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Somatic *SETBP1* mutations in myeloid neoplasms

Hideki Makishima[1,2]

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Abstract SETBP1 is a SET-binding protein regulating self-renewal potential through HOXA-protein activation. Somatic *SETBP1* mutations were identified by whole exome sequencing in several phenotypes of myelodysplastic/myeloproliferative neoplasms (MDS/MPN), including atypical chronic myeloid leukemia, chronic myelomonocytic leukemia, and juvenile myelomonocytic leukemia as well as in secondary acute myeloid leukemia (sAML). Surprisingly, its recurrent somatic activated mutations are located at the identical positions of germline mutations reported in congenital Schinzel–Giedion syndrome. In general, somatic *SETBP1* mutations have a significant clinical impact on the outcome as poor prognostic factor, due to downstream HOXA-pathway as well as associated aggressive types of chromosomal defects (-7/del(7q) and i(17q)), which is consistent with wild-type *SETBP1* activation in aggressive types of acute myeloid leukemia and leukemic evolution. Biologically, mutant SETBP1 attenuates *RUNX1* and activates *MYB*. The studies of mouse models confirmed biological significance of *SETBP1* mutations in myeloid leukemogenesis, particularly associated with *ASXL1* mutations. *SETBP1* is a major oncogene in myeloid neoplasms, which cooperates with various genetic events and causes distinct phenotypes of MDS/MPN and sAML.

✉ Hideki Makishima
makishima.hideki.8x@kyoto-u.ac.jp

[1] Department of Pathology and Tumor Biology, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

[2] Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA

Keywords SETBP1 · Myelodysplastic/myeloproliferative neoplasms · Secondary acute myeloid leukemia · Poor prognosis · Self-renewal potential

Introduction

Current advances in the development of sequencing technology enable us to identify almost all the major driver mutations in myeloid neoplasms [1–4]. In myelodysplasia including myelodysplastic syndromes (MDS) and myelodysplastic/myeloproliferative neoplasms (MDS/MPN), whole exome sequencing in about 200 cases completely revealed significant driver mutations whose frequencies were higher than 0.5% (Fig. 1) [4]. Along with these, multiple loss-of-function mutations [5–12], and recurrent activated/gain-of-function mutations [13–16] are likely to be the promising candidates for future development of novel therapy by inhibitory compounds (Fig. 2). In addition to functional significance, recent sequencing technology also uncovered clonal dynamics based on detailed information of mutated clone size. In particular, multiple samples tested at serial time points in each case can conclude acquisition timing of each mutation, clonal architecture, and intratumor heterogeneity in myelodysplasia [4, 17–20].

Using these methodologies combined with mechanistic and clinical analyses, new somatic mutations of *SET-binding protein 1* (*SETBP1*) were discovered in MDS/MPN and secondary acute myeloid leukemia (sAML) (Fig. 3). Many follow-up studies have been conducted by various groups to clarify and detail the pathogenesis associated with *SETBP1* mutations. This review article comprehensively describes genetics, biological, and clinical implication of *SETBP1* mutations, including most recent research possible owing to detailed new genetic methodology and following

