به نام خداوند جان و خرد

Evaluation of the gene expression levels of UHRF1 and P16INK4A in newly diagnosed AML patients

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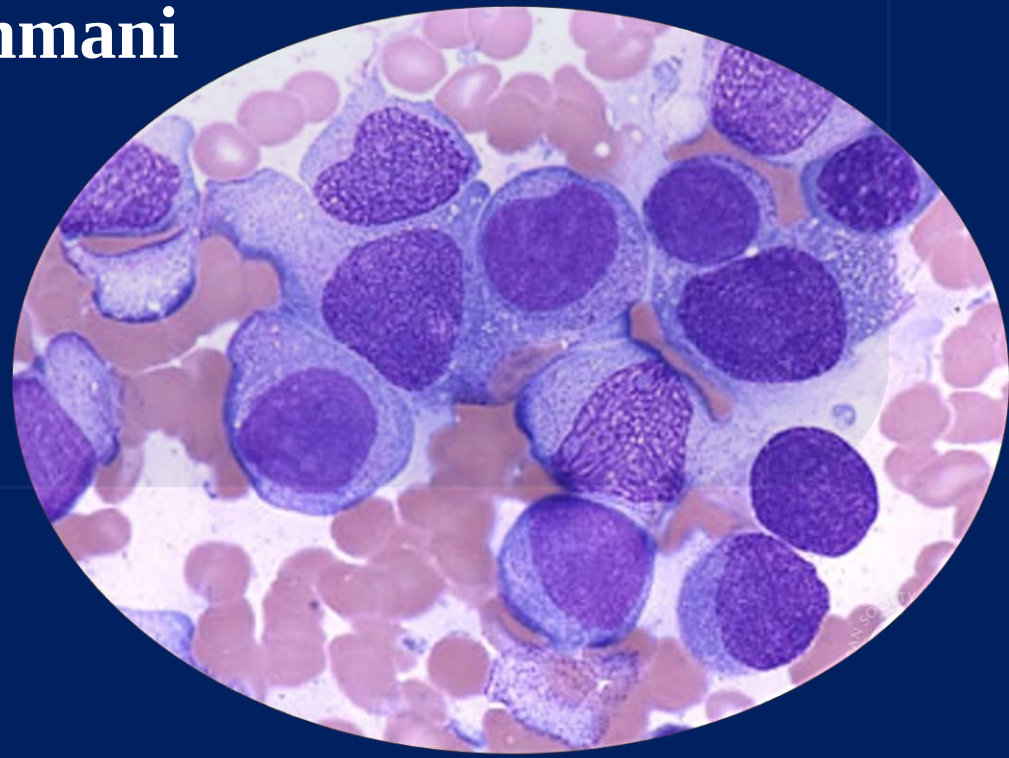


