Molecules and Cells

Minireview

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

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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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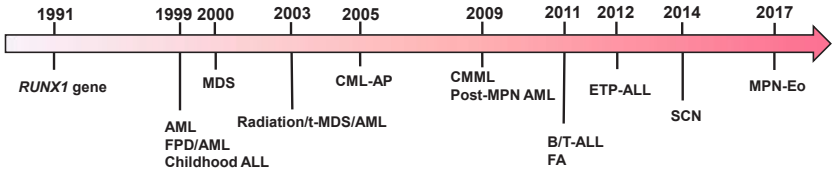

Fig. 1. The discovery procession of *RUNX1* gene and its mutations in hematological malignancies.

malities and predisposition to AML (Online Mendelian Inheritance in Man [OMIM] No. #601399). To date, more than 70 families have been reported (Cavalcante de Andrade Silva et al., 2018; Latger-Cannard et al., 2016; Sood et al., 2017; 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) 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). 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 CMML (Shiba et al., 2012). Compared with loss-of-function mutations, dominant-negative mutations of *RUNX1* are correlated to a 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 MDS AND MDS/MPN (CMML)

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 CMML 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).

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.

At least one more additional mutation was observed in 40.8% to 95% of AML patients with *RUNX1* mutations, such as Class I genes; *FLT3*-ITD/TKD and *NRAS*; Epigenetic factors; *MLL*-PTD, *ASXL1*, *IDH1/IDH2*, *TET2*, *BCOR*, and *DNMT3A*; Splicing factors; *SRSF2* and *SF3B1*, and others including *WT1* (Bullinger et al., 2017; Gaidzik et al., 2011; Haferlach et al.,

2016; Schnittger et al., 2011; Stengel et al., 2018; Tang et al., 2009). Trisomy 8 and trisomy 13 showed a high incidence of *RUNX1* mutations (Preudhomme et al., 2000; Schnittger et al., 2011). In contrast, *RUNX1* mutations were negatively associated with *NPM1* and *CEBPA* mutations (Gaidzik et al., 2011; Haferlach et al., 2016; Mendler et al., 2012; Schnittger et al., 2011; Tang et al., 2009).

In *RUNX1*-mutated AML, other aberrations were less frequent in MDS than *de novo* AML and secondary AML that progressed from MDS. Trisomy 13 was frequently found in *de novo RUNX1*-mutated AML, while trisomy 8 was exclusively harbored in *RUNX1*-mutated MDS and secondary AML. In *RUNX1*-mutated MDS, a higher frequency of *ASXL1*, *TET2*, and *EZH2* mutations was observed, while *DNMT3A* and *IDH2* mutations were more abundant in *de novo RUNX1*-mutated AML (Stengel et al., 2019).

AML with *RUNX1* mutations predicts worse prognosis, resistance to chemotherapy, and inferior event free survival (EFS), relapse free survival (RFS), and OS. Mutated *RUNX1* is an independent prognostic factor for EFS or OS (Gaidzik et al., 2011; Mendler et al., 2012; Schnittger et al., 2011; Tang et al., 2009). *RUNX1* mutations associated with *ASXL1* or *SRSF2* mutations predicted particularly poorer prognosis (Bullinger et al., 2017).

RUNX1 MUTATION-RELATED ALL

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 (Deltcheva 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; Zharlyganova 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* (Niimi et al., 2006; Pedersen-Bjergaard et al., 2008). The prognosis of *RUNX1*-mutated cases are poorer than patients without mutations. Additionally, the survial 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 followed-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 eosinophilia (MLN-Eo) with rearrangement of *PDGFRA*, *PDGFRB*, 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 *PDGFRA*-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 (Gohring 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

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

Hematological malignancies	Subtypes	Frequency of *RUNX1* mutations (%)	References
FPD/AML		> 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)
	Secondary AML	27.7	(Dicker et al., 2010)
MDS		10	(Cazzola et al., 2013; Chen et al., 2007; Haferlach et al., 2014; Steensma et al., 2005; Tsai et al., 2015)
CMML (MDS/MPN)		32.1-37	(Kuo et al., 2009; Tsai et al., 2015)
ALL	T-ALL	15.5-18.3	(Grossmann et al., 2011a; 2013)
	B-ALL	3.8	(Grossmann et al., 2011a; 2013)
	ETP-ALL	15.6	(Zhang et al., 2012)
Radiation t-MDS/AML		15.7-39	(Christiansen et al., 2004; Harada et al., 2003; 2004; Singhal et al., 2019; Zharlyganova et al., 2008)
MPN transformation	Ph^- MPN	10.3-37.5	(Beer et al., 2010; Cerquozzi and Tefferi, 2015; Ding et al., 2009; Klampfl et al., 2011; Thoennissen et al., 2010)
	Ph^+ MPN	12.9-33.3	(Branford et al., 2018; Grossmann et al., 2011b; Roche-Lestienne et al., 2008; Zhao et al., 2012)
	MPN-Eo	32-71	(Baer et al., 2018; Strati et al., 2018)
CBMF transformation	FA	20.7-31.3	(Chao et al., 2017; Quentin et al., 2011)
	SCN	64.5	(Skokowa et al., 2014)

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 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 check point 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

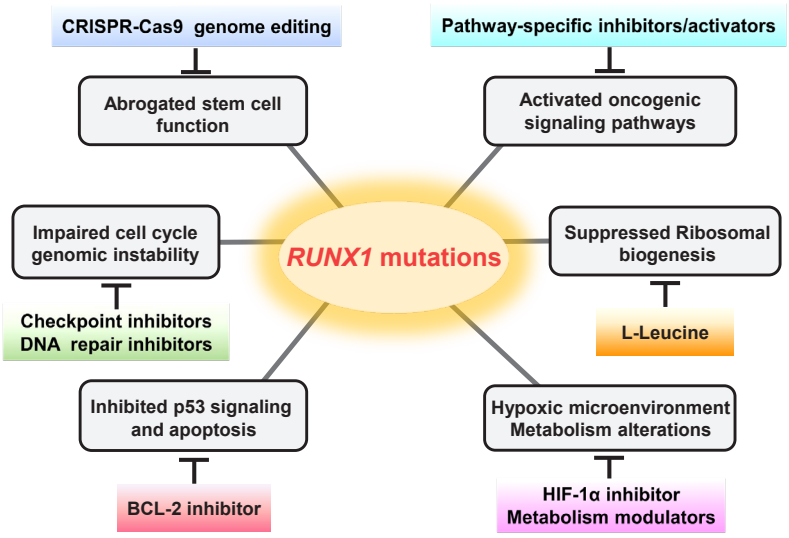

Fig. 2. The key pathophysiological mechanisms related to *RUNX1* mutations and potential therapeutic strategies.

such as *CDKN1A* and *BAX*. 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; Deltcheva 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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