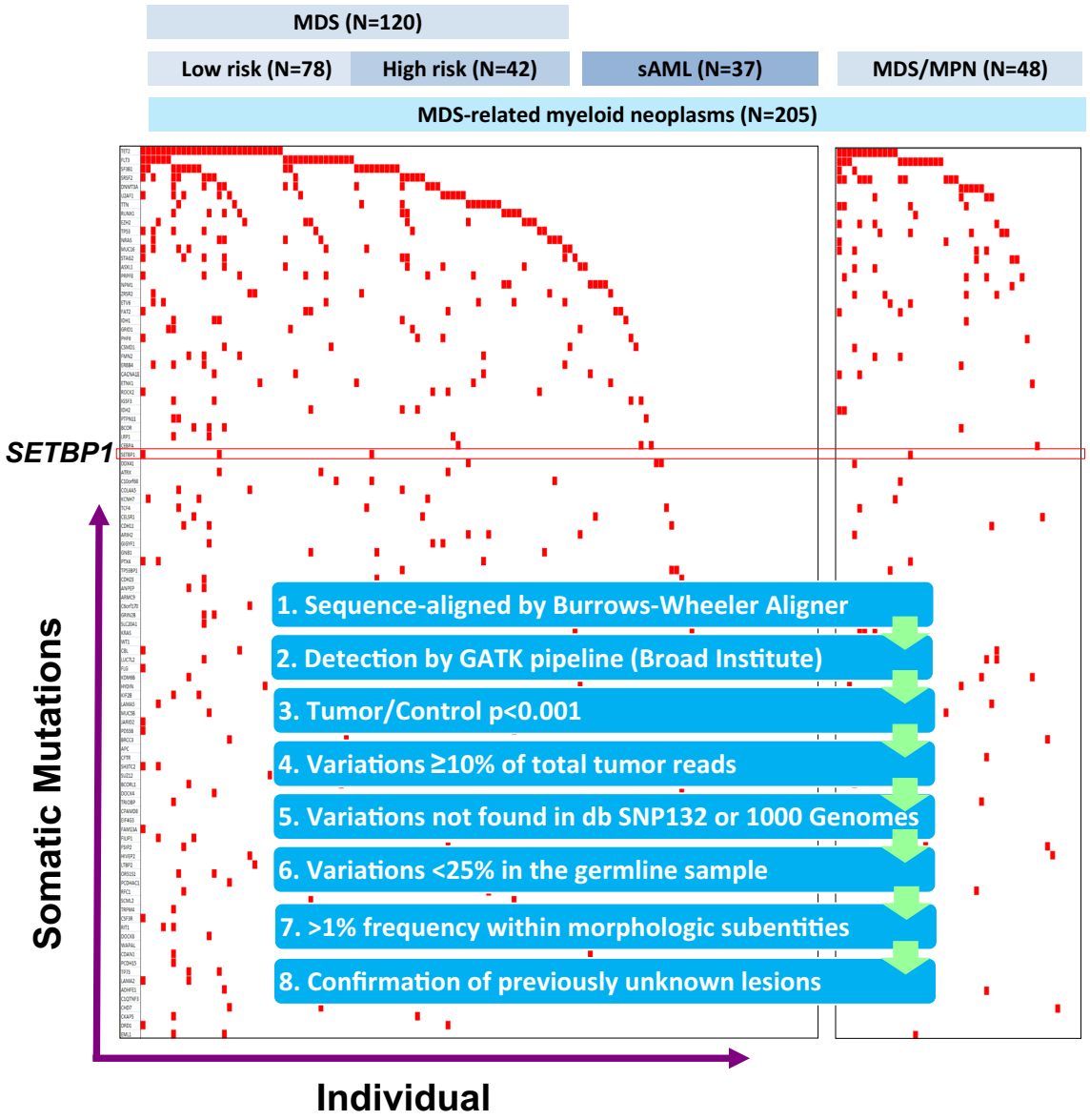

Fig. 1 Whole exome sequencing in myelodysplasia. Mutational screening by whole exome sequencing in MDS-related myeloid neoplasms. Recurrent *SETBP1* mutations are highlighted by a *red rectangle*. In-hose pipeline applied to mutation call is shown by sequential *sky-blue flowcharts*

functional investigation. Overall, of note is that recurrent *SETBP1* mutations are frequently identified in distinct phenotype of myeloid neoplasms, resulting in its obvious activation of leukemogenesis.

Activation of wild-type *SETBP1* in myeloid neoplasms

In 2001, SETBP1 was reported as a new protein binding to SET which has an inhibitory activity for protein phosphatase 2A (PP2A) [21]. Then, *SETBP1* was also found to be essential for granulocytic hematopoiesis together with *EVI1* (*MECOM*) [22]. Before discovery of somatic mutations as below, activation of wild-type *SETBP1* was already shown in various hematological neoplasms. For example, *SETBP1* is a fusion partner gene in acute T cell lymphoblastic and myeloid leukemias and primary myelofibrosis (PMF) [23–25]. It is also a downstream target gene associated with *MECOM*-mediated leukemia [26]. Clinically, in cases with AML, *SETBP1* overexpression was a poor prognostic factor [24]. In addition, *SETBP1* locus (18q12.3) was amplified in blast phase of chronic myeloid leukemia [27]. From such multiple evidence,

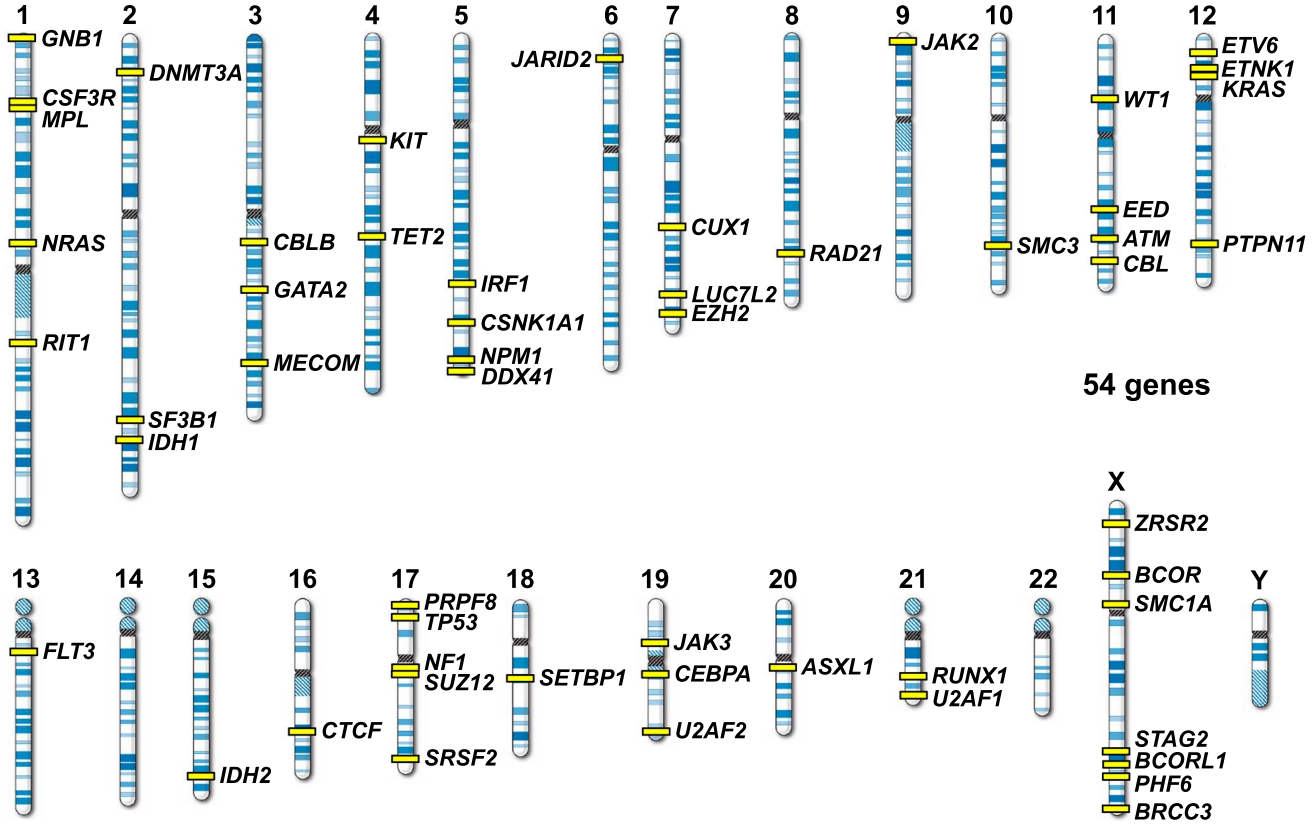

Fig. 2 Ideogram of major driver mutations validated by genetic and functional studies. So far, at least mutations of 54 genes were reported to be pathogenic in myelodysplasia

SETBP1 was most likely to be a major oncogene in myeloid neoplasms.

