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Recommended Citation

Linder, K., Iragavarapu, C., & Liu, D. (2017). SETBP1 Mutations as a Biomarker for Myelodysplasia /Myeloproliferative Neoplasm Overlap Syndrome. *Biomarker Research*, 5, 33. [https://doi.org/10.1186/s40364-017-0113-8](https://doi.org/10.1186/s40364-017-0113-8)

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SETBP1 mutations as a biomarker for myelodysplasia/myeloproliferative neoplasm overlap syndrome

Katherine Linder, Chaitanya Iragavarapu and Delong Liu*

Abstract
Myelodysplasia (MDS) /myeloproliferative neoplasm (MPN) overlap syndrome has been described since the 2001 WHO classification as disorders that have both proliferative and dysplastic changes simultaneously. Specific disorders include chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), BCR-ABL negative atypical chronic myeloid leukemia (aCML) and unclassifiable MDS/MPN (MPN/MDS-U). Recurrent gene mutations in these conditions have been described. Among them, SETBP1 mutations have been identified in up to 32% of aCML, 24% of JMML, 18% of CMML and 10% of MDS/MPN-U patients. The mutation hotspot lies in the amino acid residues 858–871 in the SETBP1 protein. SETBP1 mutations in MDS/MPN overlap syndrome is associated with accelerated transformation to leukemia and poor prognosis. In this review, we summarized the latest data on the role of SETBP1 mutations in the overlap syndrome. SETBP1 mutations may serve as a biomarker for the diagnosis and poor prognosis of the overlap syndrome.

Keywords: SETBP1, Myelodysplasia, Myeloproliferative syndrome

Background
Myelodysplasia (MDS) /myeloproliferative neoplasm (MPN) overlap syndrome (MMOS) has been described as disorders that have both proliferative and dysplastic changes simultaneously [1–5]. Specific disorders include chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), BCR-ABL negative atypical chronic myeloid leukemia (aCML) and unclassifiable MDS/MPN (MPN/MDS-U). The overlap category of the disorders was first defined in the 2001 WHO classification of myeloid neoplasms [6] with the 2016 revision adding a fifth disorder – MDS/MPN with ringed sideroblasts and thrombocytosis (MDS/MPN-RS-T) [7]. Among MMOS, MDS/MPN-U represents about 2% of patients and usually carries a very poor prognosis with median survival of 21 months [8]. The definition of MDS/MPN-U has been updated in the 2008 version of WHO classifications [1]. A recent retrospective study validated the MDS-IPSS scoring system in MDS/MPN-U with low risk patients and delineated the natural history of this elusive malignancy [9].

There are frequent mutations in MDS, MPN, and acute myeloid leukemia (AML) [10–17]. Mutations in several pathways have been found to be useful biomarkers for diagnosis and some are druggable targets [18–22]. Ruxolitinib, enasidenib, midostaurin and several other small molecules are targeted agents in clinical applications and/or development for myeloid neoplasms [23–28]. However, no specific genetic mutations have been found for the MDS/MPN overlap syndrome. This review focused on the SETBP1 gene mutations and summarized the clinical correlations of the common mutations in MMOS and secondary AML (sAML).

**SETBP1 mutations**

SETBP1 was discovered in 2001 [29]. It is localized in chromosome 18q21.1. The cDNA encodes a protein with 1542 amino-acid residues. SETBP1 is a 170-kDa nuclear protein that binds to SET protein, a protein previously noted to be associated with acute undifferentiated leukemia [30].
Through whole exome sequencing of DNA from 727 patients with various myeloid malignancies, recurrent mutations of SETBP1 were found in 52 cases (7.2%) [31]. Among them, SETBP1 mutations have been identified in up to 32% of aCML, 24% of JMML, 18% of CMML and 10% of MDS/MPN-U patients. Somatic mutations of SETBP1 were associated with −7/del(7q) and poor prognosis, possibly due to its gain-of-function which promotes myeloid leukemic transformation in patients with myelodysplastic syndromes (MDS) and CMML. These data were consistent with those from other reports [32–35].

