Int J Hematol (2015) 102:523–527
DOI 10.1007/s12185-015-1738-8

Multistep tumorigenesis in peripheral T cell lymphoma

Mamiko Sakata-Yanagimoto

Received: 3 November 2014 / Revised: 11 January 2015 / Accepted: 15 January 2015 / Published online: 28 January 2015

Abstract Peripheral T cell lymphomas (PTCL) are classified as mature T cell neoplasms. However, several new findings support the notion that premalignant cells arise in the immature stage of hematopoietic differentiation, and subsequently evolve into full-blown T-lineage tumor cells. Acquisition of (*Ten-Eleven Translocation 2*) *TET2* mutations may be an important event for the establishment of premalignant cells. In PTCL harboring features of follicular helper T cells, tumor-specific G17V *RHOA* mutations co-occur with premalignant *TET2* mutations. The G17V (*ras homolog family member A*) *RHOA* mutations may play important roles in clonal evolution of premalignant cells into tumor cells. Indeed, multistep tumorigenesis is thought to be essential for pathogenesis of PTCL.

Keywords *TET2* · *RHOA* · AITL · PTCL

Introduction

Recent advances in sequencing technologies led to the discovery of gene mutations in epigenetic regulators, including *Ten-Eleven Translocation 2* (*TET2*) [1], *DNA methyltransferase 3A* (*DNMT3A*) [2], and *isocitrate dehydrogenase 1 /2* (*IDH1/2*) [3] in hematologic malignancies. These gene mutations were first identified in myeloid malignancies [1–3]. Subsequently, they were also found in lymphoid malignancies [4–6]. The mutation frequencies were especially high in peripheral T cell lymphoma (PTCL) with features of follicular helper T (Tfh) cells, that is angioimmunoblastic T cell lymphoma (AITL) and a subtype of peripheral T cell lymphoma, not otherwise specified (PTCL-NOS) [4–9].

An intriguing observation was that these mutations were detected in premalignant cells as well as tumor cells [4, 5, 8, 10–12]. Additionally, distinct mutations for each disease were found in the full-blown tumor cells [8, 10, 12]. That is, the stepwise accumulation of mutations might contribute to the development of tumor cells. This review will especially focus on the multistep tumorigenesis in PTCL from a genetic point of view.

Origins of *TET2* and *DNMT3A* mutations in PTCL

In some cases of PTCL, *TET2* and *DNMT3A* mutations were identified not only in the T-lineage tumor cells but also in non-tumor hematopoietic cells, including B and myeloid cells as well as myeloid progenitors [4, 5, 8]. These data suggest that the mutations occurred in hematopoietic stem/multipotent hematopoietic progenitors in PTCL [4, 5, 8]. In other words, the origins of PTCL are in the immature stage of hematopoietic differentiation although the full-blown tumor cells have characteristics of terminally differentiated T-lineage cells.

TET2 and *DNMT3A* mutations were also detected in apparently normal hematopoietic stem cells (HSCs) in the leukemic phase and those at the remission state in acute myeloid leukemia (AML) [10–12]. Occasionally, both lymphoid and myeloid malignancies occurred simultaneously or serially in a patient. It has been reported that identical *TET2* and/or *DNMT3A* mutations were detected in specimens of each disease in a case with B-cell lymphoma and AML [4], and cases with AITL and myelodysplastic syndrome [5]. These data further support the notion that *TET2* and *DNMT3A* mutations may reside in premalignant cells

M. Sakata-Yanagimoto (✉)
Department of Hematology, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan
e-mail: sakatama-tky@umin.net

in a wide variety of hematopoietic malignancies in addition to PTCL.

During the aging process, a part of the blood system, especially the myeloid compartment, is occasionally replaced by cells originating from a clone [13, 14]. The mechanisms of clonal hematopoiesis are yet to be elucidated. Darwinism may explain why it occurs; one cell obtains advantages for survival over other cells; then, selection pressure accelerates substitution in the blood system by its clones.

Remarkably, *TET2* mutations were observed in 5.6 % of normal elderly individuals with non-random X-chromosome inactivation [16]. *TET2*-mutant allele burden revealed close concordance with the degree of skewing determined by the X-inactivation patterns [15]. It means that *TET2*-mutant allele burden might reflect the clonal size of blood cells [15]. Subsequently, recurrent mutations in *DNMT3A* as well as other leukemia and/or lymphoma-associated genes were also reported in the blood cells of elderly individuals without hematologic malignancies [16–18]. The allele frequencies of the mutations were low in a substantial number of cases, possibly in the early stages of clonal expansion [16].