Discovery of somatic *SETBP1* mutations

In December 2012, three independent studies of somatic *SETBP1* mutations were presented in annual meeting of American Society of Hematology. Piazza et al. reported somatic *SETBP1* mutations were frequently identified in atypical chronic myeloid leukemia (aCML) by whole exome sequencing [28]. In this study, 24% of cases with aCML were positive for mutations of this gene. Another study group from Nagoya University Department of Pediatrics (Professor Kojima group) showed that the same recurrent mutations of *SETBP1* were identified in juvenile myelomonocytic leukemia (JMML) [29]. Last of the independent studies carried out in 727 cases with various myeloid malignancies by international collaboration between Cleveland Clinic and The University of Tokyo demonstrated that 7.2% of cases ($n = 52$) were positive for the recurrent *SETBP1* mutations at Asp868, Ser869, Gly870, Ile871, and Asp880 (Fig. 3). In this large cohort, somatic *SETBP1* mutations were most frequent in chronic myelomonocytic leukemia (CMML) and sAML [30]. According to no loss of heterozygosity detected at *SETBP1* locus by single nucleotide polymorphism array analysis, these mutations were proved to be heterozygous. Allele-specific PCR of cDNA from mutant cases, the mRNA expression of mutated alleles was elevated compared to intact ones [30]. Since *SETBP1* was supposed to be an oncogene in myeloid neoplasms, it only seems plausible to hypothesize that these *SETBP1* mutations activate leukemogenic SETBP1 function. This hypothesis was proved by multiple functional studies performed using in vivo model as discussed below. Surprisingly, most of these recurrent somatic mutations are located at the same positions of germline mutations already reported in Schinzel–Giedion syndrome (Fig. 3a) [31]. This congenital disease is characterized by severe mental retardation and short-term survival [32, 33]. Since no inherited case was reported and, therefore, it is caused by de novo germline mutations [31, 34–37], this syndrome is not likely to be related to typical age-related myeloid neoplasms such as MDS/MPN and sAML. No cases with somatic *SETBP1* mutations harboring symptoms of Schinzel–Giedion syndrome have been reported till date.

