis of myelodysplasia and its clinical relevance. Blood 122, 4021-4034.

Cerquozzi, S. and Telfer, A. (2015). Blast transformation and fibrotic progression in polyclonality vera and essential thrombocythaemia: a literature review of incidence and risk factors. Blood Cancer J. 5, e366.

Chao, M.M., Thomay, K., Goehring, G., Wlodsarski, M., Pastor, V., Schlegelberger, B., Schindler, D., Kritz, C.P., and Niemeyer, C. (2017). Mutational spectrum of Fanconi anemia associated myeloid neoplasms. Klin. Padiatr. 229, 239-334.

Chen, C.Y., Lin, L.I., Tang, J.L., Ko, B.S., Tsay, W., Chou, W.C., Yao, M., Wu, S.J., Tseng, M.H., and Tsien, H.F. (2007). RUNX1 gene mutation in primary myelodysplastic syndrome--the mutation can be detected early at diagnosis or acquired during disease progression and is associated with poor outcome. Br. J. Haematol. 139, 405-414.

Christiansen, D.H., Andersen, M.K., and Pedersen-Bjergaard, J. (2004). Mutations of AML1 are common in therapy-related myelodysplasia following therapy with alkylating agents and are significantly associated with deletion or loss of chromosome arm 7q and with subsequent leukemic transformation. Blood 104, 1474-1481.

Churpek, J.E., Lorenz, R., Nedumgottti, S., Onel, K., Olopade, O.I., Sorrell, A., Owen, C.J., Bertuch, A.A., and Godley, L.A. (2013). Proposal for the clinical definition and management of patients and their family members with familial myelodysplastic syndrome/acute leukemia predisposition syndrome. Leuk. Lymphoma 54, 28-35.

Corr, S., Biggio, V., Roche-Lestienne, C., Lai, J.L., Yakoub-Agha, I., Philippe, N., Nicolini, F.E., Facon, T., and Preudhomme, C. (2005). Coexistence of AML1/RUNX1 and BCR-ABL point mutations in an imatinib-resistant form of CML. Leukemia 19, 1991-1992.

Deltcheva, E. and Nimmo, R. (2017). RUNX transcription factors at the interface of stem cells and cancer. Biochem. J. 474, 1755-1768.

Dicker, F., Haferlach, C., Sundermann, J., Wendland, N., Weiss, T., Kern, W., Haferlach, T., and Schnittger, S. (2010). Mutation analysis for RUNX1, MLL-PTD, FLT3-ITD, NPM1 and NRAS in 269 patients with MDS or secondary AML. Leukemia 24, 1528-1532.

Ding, Y., Harada, Y., Imagawa, J., Kimura, A., and Harada, H. (2009). AML1/RUNX1 point mutation possibly promotes leukemic transformation in myeloproliferative neoplasms. Blood 114, 5201-5205.

Gaidzik, VI., Bullinger, L., Schlenk, R.F., Zimmermann, A.S., Rock, J., Paschka, P., Corbacioglu, A., Kräuter, J., Schlegelberger, B., Ganzer, A., et al. (2011). RUNX1 mutations in acute myeloid leukemia: results from a comprehensive genetic and clinical analysis from the AML study group. J. Clin. Oncol. 29, 1364-1372.

Gaidzik, VI., Teleanu, V., Paaepaemanuil, E., Weber, D., Paschka, P., Hahn, J., Wahlrabenstein, T., Kolbinger, B., Kline, C.H., Horst, H.A., et al. (2016). RUNX1 mutations in acute myeloid leukemia are associated with distinct clinic-pathologic and genetic features. Leukemia 30, 2282.

Godley, L.A. (2014). Inherited predisposition to acute myeloid leukemia. Semin. Hematol. 51, 306-321.

Gohring, G., Karow, A., Steinemann, D., Wilkens, L., Lichter, P., Zeidler, C., Niemeyer, C., Welte, K., and Schlegelberger, B. (2007). Chromosomal aberrations in congenital bone marrow failure disorder--an early indicator for leukemogenesis? Ann. Hematol. 86, 733-739.

Goyama, S., Huang, G., Kurokawa, M., and Mulloy, J.C. (2015). Post-translational modifications of RUNX1 as potential anticancer targets. Oncogene 34, 3483-3492.

Grossmann, V., Haferlach, C., Weissmann, S., Roller, A., Schindela, S., Poetzinger, F., Stadler, K., Bellos, F., Kern, W., Haferlach, T., et al. (2013). The molecular profile of adult T-cell acute lymphoblastic leukemia mutations in RUNX1 and DNMT3A are associated with poor prognosis in T-ALL. Genes Chromosomes Cancer 52, 410-422.