**SETBP1 in AML transformation**

The first clear link between SETBP1 and myeloid neoplasia was demonstrated in a patient with transformed AML [36]. The karyotyping studies performed at progression from MDS to AML in this patient revealed a t(12;18)(p13q21) translocation leading to fusion between ETV6 & SETBP1. SETBP1 protects SET from protease cleavage. Overexpression of SETBP1 was shown to increase the level of SET protein, leading to increase in the formation of the SETBP1-SET-PP2A complex [36]. SETBP1 overexpression has been shown to confer growth advantage in hematopoietic progenitor cells, therefore promoting leukemogenic transformation. In a separate study of 386 patients with MDS, SETBP1 mutation was found to enhance ASXL1 mutation-induced differentiation block, and played a role as critical drivers in the leukemic transformation from MDS to AML [37].

**SETBP1 mutations in MMOS**

**SETBP1 in CMML**

One study using massive parallel sequencing investigated mutational hotspots of SETBP1 in 658 patients with MDS, CMML and sAML [38]. Among the 195 CMML patients included, 12 (6.2%) were positive for point mutations in SETBP1, a rate higher than those in MDS (2.2%) and sAML (1.7%). The mutation hotspot affected amino acid residues 858–871 in the SETBP1 protein. Those CMML patients with SETBP1 mutations had higher baseline WBC counts. SETBP1 mutations were more commonly associated with ASXL1 mutations and less commonly associated with TET2 mutations. After a median follow up of 31.1 months, SETBP1 mutated patients were noted to have worse OS [mOS: 21 months vs. 46.4 months; HR-2.23 (95% CI 1.07-4.26, p=0.028)]. Interestingly, when different CD34 positive cell fractions were genotyped by single-cell genome sequencing, all 4 potential driver mutations (ASXL1, SETBP1, ZRSR2 & SRSF2) occurred early in the hematopoietic stem cell populations. However, SETBP1 mutations were noted to occur after other driver mutations, and the mutant SETBP1 clone became predominant with progression to secondary AML [38]. The prevalence of SETBP1 mutations and their prognostic role in CMML were corroborated in other reports [39–44] (Table 1).

An independent prognostic scoring system for CMML, CPSS-Mol, was developed by incorporating clinical features and status of 38 commonly mutated genes in CMML [45]. The learning cohort consisted of 214 CMML patients, with 19 patients (8.9%) possessing SETBP1 mutations. Consistent with previous reports, SETBP1 mutations were associated with a higher WBC count (p < 0.001) and worse OS (HR for univariate: 2.49, p = 0.02; HR for multivariate: 2, p = 0.04). This scoring system was then validated in a cohort of 260 patients (24 patients possessed SETBP1 mutations; 9.2%). Based on the CPSS-Mol scores, the high-risk group had an overall survival of 17 months as opposed to mOS not yet reached in the low risk group (p < 0.001). This new scoring system may be useful in assisting clinical decision making and future clinical trials.

**SETBP1 in juvenile myelomonocytic leukemia**

SETBP1 mutation has also been reported in 4.8–7.2% of the patients with JMML [46, 47]. Most of the SETBP1 mutations co-existed with RAS pathway mutations with a lower allele burden, suggesting a secondary role in leukemogenesis [46]. Interestingly, this report also demonstrated an increasing allele burden with each round of intensive chemotherapy, suggestive of association of SETBP1 mutation with resistance to cytotoxic chemotherapy. Higher mutation rate was reported in additional studies [48, 49]. All these studies again confirmed poor prognosis in patients with SETBP1 mutations (Table 2).

**SETBP1 in atypical CML**

acML is one of the heterogeneous neoplasms in the group of myelodysplastic/ myeloproliferative (MDS/MPN) overlap syndrome. Unlike CML, there is no diagnostic hallmark identified in acML [50, 51]. Due to the

| Reference | Number of Patients | Mutation Prevalence | Impact on Survival |
|-----------|--------------------|--------------------|-------------------|
| [38] 195  | 12 (6.2%) | Yes (p=0.028) |
| [39] 179  | 8 (4.5%)  | Yes (p = 0.01)  |
| [32] 294  | 21 (7.1%) | No (p=0.798) |
| [31] 152  | 22 (14.5%) | Yes (p-NR for CMML cohort) |
| [33] 466  | 21 (5%)   | No (p=0.07)  |
| [40] 145  | 26 (18%)  | No (p-NR)   |
| [45] 214 – Learning Validation | 19 (8.9%) – Learning Validation | Yes (p=0.04) |
| [43] 1364 | NR       | Yes (p < 0.001) |