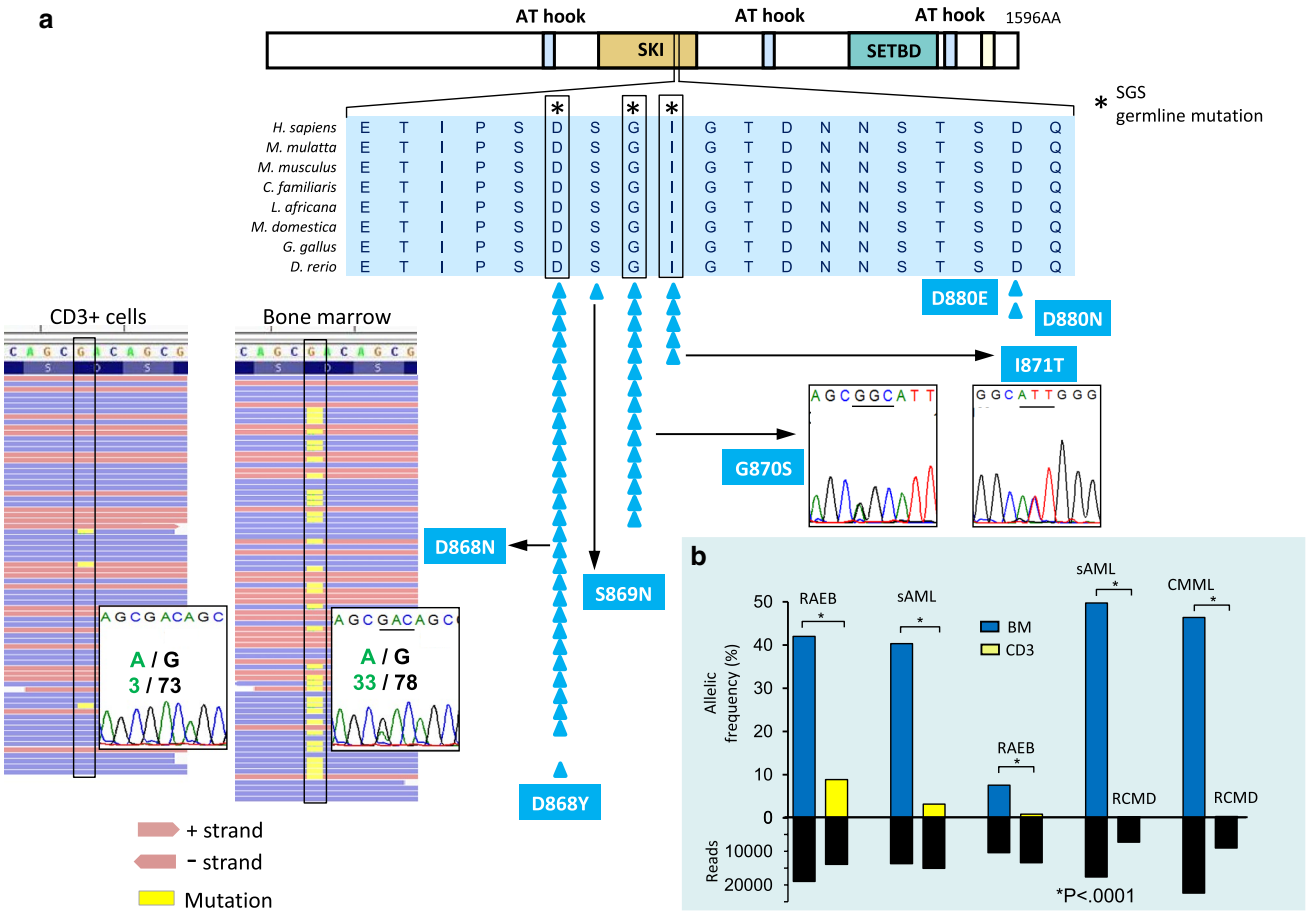

Fig. 3 Somatic and germline mutations of *SETBP1*. **a** Somatic mutations of *SETBP1* were discovered in cases with myelodysplasia. Location of the somatic mutations was identical to germline mutations of *SETBP1* (*asterisk*), causing congenital Schinzel–Giedion syndrome (SGS). **b** Targeted-deep sequencing confirmed somatic status of the mutations in myeloid neoplasms

Disease phenotype with *SETBP1* mutations

After these initial reports, many follow-up confirmatory studies of *SETBP1* mutations were published in whole myeloid neoplasms. In aCML, *SETBP1* mutations are most frequently identified (25–33%) [38], and in the other MDS/MPN, including JMML (8%) [29] and CMML (up to 15%) [30, 39, 40] mutations of this gene are also predominantly positive. In addition, *SETBP1* mutations were also significantly more prevalent in the cases with sAML (17%) ($P < 0.001$) (Fig. 4a). Similarly, somatic *SETBP1* mutations were secondary events following somatic or germline RAS-pathway mutations in JMML of a Japanese cohort [29], as well as in an Italian JMML cohort [41]. This also indicates that *SETBP1* mutations do play a significant role rather in secondary leukemic evolution than in initial disease presentation of JMML. In analogy, secondary aCML evolution from acute myelomonocytic leukemia resulted from acquisition of *SETBP1* mutation [42]. In 2 out of 25 cases with blast phase of CML, *SETBP1* mutations were identified as secondary events [30]. By targeted sequencing in case series of therapy-related MDS, *SETBP1* mutation was also identified [43, 44]. These findings suggest that *SETBP1* mutations play a main role in secondary leukemogenesis as later subclonal events, presumably required for antecedent disease initiation by other primary genetic defects [45]. Sanger sequencing could not sufficiently detect *SETBP1* mutations in CMML [39, 46] or therapy-related myeloid neoplasms [43], hence is not likely to be recommended to detect typical small clones with the mutation. In cases with another MDS/MPN subtype, refractory anemia with ring sideroblasts and thrombocytosis (RARS-T), *SETBP1* mutation was also frequently observed (13%) [47].

While classical myeloproliferative neoplasms (MPN), including polycythemia vera (PV), essential thrombocythemia (ET), and PMF are relatively less associated with *SETBP1* mutations [48]. Another MPN subtype, chronic neutrophilic leukemia (CNL), which is closely