Grossmann, V., Kern, W., Harbich, S., Alpermann, T., Jeromin, S., Schnittger, S., Haferlach, C., Haferlach, T., and Kollmann, A. (2011a). Prognostic relevance of RUNX1 mutations in T-cell acute lymphoblastic leukemia. Haematologica 96, 1874-1877.

Grossmann, V., Kollmann, A., Zenger, M., Schindela, S., Eder, C., Weissmann, S., Schnittger, S., Kern, W., Muller, M.C., Hochhaus, A., et al. (2011b). A deep-sequencing study of chronic myeloid leukemia patients in blast crisis (BC-CML) detects mutations in 76.9% of cases. Leukemia 25, 557-560.

Grossmann, V., Schnittger, S., Kollmann, A., Eder, C., Roller, A., Dicker, F., Schmid, C., Wendtner, C.M., Staub, P., Serve, H., et al. (2012). A novel hierarchical prognostic model of AML solely based on molecular mutations. Blood 120, 2963-2972.

Haferlach, T., Nagata, Y., Grossmann, V., Okuno, Y., Bacher, U., Nagae, G., Schnittger, S., Sanada, M., Kon, A., Alpermann, T., et al. (2014). Landscape
of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia 28, 241-247.

Haferlach, T., Stengel, A., Eckstein, S., Perglerova, K., Alpermann, T., Kern, W., Haferlach, C., and Meggendorfer, M. (2016). The new provisional WHO entity ‘RUNX1 mutated AML’ shows specific genetics but no prognostic influence of dysplasia. Leukemia 30, 2109-2112.

Harada, H. and Harada, Y. (2015). Recent advances in myelodysplastic syndromes: molecular pathogenesis and its implications for targeted therapies. Cancer Sci. 106, 329-336.

Harada, H., Harada, Y., Niimi, H., Kyo, T., Kimura, A., and Inaba, T. (2004). High incidence of somatic mutations in the AML1/RUNX1 gene in myelodysplastic syndrome and low blast percentage myeloid leukemia with myeloplasia. Blood 103, 2316-2324.

Harada, H., Harada, Y., Tanaka, H., Kimura, A., and Inaba, T. (2003). Implications of somatic mutations in the AML1 gene in radiation-associated and therapy-related myelodysplastic syndrome/acute myeloid leukemia. Blood 101, 673-680.

Hayashi, Y., Harada, Y., Huang, G., and Harada, H. (2017). Myeloid neoplasms with germ line RUNX1 mutation. Int. J. Hematol. 106, 183-188.

Hayashi, Y., Yokota, A., Harada, H., and Huang, G. (2019). Hypoxia/ pseudohypoxia-mediated activation of hypoxia-inducible factor-1alpha in cancer. Cancer Sci. 110, 1510-1517.

Hong, D., Messier, T.L., Tye, C.E., Dobson, J.R., Fritz, A.J., Sikora, K.R., Browne, G., Stein, J.L., Lian, J.B., and Stein, G.S. (2017). Runx1 stabilizes the mammary epithelial cell phenotype and prevents epithelial to mesenchymal transition. Oncotarget 8, 17610-17627.

Hou, H.A., Kuo, Y.Y., Liu, C.Y., Lee, M.C., Tang, J.L., Chen, C.Y., Chou, W.C., Huang, C.F., Lee, F.Y., Liu, M.C., et al. (2013). Distinct association between aberrant methylation of Wnt inhibitors and genetic alterations in acute myeloid leukemia. Br. J. Cancer 105, 1927-1933.

Ichikawa, M., Asai, T., Saito, T., seo, S., Yamazaki, I., Yamagata, T., Mitani, K., Chiba, S., Ogawa, S., Kurokawa, M., et al. (2004). AML-1 is required for myeloid leukaemia. Br. J. Cancer 89, 1426-1431.

Kuo, M.C., Liang, D.C., Huang, C.F., Shih, Y.S., Wu, J.H., Lin, T.L., and Shih, L.Y. (2009). RUNX1 mutations are frequent in chronic myelomonocytic disease progression. Blood 113, 240-248.

Krugler, D., Singh, B., Satagopan, J., Batish, S.D., Berwick, M., Giampietro, P.F., Hanenberg, H., and Auerbach, A.D. (2003). A 20-year perspective on the International Fanconi Anemia Registry (IFAR). Blood 101, 1249-1256.