The functions of *TET2* and *DNMT3A* genes in the blood system have been extensively examined in knockout mouse studies. It has been reported by several groups that deletion of *TET2* in mice leads to an increase in the self-renewal capacity of hematopoietic stem cells (HSC) [4, 19–22]. Deletion of *DNMT3A* also enhances the self-renewal capacity, while it markedly inhibits cellular differentiation [23].

Given the results of knockout mouse experiments, functional impairment of *TET2* or *DNMT3A* by gene mutations would give superiority to the mutation-bearing cells over non-mutated cells, and contribute to the establishment of clonal hematopoiesis during aging. Finally, the mutation-bearing hematopoietic progenitors may evolve into preleukemic/prelymphoma stem cells (Fig. 1). In fact, the presence of somatic mutations in the blood was associated with significantly higher risk of hematologic malignancies [17, 18], while impact of these mutations on incidence of PTCL remains to be elucidated.

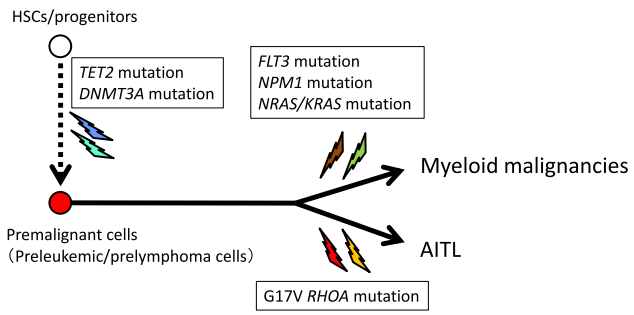

Fig. 1 Multistep tumorigenesis in PTCL. *TET2*- or *DNMT3A*-mutated hematopoietic progenitors evolve into preleukemic/prelymphoma stem cells. Both myeloid and lymphoid malignancies can emerge from the preleukemic/lymphoma cells. Subsequent genetic events determine the cell fate of preleukemic/prelymphoma cells

Clonal evolution of mutation-bearing prelymphoma cells

Both myeloid and lymphoid malignancies can emerge from *TET2*-or *DNMT3A*-mutated preleukemic/lymphoma stem cells (Fig. 1). So, what kinds of mechanisms are required for the development of each disease?

Gene mutations in myeloid malignancies have been extensively analyzed since the 1980s. First, mutations in *neuroblastoma RAS viral* (*v-ras*) *oncogene homolog* (*NRAS*) were discovered in myelodysplastic syndrome in 1987 [24]. Subsequently, mutations in *fms-related tyrosine kinase3* (*FLT3*) [25], *CCAAT/enhancer binding protein* (*C/EBP*)*, alpha* [26], and *nucleophosmin* (*NPM1*) [27] were identified in AML. To date, mutations have been identified in more than 100 genes [28–30], most of which are known to be essential in the differentiation and proliferation/apoptosis of myeloid cells.

In contrast, the mutational profiles of PTCL were not elucidated until very recently. By comprehensive gene-mutation analysis, we and others found novel recurrent mutations in *ras homolog family member A* (*RHOA)* in PTCL with features of Tfh cells: 53–71 % of AITL [8, 9, 31] and 62 % of AITL-like PTCL-NOS [8]. Most of the *RHOA* mutations found in PTCL were confined to c. 50G>T, resulting in conversion from glycine to valine at the 17th position of the RHOA protein (G17V RHOA) [8, 9, 31].

RHOA mutations were also reported in 8.5 % of Burkitt lymphoma, though the distribution of mutations was different from those in PTCL [32]. The *RHOA* mutations in Burkitt lymphoma were concentrated at c.14C>G, resulting in conversion from arginine to glutamine at the 5th position, while G17V *RHOA* mutations were not detected [32]. Also, G17V *RHOA* mutations were not detected in myeloid malignancies or other B-cell malignancies in our cohort [8].

Remarkably, the *RHOA*-mutated samples had the *TET2* mutations [8]. The coexistence of the *RHOA* and *TET2* mutations suggests that the crosstalk of these mutations might contribute to the pathogenesis of AITL.