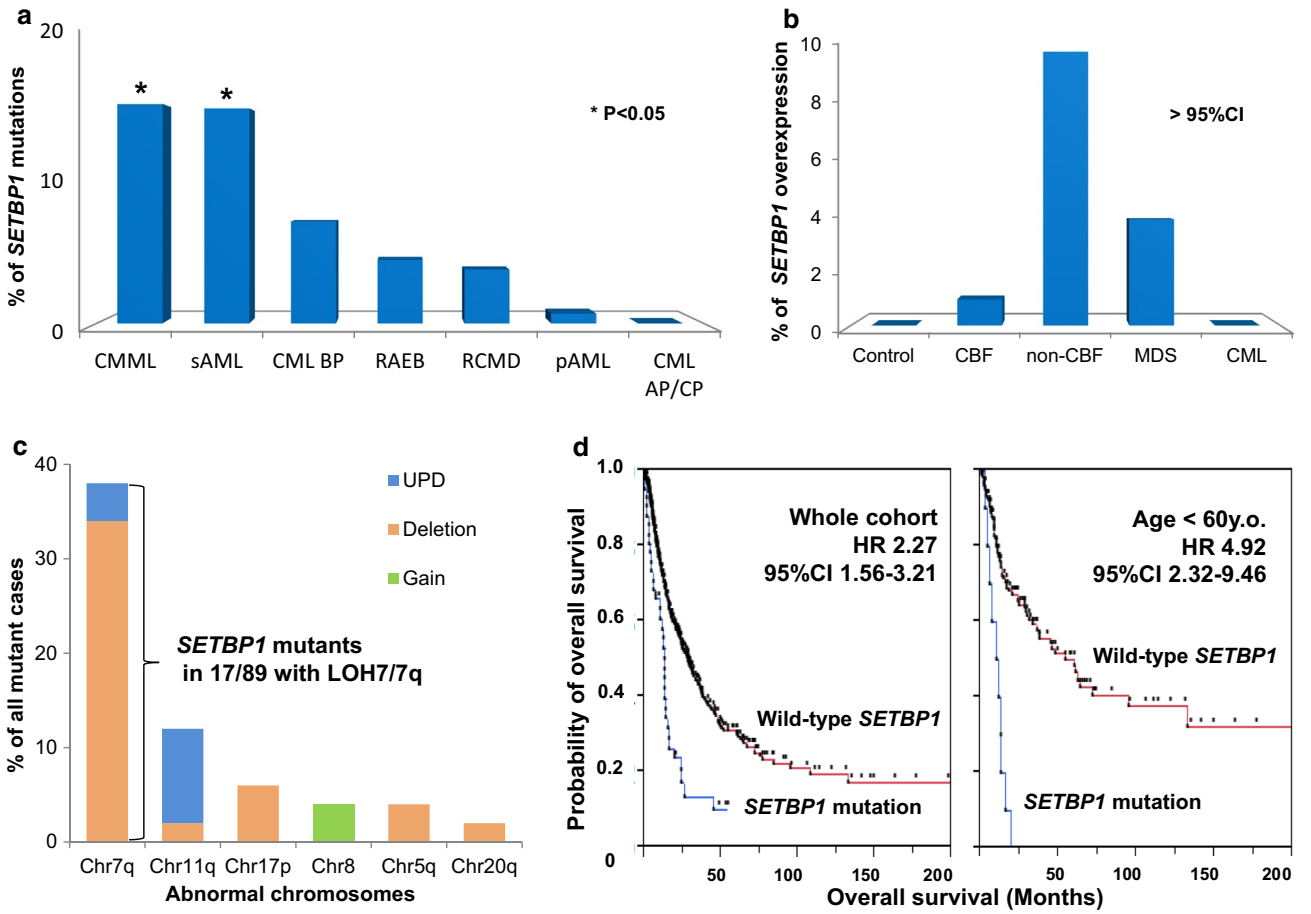

Fig. 4 Clinical phenotype resultant from *SETBP1* mutations. High frequency of *SETBP1* mutations (**a**) and overexpression (**b**) in CMML and secondary AML (non-CBF leukemia). **c** *SETBP1* mutations are associated with loss of heterozygosity in chromosome 7/7q. **d** *SETBP1* mutations are significantly associated with shorter overall survival

related to *CSF3R* mutations [49], is also frequently affected by *SETBP1* mutations (14–56%) [50–52]. *SETBP1* mutations in CNL cases are usually subclonal events following initial *CSF3R* mutations with a reported exceptional case [53]. Interestingly, *SETBP1* mutations are more prevalent in cases with *CSF3R* mutations than in those with wild-type *CSF3R* [50]. In fact, simultaneous decrease of allele frequencies for both *CSF3R* and *SETBP1* mutations was found after treatment for a CNL case with Ruxolitinib [54].

Contrary to MDS/MPN or sAML, cases with de novo AML were less affected by *SETBP1* mutations (frequency of mutations was <1%) ($P < 0.001$) (Fig. 4b). Similarly, *SETBP1* mutation was not identified in childhood AML cohort [55, 56]. Overall, *SETBP1* mutations are tissue-specific events acquired by myeloid lineages, and most likely to provide the cells with myeloproliferative potential.

Coordination with additional genetic events

For coordinating leukemogenesis, several genetic events were reported to be frequently detected in *SETBP1*-mutated cases. As described above, *SETBP1* mutations are frequently mutated in CMML, aCML, and JMML, where mutations of *ASXL1*, *SRSF2*, and *CBL* are also prevalent (Fig. 5a). Therefore, mutations in *ASXL1*, *SRSF2*, *CBL*, and *SETBP1* are frequently correlated with each other to present the MDS/MPN phenotypes [28, 30, 48, 57–59]. Among these, a synergistic effect of concomitant *SETBP1* and *ASXL1* mutations was functionally confirmed by the experiments using in vivo model, which revealed that *ASXL1* defects initiate differentiation block and that *SETBP1* activation adds proliferative potential [60]. In another context, *SETBP1* mutations are also acquired by the cells which already harbor the condition of clonal expansion due to initial genetic events,