Laagner-Cannard, V., Philippe, C., Bouquet, A., Baccini, V., Alessi, M.C., Anki, A., Bauters, F., Bayart, S., Bauters, F., Lai, J.L., Nicolini, F.E., and Preudhomme, C. (2008). 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. II, 49.

Mangan, I.K. and Speck, N.A. (2011). RUNX1 mutations in clonal myeloid disorders: from conventional cytogenetics to next generation sequencing, a story 40 years in the making. Crit. Rev. Oncog. 16, 77-91.

Mendler, J.H., Maharry, K., Radmacher, M.D., Mrozek, K., Becker, H., Metzler, K.H., Schmid, S., Whitleman, S.P., Khalfé, J., Kohlschmidt, J., et al. (2012). 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. 30, 3109-3118.

Migas, A., Savva, N., Mishikova, O., and Aleinikova, O.V. (2011). AML1/RUNX1 gene point mutations in childhood myeloid malignancies. Pediatr. Blood Cancer 57, 583-587.

Motoda, L., Osato, M., Yamashita, N., Jacob, B., Chen, L.Q., Yanagida, M., Ida, H., Wee, H.J., Sun, A.X., Taniuchi, I., et al. (2007). Runx1 protects hematopoietic stem/progenitor cells from oncogenic insult. Stem Cells (Dayton, Ohio) 25, 2976-2986.

Niimi, H., Harada, H., Harada, Y., Ding, Y., Imagawa, J., Inaba, T., Kyo, T., and Kimura, A. (2006). Hyperactivation of the RAS signaling pathway in myelodysplastic syndrome with AML/RUNX1 point mutations. Leukemia 20, 635-644.

Nishimoto, N., Imai, Y., Ueda, K., Nakagawa, M., Shinohara, A., Ichikawa, M., Nannya, Y., and Kurokawa, M. (2010). T cell acute lymphoblastic leukemia arising from a familial platelet disorder: Int. J. Hematol. 92, 194-197.

Osato, M. (2004). Point mutations in the RUNX1/AML1 gene: another actor in RUNX leukemia. Oncogene 23, 4284-4296.

Osato, M., Asou, N., Abdalla, E., Hoshino, K., Yamasaki, H., Okubo, T., Suzushima, H., Takatsuki, K., Kanno, T., Shigesada, K., et al. (1999). Biallelic and heterozygous point mutations in the runt domain of the AML1/PEBP2alphaB gene associated with myeloblastic leukemias. Blood 93, 1817-1824.

Owen, C., Barnett, M., and Fitzgibbon, J. (2008a). Familial myelodysplasia and acute myeloid leukaemia—a review. Br. J. Haematol. 140, 123-132.

Owen, C.J., Toze, C.L., Koochin, A., Forrest, D.L., Smith, C.A., Stevens, J.M., Jackson, S.C., Poon, M.C., Sinclair, G.D., Leber, B., et al. (2008b). Five new pedigrees with inherited RUNX1 mutations causing familial platelet disorder with propensity to myeloid malignancy. Blood 112, 4639-4645.

Pedersen-Bjergaard, J., Andersen, M.K., Andersen, M.T., and Christiansen, D.H. (2008). Genetics of therapy-related myelodysplasia and acute myeloid leukemia. Leukemia 22, 240-248.

Pedersen-Bjergaard, J., Christiansen, D.H., Desta, F., and Andersen, M.K. (2006). Alternative genetic pathways and cooperating genetic abnormalities in the pathogenesis of therapy-related myelodysplasia and acute myeloid leukemia. Leukemia 20, 1943-1949.

Peng, Z.G., Zhou, M.Y., Huang, Y., Qiu, J.H., Wang, L.S., Liao, S.H., Dong, S., and Chen, G.Q. (2008). Physical and functional interaction of Runt-related protein 1 with hypoxia-inducible factor-1alpha. Oncogene 27, 839-847.

Preudhomme, C., Renneville, A., Bourdon, V., Philippe, N., Roche-Lestienne, C., Boissel, N., Dhenin, O., Andre, J.M., Cornillet-Lefebvre, P., Baruchel, A., et al. (2009). High frequency of RUNX1 biallelic alteration in acute myeloid leukemia secondary to familial platelet disorder. Blood 113, 5583-5587.

Preudhomme, C., Warot-Loze, D., Roumier, C., Grardel-Duflos, N., Garand, R., Lai, J.J., Dastugue, N., Maigny, D., Denis, C., Bauters, F., et al. (2000). High incidence of biallelic point mutations in the Runt domain of the AML1/PEBP2 alpha B gene in Mo acute myeloid leukemia and in myeloid malignancies with acquired trisomy 21. Blood 96, 2862-2869.

