Rare Occurrence of the JAK1 Mutation in Acute Promyelocytic Leukemia Patients

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Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia characterized by a chromosome translocation of t(15;17)(q24;q21) which involves fusion of the retinoic acid receptor α (RARα) gene in chromosome 17 and the promyelocytic leukemia (PML) gene in chromosome 15. The fusion protein encoded by the PML/RARα gene makes APL sensitive to all-trans retinoic acid, a derivative of vitamin A. With the introduction of all-trans retinoic acid and arsenic trioxide in the past several decades, the complete remission (CR) rate and 5-year disease-free survival for APL were elevated to more than 90% [1].

The Janus kinase (JAK) is a nonreceptor tyrosine kinase, including 4 family members, i.e. JAK1, JAK2, JAK3, and TYK2. The JAK1 gene is organized into 25 exons, including 24 coding exons, and spans about 133.28 Kb in the chromosome 1p31.3 region, which is responsible for transducing cytokine-induced signals via JAK-STAT pathway aberrations; JAK1 signal activation is partially responsible for leukemogenesis. Recently, Wartman et al. [2] found Jak1 (V657F) in a murine APL model via whole genomic sequencing. This Jak1 (V657F) was identified in 6 other mice that were not closely related to the proband [2]. After analyzing 186 acute adulthood leukemias, 30 multiple myelomas, and 278 common solid cancers, Jeong et al. [3] discovered 4 JAK1 mutations in patients with acute leukemia. Among them, the JAK1 mutations V658F and L783F occurred in 4 leukemia patients, while the p.V658F mutation was found in 1 patient with APL [3]. In our previous report, the JAK1 mutation was found in 3 out of 49 in acute T-lymphocytic leukemia patients [4]. To explore the frequency of the JAK1 mutation in APL, we performed JAK1 gene sequencing in a group of APL patients in our center. This study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University. Informed consent was provided following the Declaration of Helsinki.

A total of 86 patients with de novo APL were screened in all 24 exons of JAK1 using genomic DNA-PCR amplification sequencing. The clinical characteristics of these patients are listed in table 1. Bone marrow was aspirated and cultured with colcemid overnight at 37°C and harvested according to standard procedures [5]. Karyotypic analysis was performed on R-banded metaphases and described according to the recommendations of the ISCN. Metaphases were analyzed by R banding and karyotype showed that 82 out of 84 patients were t(15;17) with a positive PML/RARα fusion gene, while 1 patient displayed t(11;17) with the PLZF/RARα fusion gene. Total DNA was extracted from bone marrow using a DNA...
DNA sequencing analysis of the JAK1 gene found 4 novel heterozygous single-nucleotide variations which were not included in the NCBI SNP database. c.1659C>T (Asn553Asn) was a synonymous mutation and the other three were nonsynonymous mutations. All four mutations were genomic variants rather than somatic mutations since they were identified in the CR samples (table 2).

The genetic variation of the JAK1 gene in APL patients is unknown. By sequencing a large cohort of patients, we found 4 novel SNPs in patients with CR. Thus, our results have shown that JAK1 mutation is rare in newly diagnosed APL patients, suggesting that these mutations in JAK1 were unlikely to be involved in the pathogenesis of APL. Earlier studies identified the mutations in the same amino acid (or homologous amino acids) of V658F; however, we did not find these mutations in any of the 84 specimens (fig. 1). Because of the low frequency of the JAK1 mutation in APL, larger patient cohorts are needed for further study.

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References


