The mechanism of acquiring cell adhesion mediated-drug resistance (CAM-DR) in acute myelogenous leukemia cells

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Acute myelogenous leukemia (AML) cells acquire drug resistance against anticancerous drugs through adhesion to stromal cells or fibronectin (FN) in bone marrow. This phenomenon, termed “cell adhesion-mediated-drug resistance (CAM-DR)”, forms the minimal residual disease, which causes relapse after chemotherapy. We recently found that combination therapy of an anticancer drug with FNIII14, an antiadhesive peptide derived from FN, effectively overcomes CAM-DE of AML. It is expected that our peptide enables “total cell kill”, a goal of leukemia treatment, which may provide the eradication therapy for leukemia. However, the mechanism of acquiring CAM-DR in AML cells has not been fully understood. In this study, we investigate the molecular basis underlying leukemic cells acquire the CAM-DR.

Two steps are implicated in acquisition of CAM-DR; (1) getting adhesiveness in AML cells, (2) acquiring anti-cancer drug resistance by cell adhesion. Labbaye et al. recently reported that the impaired function of PLZF (Promyelocytic Leukemia Zink Finger Protein), which is often found in AML patients, increases the integrin expression level and thereby enhances adhesiveness of AML cells. However, in our study, down-regulation of PLZF expression by RNA interference made AML cells more resistant to antiadhesive effect of FNIII14 without any change in integrin expression levels. This suggests that PLZF may contribute to the maintenance of the activation status of integrins, resulting in increased adhesiveness of AML cells.

Regarding cell adhesion-dependent drug resistance, we examined the effect of adhesion on cell cycle distribution of AML cells, as evaluated by BrdU-incorporation. It was found that the population of S-phase cells decreased when adhered to FN, suggesting that delay in the cell cycle progression reduced susceptibility of cells to anti-cancer drug.

Taken altogether, it might be presumed that the impaired function of PLZF induces sustained activation of integrin, which causes acquiring adhesiveness of AML cells. By adhesion to FN, the progression of cell cycle becomes delayed, which made cells more resistant to anti-cancer drugs.