Quintin, S., Cuccurullo, W., Cecaldi, R., Nibourel, O., Pondarre, C., Pages, M.P., Vasques, N., Dubois d’Enghien, C., Larghero, J., Peffault de Latour, R., et al. (2011). Myelodysplasia and leukemia of Fanconi anemia are associated with a specific pattern of genomic abnormalities that includes cryptic RUNX1/AML1 lesions. Blood 117, e161-e170.

Roche-Lestienne, C., Deluche, L., Corn, S., Tigaud, I., Jocha, S., Philippe, N., Geffroy, S., Lai, J.L., Nicolini, F.E., and Preudhomme, C. (2008). RUNX1 DNA-binding mutations and RUNX1-PRDM16 cryptic fusions in BCR-ABL+ leukemias are frequently associated with secondary trisomy 21 and may contribute to clonal evolution and imatinib resistance. Blood 111, 3735-3741.

Ruggiero, D. and Shimamura, A. (2014). Marrow failure: a window into ribosome biology. Blood 124, 2784-2792.

Schlegelberger, B. and Heller, P.G. (2017). RUNX1 deficiency (familial platelet disorder with predisposition to myeloid leukemia, FPDMM). Semin. Hematol. 54, 75-80.
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Schmidt, M., Rinken, J., Schafer, V., Schnittger, S., Kohlmann, A., Obstfelder, E., Kunert, C., Ziemann, J., Winkelmann, N., Eigendorff, E., et al. (2014). Molecular-defined clonal evolution in patients with chronic myeloid leukemia independent of the BCR-ABL status. Leukemia 28, 2292-2299.

Schnittger, S., Dicker, F., Kern, W., Wendland, N., Sundermann, J., Alpermann, T., Haferlach, C., and Haferlach, T. (2011). RUNX1 mutations are frequent in de novo AML with noncomplex karyotype and confer an unfavorable prognosis. Blood 117, 2348-2357.

Shiba, N., Hasegawa, D., Park, M.J., Murata, C., Sato-Otsubo, A., Ogawa, C., Manabe, A., Arakawa, H., Ogawa, S., and Hayashi, Y. (2012). CBL mutation in chronic myelomonocytic leukemia secondary to familial platelet disorder with propensity to develop acute myeloid leukemia (FPA/AML). Blood 119, 2612-2614.

Shih, A.H., Chung, S.S., Dolezal, E.K., Zhang, S.J., Abdel-Wahab, O.J., Park, C.Y., Nimer, S.D., Levine, R.L., and Klimk, V.M. (2013). Mutational analysis of therapy-related myelodysplastic syndromes and acute myelogenous leukemia. Haematologica 98, 908-912.

Singhal, D., Wee, L.Y.A., Kutyna, M.M., Chhetri, R., Geoghegan, J., Schreiber, A.W., Feng, J., Wang, P.P., Babic, M., Parker, W.T., et al. (2019). The mutational burden of therapy-related myeloid neoplasms is similar to primary myelodysplastic syndrome but has a distinctive distribution. Leukemia 33, 2842-2853.

Skokowa, J., Steinemann, D., Katsman-Kuipers, J.E., Zeidler, C., Klimenkova, O., Klimiankou, M., Unalan, M., Kandabarau, S., Makaryan, V., Beekman, R., et al. (2014). Cooperativity of RUNX1 and CSF3R mutations in severe congenital neutropenia: a unique pathway in myeloid leukemogenesis. Blood 123, 2229-2237.

Song, W.J., Sullivan, M.G., Legare, R.D., Hutchings, S., Tan, X., Kufrin, D., Ratajczak, J., Resende, I.C., Haworth, C., Hock, R., et al. (1999). Haplo-insufficiency of CBFA2 causes familial thrombocytopenia with propensity to develop acute myelogenous leukemia. Nat. Genet. 23, 166-175.

Sood, R., Kamikubo, Y., and Liu, P. (2017). Role of RUNX1 in hematological malignancies. Blood 129, 2070-2082.

Steensma, D.P., Gibbons, RJ, Masa, R.A., Tefferi, A., and Higgs, D.R. (2005). Somatic point mutations in RUNX1/CFBFA2/AML1 are common in high-risk myelodysplastic syndrome, but not in myelofibrosis with myeloid metaplasia. Eur. J. Haematol. 74, 47-53.

Stengel, A., Kern, W., Meggendorfer, M., Haferlach, T., and Haferlach, C. (2019). RUNX1 mutations in MDS, s-AML, and de novo AML: differences in accompanying genetic alterations and outcome. Leuk. Lymphoma 60, 1334-1336.