As described, *TET2* mutations existed in the preleukemic/prelymphoma cells. The allele frequencies of the *RHOA* mutations were statistically lower than those of the *TET2* mutations in the samples with both mutations [8]. These data suggest that the G17V *RHOA* mutations occurred later than the *TET2* mutations. Furthermore, *RHOA* mutations were not detected in the non-tumor hematopoietic cells, whereas *TET2* mutations were

detected both in tumor cells and non-tumor hematopoietic cells [8].

From these pieces of genetic evidence, it seems likely that G17V *RHOA* mutations play a main role in the development of PTCL with features of Tfh cells. The G17V *RHOA* mutations in *TET2*-mutated prelymphoma cells may facilitate the selective differentiation of these cells into Tfh-like tumor cells (Fig. 1).

Functions of the G17V RHOA mutants

As described above, *RHOA* mutations might play an essential role in the multistep tumorigenesis of PTCL [8]. RHOA is a small GTPase, cycling between an active GTP-bound state and an inactive GDP-bound state [33]. The activation of RHOA is mediated by guanine exchange factors (GEFs) [33]. The G17V RHOA mutant cannot bind GTP and exhibits defective RHOA signaling in the cells [8, 9, 31]. The roles of the G17V RHOA mutant in AITL development have not been clarified. Inhibition of RHOA signaling by expressing C3 transferase, an inhibitor of RHO signaling under the lck promoter, was reported to provoke fatal T cell malignancies in mice [34].

Recently, frequent *RHOA* mutations were reported in diffuse-type gastric cancers [35–37]. The *RHOA* mutations in gastric cancers resulted in defective *RHOA* signaling in the cells [37], although the hotspot sites of *RHOA* mutations in gastric cancers were different from those in AITL [35–37]. Genetic alterations of *RHOA* might have functional properties for cancer development greater than expected.

Coexistence of *TET2* and *DNMT3A* mutations in prelymphoma cells

Eventually, both of *TET2* and *DNMTA*, frequently mutated in prelymphoma cells in PTCL, encode DNA modifying enzymes. The downstream molecular events of these mutations in prelymphoma cells are unclear.

TET2 encodes a methylcytosine dioxygenase, converting methylcytosine to hydroxymethylcytosine, formylcytosine, and carboxylcytosine [38–40]. One of the functions of TET2 protein is thought to be to mediate the demethylation process. On the other hand, *DNMT3A* encodes a methylcytosine transferase, converting cytosine to methylcytosine. Considering the physiological functions of these epigenetic regulators, loss-of-function mutations in these genes might have the opposite roles in the DNA methylation process. Epigenetic profiles of *TET2*- or -*DNMT3A*-mutated tumors in myeloid malignancies have been studied by several groups [41–45]. It is controversial whether the functional impairment of *TET2/DNMT3A* results in hypermethylation/hypomethylation [2, 41–47], respectively. Namely, the samples with *TET2* mutations had hypermethylation profiles in some reports [42, 44, 45], while opposite results were reported in others [41, 43]. In parallel, differential methylation patterns, either hypomethylation or hypermethylation, were observed in more than 3000 genomic regions between those with or without *DNMT3A* mutations in one report [46], while *DNMT3A* mutations were associated with hypomethylation in less than 200 genomic regions in another report [2]. Furthermore, it is more complicated for understanding that *TET2* and *DNMT3A* mutations are simultaneously identified in a substantial number of samples in both PTCL [8, 9] and myeloid malignancies [28, 48, 49]. Until now, there are no reports describing impact of *TET2*/*DNMT3A* mutations on methylation status in PTCL.

IDH2 mutations; their origins and correlations with *TET2* mutations

IDH2 mutations were detected in both PTCL and myeloid malignancies although the hotspots differed among the diseases. In PTCL, the mutations were restricted to those affecting the R172 position [6, 8, 9], while both R140 and R172 mutations were found in myeloid malignancies [28, 50]. Moreover, mutations in the *IDH1* gene, another member of the IDH family, were detected in AML at similar frequencies to those of the *IDH2* mutations [50], while they have been rarely identified in PTCL [5, 6, 8]. *IDH2* and *TET2* mutations are known to be exclusive in myeloid malignancies [42, 49, 51]. This is explained by the hypothesis that 2-hydroxyglutarate, which is produced by the IDH2 mutant, is known to inhibit the function of alpha-ketoglutarate (alpha-KG)-dependent dioxygenases, including the TET2 protein [42, 52]. As a result, the *IDH1/2*-mutated and the *TET2*-mutated myeloid malignancies were reported to have similar hypermethylation patterns [42]. In contrast, *IDH2* mutations were detected in a part of the *RHOA*-*TET2* mutated samples in PTCL [8]. The coexistence of *IDH2* and *TET2* mutations in PTCL suggests that the downstream mechanisms of *IDH2* mutations in PTCL might be different from those in myeloid malignancies (Fig. 2).

