Multistep tumorigenesis in peripheral T-cell lymphoma

Review article

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Running title: Disease specific mutations might determine the cell fate of premalignant cells

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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 *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 *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.

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 *isocytrate dehydrogenease 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 tumorigeneis 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 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 (Figure1). 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.

Clonal evolution of mutation-bearing prelymphoma cells

Both myeloid and lymphoid malignancies can emerge from *TET2*-or *DNMT3A*-mutated preleukemic/lymphoma stem cells (Figure1). 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 *nucleophomin* (*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[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 (Figure1).

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 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 dioxigenases, 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 (Figure2).

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

Figure legends

Figure1 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.

Figure2 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.

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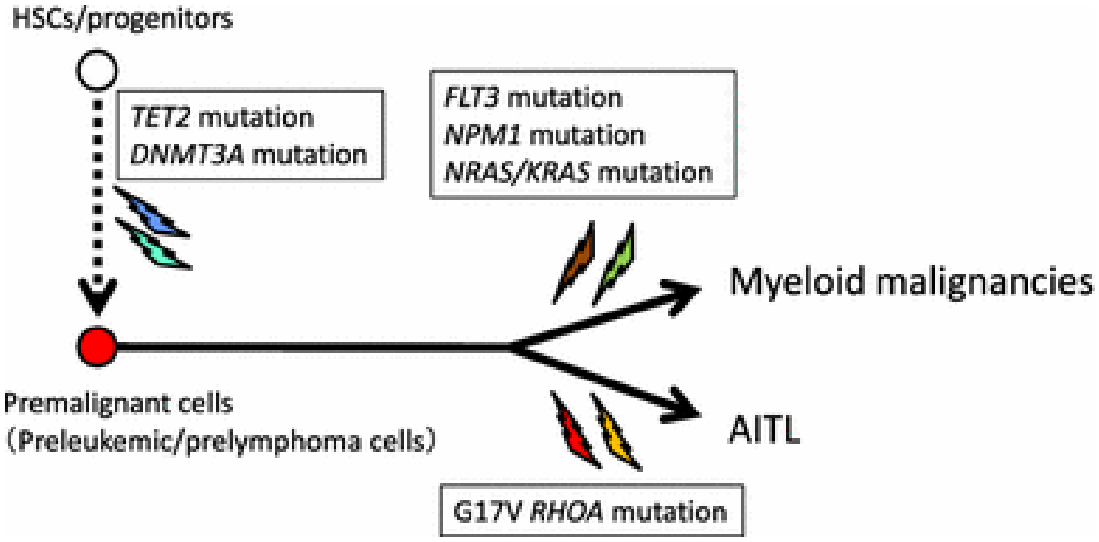
HSCs/progenitors
TET2 mutation
DNMT3A mutation
FLT3 mutation
NPM1 mutation
NRAS/KRAS mutation
Myeloid malignancies
Premalignant cells
(Preleukemic/prelymphoma cells)
AITL
G17V RHOA mutation

Fig. 1

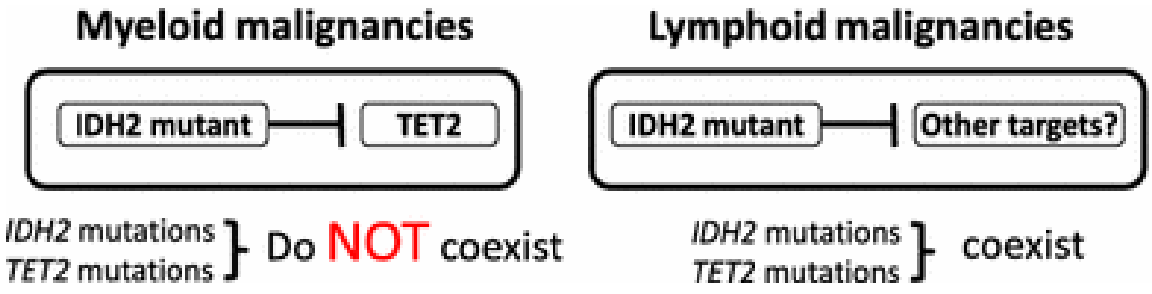
Myeloid malignancies
IDH2 mutant
TET2
IDH2 mutations
TET2 mutations
Do NOT coexist
Lymphoid malignancies
IDH2 mutant
Other targets?
IDH2 mutations
TET2 mutations
coexist

Fig. 2