Stengel, A., Kern, W., Meggendorfer, M., Nadarajah, N., Pergierova, K., Haferlach, T., and Haferlach, C. (2018). Number of RUNX1 mutations, wild-type allele loss and additional mutations impact on prognosis in adult RUNX1-mutated AML. Leukemia 32, 295-302.

Strati, P., Tang, G., Duose, D.Y., Mallampati, S., Luthra, R., Patel, K.P., Hussaini, M., Mirza, A.S., Komrokji, R.S., Oh, S., et al. (2018). Myeloid/lymphoid neoplasms with FGFR1 rearrangement. Leuk. Lymphoma 59, 1672-1676.

Tang, J.L., Hou, H.A., Chen, C.Y., Liu, C.Y., Chou, W.C., Tseng, M.H., Huang, C.F., Lee, F.Y., Liu, M.C., Yao, M., et al. (2009). AML1/RUNX1 mutations in 470 adult patients with de novo acute myeloid leukemia: prognostic implication and interaction with other gene alterations. Blood 114, 5352-5361.

Tanuchi, I., Osato, M., Egawa, T., Sunshine, M.J., Bae, S.C., Komori, T., Ito, Y., and Littman, D.R. (2002). Differential requirements for Runx proteins in CD4 repression and epigenetic silencing during T lymphocyte development. Cell 111, 621-633.

Thoenissen, N.H., Krug, U.O., Lee, D.H., Kawamata, N., Iwanski, G.B., Lasho, T., Weiss, T., Nowak, D., Koren-Michowicz, M., Kato, M., et al. (2010). Prevalence and prognostic impact of allelic imbalances associated with leukemic transformation of Philadelphia chromosome-negative myeloproliferative neoplasms. Blood 115, 2882-2890.

Tsai, S.C., Shih, L.Y., Liang, S.T., Huang, Y., Kuo, M.C., Huang, C.F., Shih, Y.S., Lin, T.H., Chi, M.C., and Liang, D.C. (2015). Biological activities of RUNX1 mutants predict secondary acute leukemia transformation from chronic myelomonocytic leukemia and myelodysplastic syndromes. Clin. Cancer Res. 21, 3541-3551.

Vormittag-Nocto, E., Ni, H., Schmidt, M.L., and Lindgren, V. (2019). Thrombocytopenia and predisposition to acute myeloid leukemia due to mosaic ring 21 with loss of RUNX1: cytogenetic and molecular characterization. Mol. Syndromol. 9, 306-311.

Wu, D., Ozaki, T., Yoshihara, Y., Kubo, N., and Nakagawara, A. (2013). Runt-related transcription factor 1 (RUNX1) stimulates tumor suppressor p53 protein in response to DNA damage through complex formation and acetylation. J. Biol. Chem. 288, 1353-1364.

Xu, F., Wu, L.Y., He, Q., Wu, D., Zhang, Z., Song, L.X., Zhao, Y.S., Su, J.Y., Zhou, L.Y., Guo, J., et al. (2017). Exploration of the role of gene mutations in myelodysplastic syndromes through a sequencing design involving a small number of target genes. Sci. Rep. 7, 43113.

Yoshimi, A., Toya, T., Kawazu, M., Ueno, T., Tsukamoto, A., Iizuka, H., Nakagawa, M., Nannya, Y., Arai, S., Harada, H., et al. (2014). Recurrent CDC25C mutations drive malignant transformation in FPD/AML. Nat. Commun. 5, 4770.

Zhang, J., Ding, L., Holmfeldt, L., Wu, G., Heatley, S.L., Payne-Turner, D., Easton, J., Chen, X., Wang, J., Rusch, M., et al. (2012). The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature 481, 157-163.

Zhang, J., Chuang, W.Y., Li, G., Ma, L.Y., Xiong, S.M., Weng, X.Q., Zhang, W.N., Zhao, L.J., Wang, Y.Y., Li, G., Ma, L.Y., Xiong, S.M., Weng, X.Q., Zhang, W.N., et al. (2012). Functional features of RUNX1 mutations in acute transformation of chronic myeloid leukemia and their contribution to inducing murine full-blown leukemia. Blood 119, 2873-2882.

Zharlyganova, D., Harada, H., Harada, Y., Shinkarev, S., Zhumadianov, Z., Zhunusova, A., Tchaizhunusova, N.J., Apasilok, K.N., Kemaikin, V., Zhumadianov, K., et al. (2008). High frequency of AML1/RUNX1 point mutations in radiation-associated myelodysplastic syndrome around Semipalatinsk nuclear test site. J. Radiat. Res. 49, 549-555.