It has been reported that *IDH2* mutations existed in preleukemic cells in AML [10, 12]. In PTCL, the allele

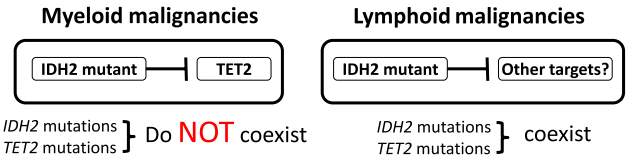

Fig. 2 Relationship between *IDH2* and *TET2* mutations in hematologic malignancies. *IDH2* and *TET2* mutations are known to be exclusive in myeloid malignancies, because the IDH2 mutants contribute to myeloid malignancies through inhibition of TET2 function. The coexistence of *IDH2* and *TET2* mutations in PTCL suggests that the targets of the IDH2 mutants in PTCL might be different from those in myeloid malignancies

frequencies of *IDH2* mutations were much lower than those of *TET2* mutations, suggesting that *IDH2* mutations occur later than *TET2* mutations [8]. In addition, *IDH2* mutations were not detected in non-tumor hematopoietic cells in PTCL [8]. These data suggest that the *IDH2* mutations are a relatively late event in most PTCL cases.

The specific inhibitors for IDH mutants have been developed and are now under clinical trial in AML [53]. Considering the different distribution of *IDH2* mutations in AML and PTCL, the clinical significance of the IDH inhibitors should be independently examined in PTCL.

Conclusion

For more than 20 years PTCLs have been thought to be mature T cell malignancies. However, the origins of PTCLs can be tracked back to the immature stage of hematopoiesis. Specific genetic events contribute to clonal evolution of prelymphoma cells into characteristic tumor cells. Understanding multistep tumorigenesis in PTCL will enable us to find new strategies for treating such dire diseases.