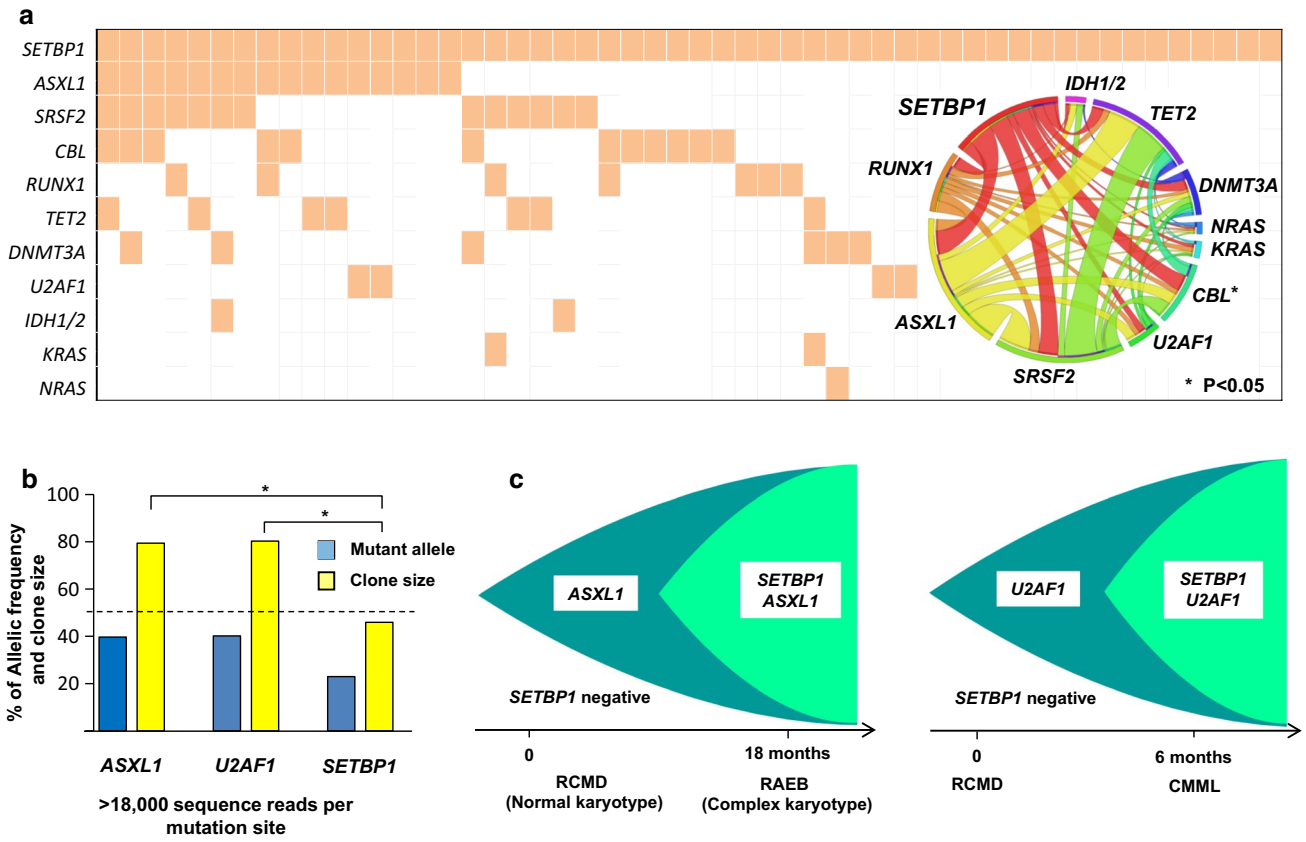

Fig. 5 Accessory molecular events associated with *SETBP1* mutations. **a** *SETBP1* mutations coincide with various mutations of other driver genes. **b** Subclonal *SETBP1* mutation was acquired by cells with a *U2AF1*- and *ASXL1*-mutated ancestral clone. **c** Serial sequencing confirmed secondary nature of *SETBP1* mutations

for example MDS (Fig. 5b, c) [45]. Consequently, typical primary genetic events of MDS including *U2AF1*, and *RUNX1* were also associated with *SETBP1* mutations [28, 30]. However, common primary mutations of *TET2* and secondary *SETBP1* mutations tended to be mutually exclusive [58].

In addition to these somatic mutations, particular chromosomal alterations are associated with *SETBP1* mutations. -7/del(7q) are remarkably coincident with *SETBP1* mutations, which is confirmed by multiple independent studies (Fig. 4c) [30, 45, 57, 61]. Isochromosome 17q (i(17q)) is also associated with *SETBP1* mutations (54%) [45, 48, 57, 62]. Especially, *TP53* and *SETBP1* mutations were completely exclusive in cases with i(17q), suggesting that these two major prognostic events are independently involved in poor outcome in myeloid neoplasms [63]. Such concomitant poor prognostic chromosomal lesions are compatible with worse prognosis in cases with *SETBP1* mutations as mentioned below.

Clinical implications and prognostic impacts

Clinically, *SETBP1* mutations have remarkable impacts on patients' characteristics and outcome. In a large adult cohort, *SETBP1* mutations were significantly more frequent in older cases (>60 years old) ($P = 0.01$), cases with -7/del(7q) ($P = 0.01$), sAML ($P < 0.001$), and CMML ($P = 0.002$), most of which are well-known poor prognostic factors. Clustering analysis of gene-expression profiles revealed that cases with *SETBP1* mutations and those with high expression of wild-type *SETBP1* belonged to the closely clustered groups characterized by high expression of putatively oncogenic *MECOM*, *TCF4*, *BCL11B*, and *DNTT* genes [30], suggesting poor outcome in mutant cases. *MECOM* overexpression is recapitulated in a CNL case with *SETBP1* mutation [64]. In fact, *SETBP1* mutation is really a poor prognostic factor. In whole cohort of adult cases, overall survival is significantly shorter in cases with the mutations (HR = 2.3, 95% CI = 1.6–3.2, $P < 0.001$), and this tendency is more evident in younger cases (HR = 4.9,

95% CI = 2.3–5.4, $P < 0.001$) (Fig. 4d) [30]. These findings were reproduced in many other studies [28, 45, 57, 58, 65, 66]. By multivariable analysis including clinical factors and other genetic events as variables, *SETBP1* mutation was an independent factor for overall survival (HR = 2.9, 95% CI = 1.7–4.8, $P < 0.001$) as well as male sex, higher age (>60 years old), and *ASXL1*, *CBL*, and *DNMT3A* mutations. While it was a significant worse prognostic factor by univariate analysis, -7/del(7q) abnormality was qualified after multivariable analysis because of confounding *SETBP1* mutation. By following subgroup multivariable analysis in the cohort of MDS and CMML (with white blood cell count less than 12,000/μl) to which international prognostic scoring system (IPSS) score is applicable, *SETBP1* mutation was an independent prognostic factor (HR = 1.8, 95% CI = 1.0–3.1, $P = 0.04$) as well as higher IPSS score. To further clarify a clinical effect of concomitant mutations, most significant genetic combination of *CBL* and *SETBP1* mutations was assessed. Cases with both mutations showed significantly shorter OS than those without either of mutations [30]. Finally, in cases with JMML, secondary *SETBP1* mutation was also significantly associated with poor prognosis (shorter transplantation-free survival) [29, 67]. Collectively, *SETBP1* mutations are significantly associated with poor prognosis in any disease subset.

Molecular biology

Discovery of somatic *SETBP1* mutations in myeloid neoplasms prompted multiple groups to clarify leukemogenic mechanisms induced by mutated SETBP1 (Fig. 6). As described above, mutant alleles are highly expressed compared to wild-type alleles [30]. In addition, protein degradation is attenuated through the mutations located at SETBP1 SKI homology region resulting in increase of protein stability [28, 30]. Therefore, at least, higher amount of mutant SETBP1 protein in cases with *SETBP1* mutations are supposed to be a major consequence similar to overexpression of wild-type protein as a dose effect (Fig. 4b) [30]. Moreover, by comparison between the same amount of wild-type and mutant SETBP1 proteins, more proliferative potential was observed in the mutant experiments [30]. Mutated proteins also bind more efficiently to DNA at promotor sites of target genes [68, 69]. Altogether, *SETBP1* mutations were supposed to have both quantitatively and qualitatively activating effects on SETBP1 functions.