NR Not reported; * Meta-analysis
poor understanding of the molecular pathogenesis of this disease, diagnosis has remained elusive and the prognosis is far worse than that of CML (median survival of 37 months after diagnosis) [52]. SETBP1 mutations were reported in 17/70 aCML patients (24%) using high throughput sequencing [34]. SETBP1 mutation was associated with worsened survival (22 months vs. 77 months, HR for death = 2.27, p = 0.01) and higher WBC counts (81 × 10^3 vs. 38.5 × 10^3 /µL, p = 0.008). In a separate study that included 60 aCML patients [32], 19/60 (32%) patients were noted to have SETBP1 mutations. SETBP1 appears to occur with significant frequency in aCML with negative impact on prognosis. SETBP1 mutations may be a new biomarker for aCML diagnosis and prognosis (Table 3).

**SETBP1 in MDS/MPN-U**

In a large study of 1130 patients with myeloid neoplasms, SETBP1 mutations were found in 20/240 (9.3%) MDS/MPN-U patients [32]. SETBP1 mutated (mSETBP1) patients had significantly higher WBC counts and lower platelet counts and hemoglobin levels than those patients with wild-type SETBP1. Dysplastic morphology was more common in mSETBP1 than those patients with wide-type SETBP1. Dysplastic morphology was associated with worsened survival (22 months vs. 77 months, HR for death = 2.27, p = 0.01) and higher WBC counts (81 × 10^3 vs. 38.5 × 10^3 /µL, p = 0.008). In a separate study that included 60 aCML patients [32], 19/60 (32%) patients were noted to have SETBP1 mutations. SETBP1 appears to occur with significant frequency in aCML with negative impact on prognosis. SETBP1 mutations may be a new biomarker for aCML diagnosis and prognosis (Table 3).

**Table 2** SETBP1 mutations in juvenile myelomonocytic leukemia

| Reference | Number of Patients | Mutation Prevalence | Impact on Survival |
|-----------|--------------------|---------------------|--------------------|
| [46]      | 92                 | 7 (7.6%)            | Yes* (p-NR)        |
| [47]      | 42                 | 2 (4.8%)            | NR                 |
| [48]      | 66                 | 23 (24.8%)          | No (p=0.258 – Univariate) Yes (p=0.026 – Multivariate) |
| [49]      | 70                 | 7 (10%)             | Yes (p=0.03)       |

NR Not reported; * Survival analysis was done in patients harboring SETBP1 or JAK3 mutations compared to patients without either mutation.

**Conclusion**

SETBP1 mutations are relatively common in MDS/MPN overlap syndrome. The mutation hotspot lies in the amino acid residues 858–871 in the SETBP1 protein. SETBP1 overexpression is associated with accelerated transformation to leukemia and poor prognosis. SETBP1 mutations may serve as a biomarker for the diagnosis and poor prognosis for the overlap syndrome.

**Abbreviations**

aCML: atypical chronic myeloid leukemia; CMML: Chronic myelomonocytic leukemia; JMML: Juvenile myelomonocytic leukemia; MDS: Myelodysplasia; MPN: Myeloproliferative neoplasm; MPN/MPN-U: Unclassifiable MDS/MPN

**Acknowledgements**

None.

**Funding**

There was no funding involved in this study.

**Availability of data and materials**

All data are published in the study.

**Authors’ contributions**

DL designed the study. All authors drafted and approved the final manuscript.

**Ethics approval and consent to participate**

This is not applicable.

**Consent for publication**

This is not applicable.

**Competing interests**

The authors have no relevant competing interests.

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**Received**: 25 September 2017 **Accepted**: 28 November 2017

**Published online**: 06 December 2017

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**Table 3** SETBP1 mutations in atypical CML and unclassifiable MDS/MPN

| Reference | Number of Patients | Mutation Prevalence | Impact on Survival |
|-----------|--------------------|---------------------|--------------------|
| Atypical CML [34] | 70 | 17 (24.3%) | Yes (p=0.01) |
| [32] | 60 | 19 (32.1%) | No (p=0.191) |
| Unclassifiable MDS/MPN [34] | 30 | 3 (10%) | NR |
| [32] | 240 | 20 (9.3%) | NR |

NR Not reported.
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