References

1. Delhommeau F, Dupont S, Della Valle V, James C, Trannoy S, Masse A, et al. Mutation in TET2 in myeloid cancers. N Engl J Med. 2009;360:2289–301.
2. Ley TJ, Ding L, Walter MJ, McLellan MD, Lamprecht T, Larson DE, et al. DNMT3A mutations in acute myeloid leukemia. N Engl J Med. 2010;363:2424–33.
3. Mardis ER, Ding L, Dooling DJ, Larson DE, McLellan MD, Chen K, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. N Engl J Med. 2009;361:1058–66.
4. Quivoron C, Couronne L, Della Valle V, Lopez CK, Plo I, Wagner-Ballon O, et al. TET2 inactivation results in pleiotropic hematopoietic abnormalities in mouse and is a recurrent event during human lymphomagenesis. Cancer Cell. 2011;20:25–38.
5. Couronne L, Bastard C, Bernard OA. TET2 and DNMT3A mutations in human T-cell lymphoma. N Engl J Med. 2012;366:95–6.
6. Cairns RA, Iqbal J, Lemonnier F, Kucuk C, de Leval L, Jais JP, et al. IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. Blood. 2012;119:1901–3.
7. Lemonnier F, Couronne L, Parrens M, Jais JP, Travert M, Lamant L, et al. Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. Blood. 2012;120:1466–9.
8. Sakata-Yanagimoto M, Enami T, Yoshida K, Shiraishi Y, Ishii R, Miyake Y, et al. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. Nat Genet. 2014;46:171–5.
9. Palomero T, Couronne L, Khiabanian H, Kim MY, Ambesi-Impiombato A, Perez-Garcia A, et al. Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. Nat Genet. 2014;46:166–70.
10. Shlush LI, Zandi S, Mitchell A, Chen WC, Brandwein JM, Gupta V, et al. Identification of pre-leukaemic haematopoietic stem cells in acute leukaemia. Nature. 2014;506:328–33.
11. Jan M, Snyder TM, Corces-Zimmerman MR, Vyas P, Weissman IL, Quake SR. Clonal evolution of preleukemic hematopoietic stem cells precedes human acute myeloid leukemia. Sci Transl Med. 2012;4:149ra118–149ra118.
12. Corces-Zimmerman MR, Hong WJ, Weissman IL, Medeiros BC, Majeti R. Preleukemic mutations in human acute myeloid leukemia affect epigenetic regulators and persist in remission. Proc Natl Acad Sci USA. 2014;111:2548–53.
13. Busque L, Mio R, Mattioli J, Brais E, Blais N, Lalonde Y, et al. Nonrandom X-inactivation patterns in normal females: lyonization ratios vary with age. Blood. 1996;88:59–65.
14. Gale RE, Fielding AK, Harrison CN, Linch DC. Acquired skewing of X-chromosome inactivation patterns in myeloid cells of the elderly suggests stochastic clonal loss with age. Br J Haematol. 1997;98:512–9.
15. Busque L, Patel JP, Figueroa ME, Vasanthakumar A, Provost S, Hamilou Z, et al. Recurrent somatic TET2 mutations in normal elderly individuals with clonal hematopoiesis. Nat Genet. 2012;44:1179–81.
16. Xie M, Lu C, Wang J, McLellan MD, Johnson KJ, Wendl MC, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med. 2014;20:1472–8.
17. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371(26):2488–98.
18. Genovese G, Kahler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoum SF, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med. 2014;371(26):2477–87.
19. Moran-Crusio K, Reavie L, Shih A, Abdel-Wahab O, Ndiaye-Lobry D, Lobry C, et al. Tet2 loss leads to increased hematopoietic stem cell self-renewal and myeloid transformation. Cancer Cell. 2011;20:11–24.
20. Ko M, Bandukwala HS, An J, Lamperti ED, Thompson EC, Hastie R, et al. Ten-Eleven-Translocation 2 (TET2) negatively regulates homeostasis and differentiation of hematopoietic stem cells in mice. Proc Natl Acad Sci USA. 2011;108:14566–71.
21. Kunimoto H, Fukuchi Y, Sakurai M, Sadahira K, Ikeda Y, Okamoto S, et al. Tet2 disruption leads to enhanced self-renewal and altered differentiation of fetal liver hematopoietic stem cells. Sci Rep. 2012;2:273.
22. Shide K, Kameda T, Shimoda H, Yamaji T, Abe H, Kamiunten A, et al. TET2 is essential for survival and hematopoietic stem cell homeostasis. Leukemia. 2012;26:2216–23.
23. Challen GA, Sun D, Jeong M, Luo M, Jelinek J, Berg JS, et al. Dnmt3a is essential for hematopoietic stem cell differentiation. Nat Genet. 2012;44:23–31.
24. Hirai H, Kobayashi Y, Mano H, Hagiwara K, Maru Y, Omine M, et al. A point mutation at codon 13 of the N-ras oncogene in myelodysplastic syndrome. Nature. 1987;327:430–2.
25. Nakao M, Yokota S, Iwai T, Kaneko H, Horiike S, Kashima K, et al. Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia. 1996;10:1911–8.
26. Pabst T, Mueller BU, Zhang P, Radomska HS, Narravula S, Schnittger S, et al. Dominant-negative mutations of CEBPA, encoding CCAAT/enhancer binding protein-alpha (C/EBPalpha), in acute myeloid leukemia. Nat Genet. 2001;27:263–70.
27. Falini B, Mecucci C, Tiacci E, Alcalay M, Rosati R, Pasqualucci L, et al. Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. N Engl J Med. 2005;352:254–66.
28. Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med. 2013;368:2059–74.
29. Yoshida K, Sanada M, Shiraishi Y, Nowak D, Nagata Y, Yamamoto R, et al. Frequent pathway mutations of splicing machinery in myelodysplasia. Nature. 2011;478:64–9.

