A DNA repair gene, OGG1, polymorphism affects relapse risk of acute myeloid leukemia

Approximately 80% of acute myeloid leukemia (AML) patients can achieve complete remission, but around half of them relapse within five years. Defining the mechanism of relapse is essential to improve the prognosis of AML. Recently, a clonal evolution model has been proposed as a mechanism for AML relapse. AML cells constitute a heterogeneous population, and form subclones that acquired new mutations based on the founder clone. Relapse of AML is considered to be derived from clones that could not be killed by the treatment or clones that acquired new mutations during treatment. Theses observation suggest that anti-cancer drug treatment-related DNA damage is associated with AML recurrence.

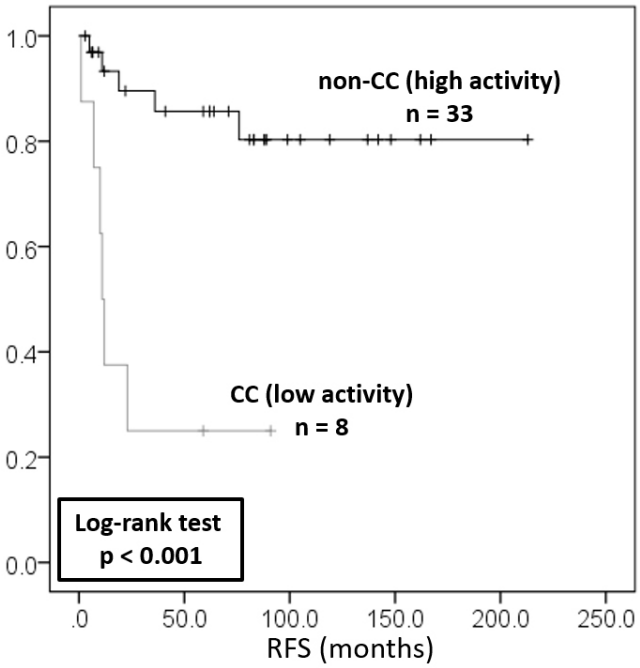

Fig. 1.

Reactive oxygen species (ROS) are one of the major sources of DNA damage. Several anti-cancer agents produce ROS. For example, doxorubicin, anti-cancer drug for AML, induces 8-oxoguanine (8-OG) production in AML cells via ROS generation. 8-OG is an oxidatively damaged mutagenic base, which causes G:C to T:A transversion mutations in DNA. Recent studies have shown that relapsed AML has more transversion mutations than primary AML. The base excision repair (BER) pathway corrects oxidatively damaged mutagenic bases and plays an important role in the maintenance of genetic stability. We hypothesized that BER polymorphisms affect AML relapse

risk, and focused on five major functional BER polymorphisms: OGG1 S326C (rs1052133), MUTYH Q324H (rs3219489), APE1 D148E (rs1130409), XRCC1 R194W (rs1799782), and XRCC1 R399Q (rs25487).

Ninety-four adults with AML who achieved first complete remission were recruited. The OGG1 S326C CC genotype (associated with lower OGG1 activity) was observed more frequently in patients with AML relapse (28.9% vs. 8.9%, odds ratio [OR] = 4.10, 95% confidence interval [CI] = 1.35-12.70, P = 0.01). Patients with the CC genotype exhibited shorter relapse-free survival (RFS). Moreover, the TCGA database suggested that low OGG1 expression in AML cells is associated with a higher frequency of mutations.

OGG1 is an important DNA repair enzyme that removes 8-OG from genomic DNA, thereby suppressing the G:C to T:A transversion mutation induced by 8-OG. The OGG1 S326C polymorphism is located in a domain that is important for this activity. Previous study has shown that the glycosylase activity of the OGG1-C326 protein is lower than that of OGG1-S326. Therefore, we hypothesized that low OGG1 activity promotes genetic mutation in AML cells, eventually leading to relapse.

In conclusion, our data suggest that OGG1 S326C can be a prognostic factor for AML relapse. To the best of our knowledge, this is the first report about relationship between DNA repair enzyme gene polymorphism and AML relapse. Although further studies of larger populations are necessary to confirm these data, our findings provide novel insights into the relationship between DNA repair and AML relapse.

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