SETBP1 protein is involved in various other leukemogenic functions which were previously confirmed by various study groups. Out of these, its activated function as a transcription factor induces overexpression of *HOXA9*

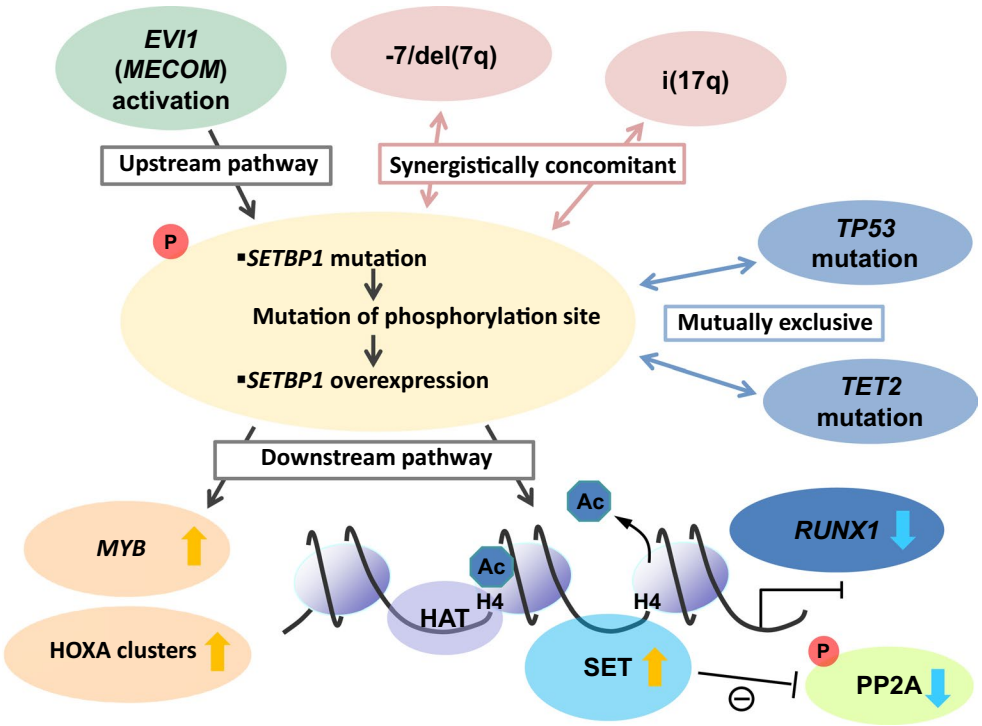

Fig. 6 Functional implication of activated SETBP1. Various genetic alterations were supposed to contribute to *SETBP1*-mediated leukemogenesis. Up- and downstream pathways, concomitant chromosomal defects, and exclusive mutations are distinctly observed in myeloid neoplasms with *SETBP1* mutations

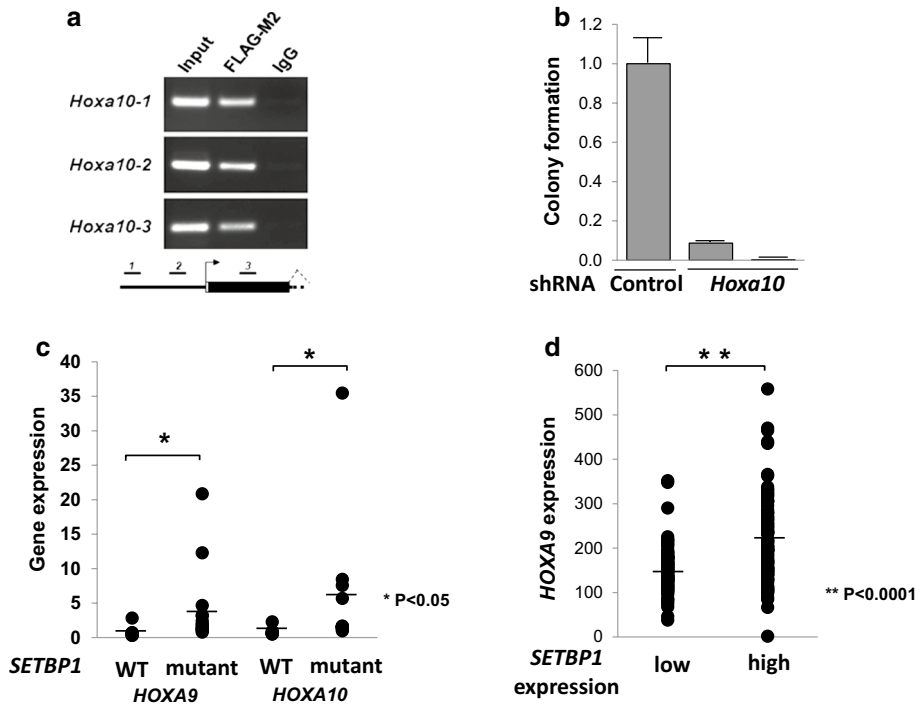

Fig. 7 *SETBP1* activation causes *HOXA9/10* induction. **a** Setbp1 binds to *Hoxa10* promoter (ChIP assay). **b** *Hoxa10* knockdown suppresses colony formation of cells immortalized by *Setbp1* transduction. **c** *HOXA9* and *HOXA10* are overexpressed in *SETBP1* mutants. **d** *HOXA9* and *SETBP1* expressions correlate in patients with myeloid neoplasms