30. Naoe T, Kiyoi H. Gene mutations of acute myeloid leukemia in the genome era. Int J Hematol. 2013;97:165–74.
31. Yoo HY, Sung MK, Lee SH, Kim S, Lee H, Park S, et al. A recurrent inactivating mutation in RHOA GTPase in angioimmunoblastic T cell lymphoma. Nat Genet. 2014;46(4):371–5.
32. Rohde M, Richter J, Schlesner M, Betts MJ, Claviez A, Bonn BR, et al. Recurrent RHOA mutations in pediatric Burkitt lymphoma treated according to the NHL-BFM protocols. Genes Chromosomes Cancer. 2014;53(11):911–6.
33. Etienne-Manneville S, Hall A. Rho GTPases in cell biology. Nature. 2002;420:629–35.
34. Cleverley SC, Costello PS, Henning SW, Cantrell DA. Loss of Rho function in the thymus is accompanied by the development of thymic lymphoma. Oncogene. 2000;19:13–20.
35. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513(7517):202–9.
36. Kakiuchi M, Nishizawa T, Ueda H, Gotoh K, Tanaka A, Hayashi A, et al. Recurrent gain-of-function mutations of RHOA in diffuse-type gastric carcinoma. Nat Genet. 2014;46:583–7.
37. Wang K, Yuen ST, Xu J, Lee SP, Yan HH, Shi ST, et al. Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. Nat Genet. 2014;46:573–82.
38. Tahiliani M, Koh KP, Shen Y, Pastor WA, Bandukwala H, Brudno Y, et al. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. Science. 2009;324:930–5.
39. He YF, Li BZ, Li Z, Liu P, Wang Y, Tang Q, et al. Tet-mediated formation of 5-carboxylcytosine and its excision by TDG in mammalian DNA. Science. 2011;333:1303–7.
40. Ito S, Shen L, Dai Q, Wu SC, Collins LB, Swenberg JA, et al. Tet proteins can convert 5-methylcytosine to 5-formylcytosine and 5-carboxylcytosine. Science. 2011;333:1300–3.
41. Ko M, Huang Y, Jankowska AM, Pape UJ, Tahiliani M, Bandukwala HS, et al. Impaired hydroxylation of 5-methylcytosine in myeloid cancers with mutant TET2. Nature. 2010;468:839–43.
42. Figueroa ME, Abdel-Wahab O, Lu C, Ward PS, Patel J, Shih A, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. Cancer Cell. 2010;18:553–67.
43. Perez C, Martinez-Calle N, Martin-Subero JI, Segura V, Delabesse E, Fernandez-Mercado M, et al. TET2 mutations are associated with specific 5-methylcytosine and 5-hydroxymethylcytosine profiles in patients with chronic myelomonocytic leukemia. PLoS One. 2012;7:e31605.
44. Yamazaki J, Taby R, Vasanthakumar A, Macrae T, Ostler KR, Shen L, et al. Effects of TET2 mutations on DNA methylation in chronic myelomonocytic leukemia. Epigenetics. 2012;7:201–7.
45. Nischal S, Bhattacharyya S, Christopeit M, Yu Y, Zhou L, Bhagat TD, et al. Methylome profiling reveals distinct alterations in phenotypic and mutational subgroups of myeloproliferative neoplasms. Cancer Res. 2013;73:1076–85.
46. Yan XJ, Xu J, Gu ZH, Pan CM, Lu G, Shen Y, et al. Exome sequencing identifies somatic mutations of DNA methyltransferase gene DNMT3A in acute monocytic leukemia. Nat Genet. 2011;43:309–15.
47. Yamazaki J, Issa JP. Epigenetic aspects of MDS and its molecular targeted therapy. Int J Hematol. 2013;97:175–82.
48. Haferlach T, Nagata Y, Grossmann V, Okuno Y, Bacher U, Nagae G, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia. 2014;28:241–7.
49. Papaemmanuil E, Gerstung M, Malcovati L, Tauro S, Gundem G, Van Loo P. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013;122:3616–27 quiz 99.
50. Dang L, Jin S, Su SM. IDH mutations in glioma and acute myeloid leukemia. Trends Mol Med. 2010;16:387–97.
51. Itzykson R, Kosmider O, Renneville A, Gelsi-Boyer V, Meggendorfer M, Morabito M, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. J Clin Oncol. 2013;31:2428–36.
52. Xu W, Yang H, Liu Y, Yang Y, Wang P, Kim SH, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. Cancer Cell. 2011;19:17–30.
53. Stein E, Tallman M, Pollyea DA, Flinn IW, Fathi AT, Stone RM, et al. Clinical safety and activity in a Phase I trial of AG-221, a first in class, potent inhibitor of the IDH2-mutant protein, in patients with IDH2 mutant positive advanced hematologic malignancies. Presented at: 2014 AACR Annual Meeting; April 5-9, 2014; San Diego, CA. Abstract CT103.