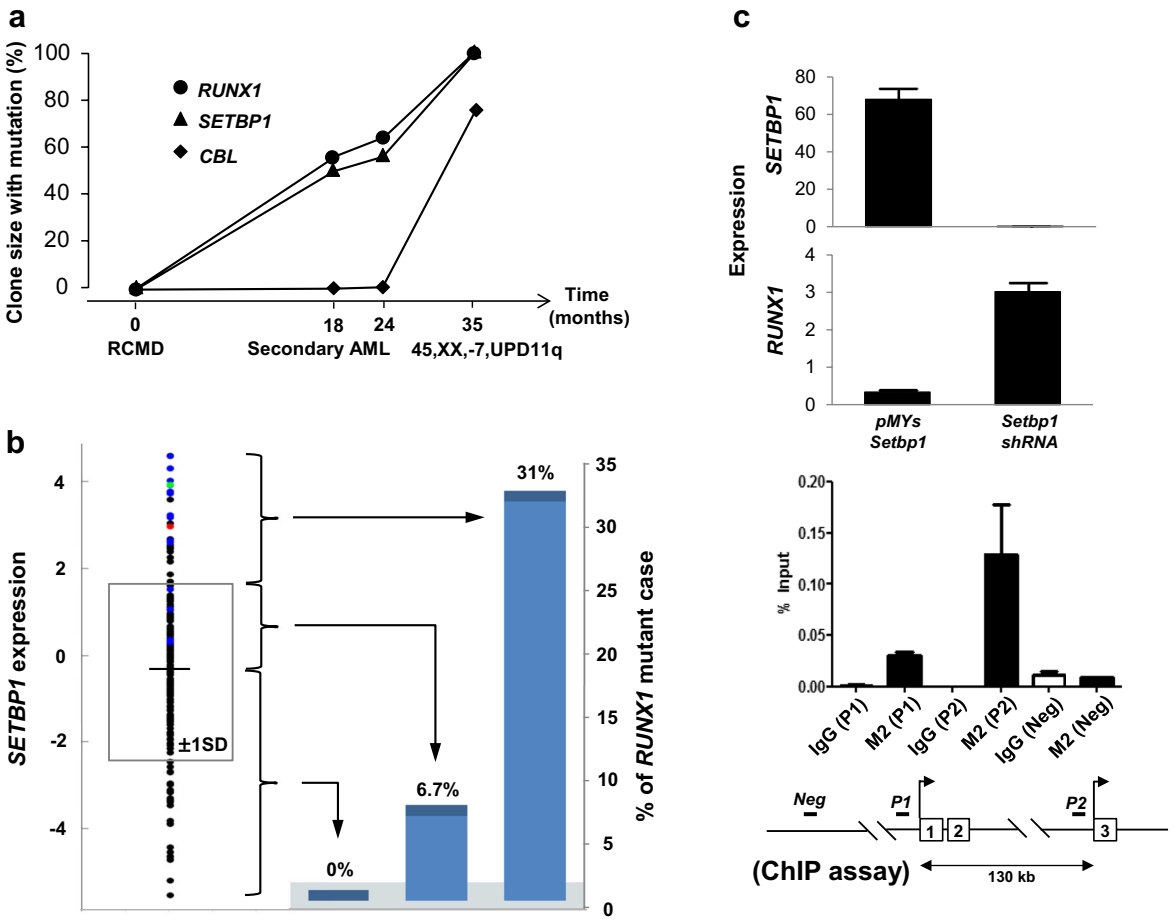

Fig. 8 Synergism between *SETBP1* and *RUNX1*. **a** Concomitant acquisition of *SETBP1* and *RUNX1* mutations. **b** *RUNX1* mutations are associated with *SETBP1* overexpression. **c** Inverse correlation between wild-type *SETBP1* and *RUNX1*

and *HOXA10*, resulting in upregulation of self-renewal potential in myeloid neoplasms (Fig. 7) [30, 70]. Another *SETBP1*-mediated oncogenic potential is induced by down-regulation of tumor suppressor *RUNX1*, whose expression is attenuated through activation of SETBP1 binding more efficiently to promotor sites of *RUNX1* (Fig. 8) [68]. An additional target of activated SETBP1 is a well-known oncogene *MYB*. Mutant forms of SETBP1 bind to *MYB* promotor sites and cause overexpression of this gene [69]. For these *HOXA9/10*, *RUNX1*, and *MYB* studies, transplantation experiments in mouse models were performed to confirm biological significance of mutated *SETBP1* in myeloid leukemogenesis.

SET-PP2A pathway is in the downstream of classical SETBP1 activation. In hematopoietic progenitor cells immortalized by forced expression of mutant SETBP1, phosphorylation of PP2A was accelerated (Fig. 6) [28, 30]. Mouse transplantation model of mutated SETBP1 also showed PP2A inhibition and *HOXA9/10* activation [60]. These findings suggest that phosphorylated (loss-of-function) PP2A could be a therapeutic target of PP2A activators.

A most recent study has proposed very surprising but interesting concepts by comparing somatic and germline *SETBP1* mutations [71]. They described that consequence of *SETBP1* mutations are different among substitutions in SETBP1 residues. Mutations at I871 resulted in a weak increase in protein levels and are significantly more frequent in Schinzel–Giedion syndrome (germline) than in myeloid neoplasms (somatic). On the other hand, substitutions in residue D868 led to the largest increase in protein levels. Cases with germline mutations affecting D868 have enhanced cell proliferation in vitro and higher incidence of cancer compared to patients with other germline *SETBP1* mutations [71]. While these updated functional studies are helpful to understand biological mechanisms of leukemogenesis, therapeutic strategy to this distinct molecular target, *SETBP1* mutation, is not established yet and requires further investigation.

Summary

Approximately 13 years after cloning *SETBP1*, this gene is now commonly recognized as a driver oncogene almost exclusively in myeloid neoplasms. Somatic mutations in myeloid neoplasms are identical to germline mutations in Schinzel–Giedion syndrome. Activating *SETBP1* mutations is a poor prognostic factor and frequently acquired as secondary event. Functionally, these mutations are involved in various leukemogenic mechanisms through phosphorylated PP2A, HOXA clusters, *RUNX1*, *MYB*, other associated mutations, and chromosomal abnormalities. Activation of SETBP1 results in a distinct disease entity and inhibition of this protein as a molecular target should be an attractive therapeutic strategy.

Compliance with ethical standards

Conflict of interest No conflict of interest to disclose.

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