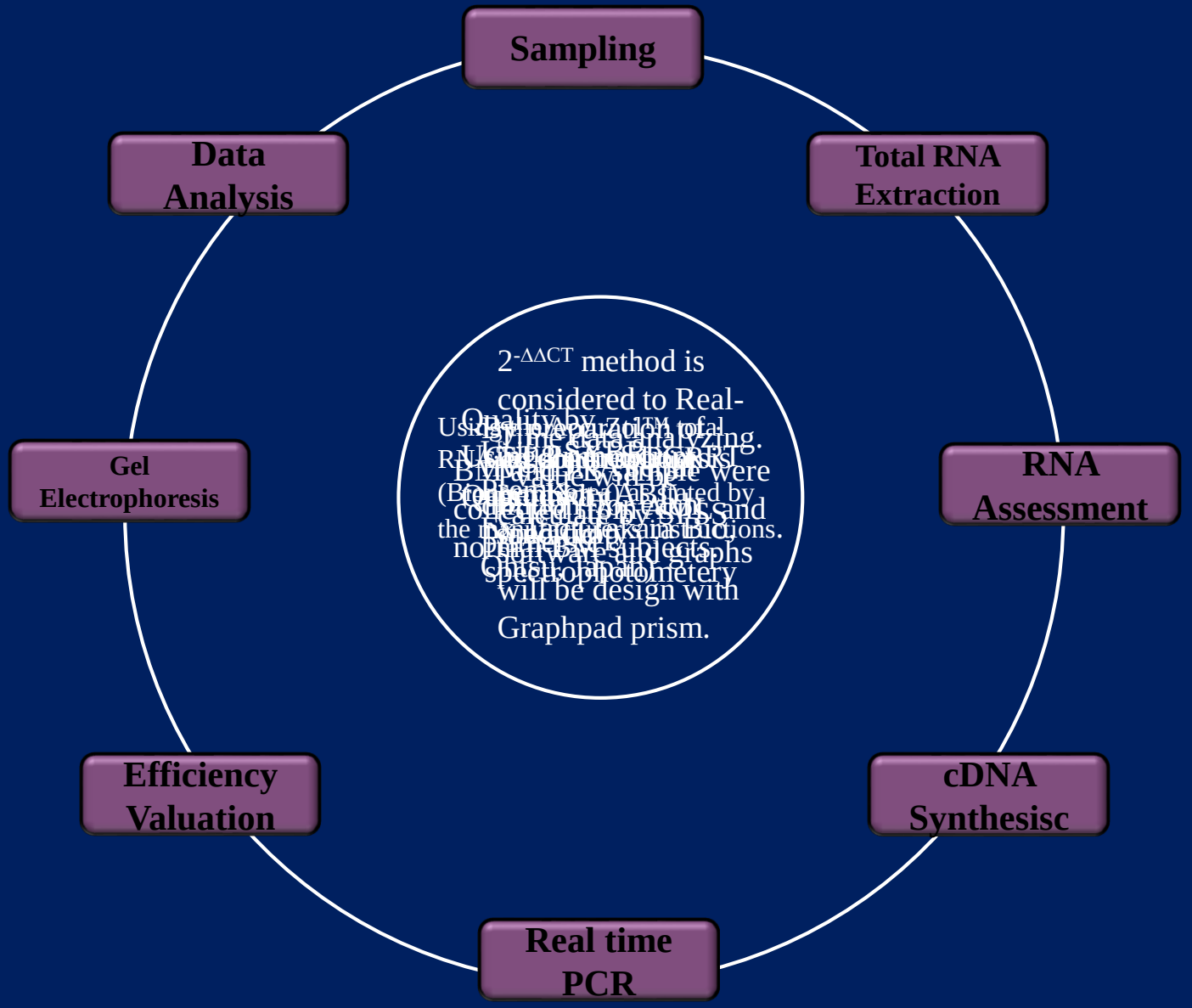
Introduction

- AML has one of the lowest mutation rate per case compared with others human cancers
- In contrast to solid tumors, sequencing results showed an infrequent rate of mutations in TSGs in AML patients
- In comparison with solid tumors, leukemic myeloblasts mainly undergo genome-wide hypermethylation which represses mainly gene expression of TSGs

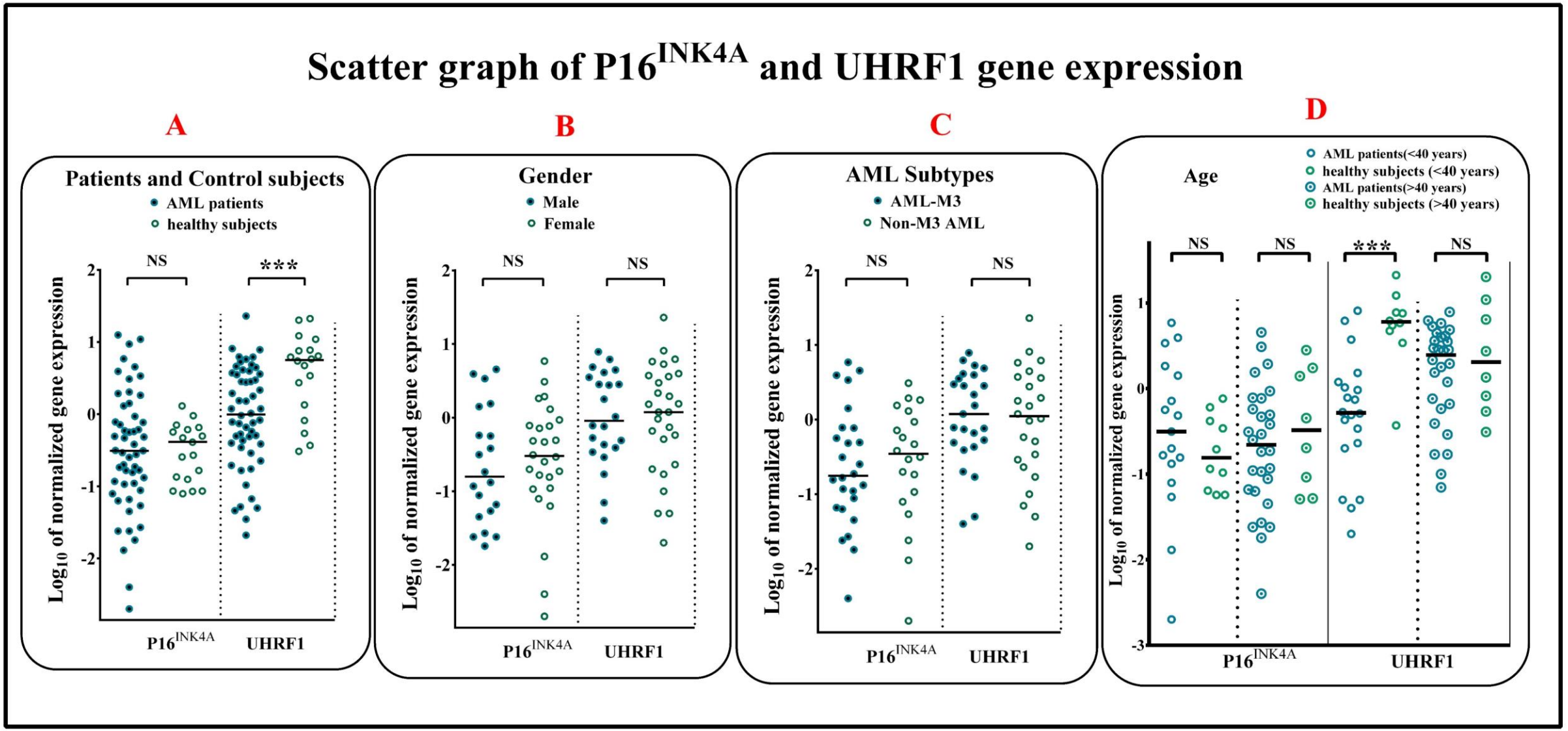
Introduction

- The expression of some TSGs is an age-dependent process and increases with aging, probably to prevent clonal expansion of cells that have sufficient number of tumorigenic mutations
- CDKN2A locus encoding P16INK4A protein has this pattern of gene expression and has an important role in tumor prevention
- However, in malignant condition such as AML, P16INK4A gene expression reduces whit aging, which is mainly due to hypermethylation of the CDKN2A promoter
- Some demethylase agents such as cladribine and clofarabine enhances the cytotoxic effect of routine AML therapies by epigenetic modulation of tumor suppressor genes such as CDKN2A

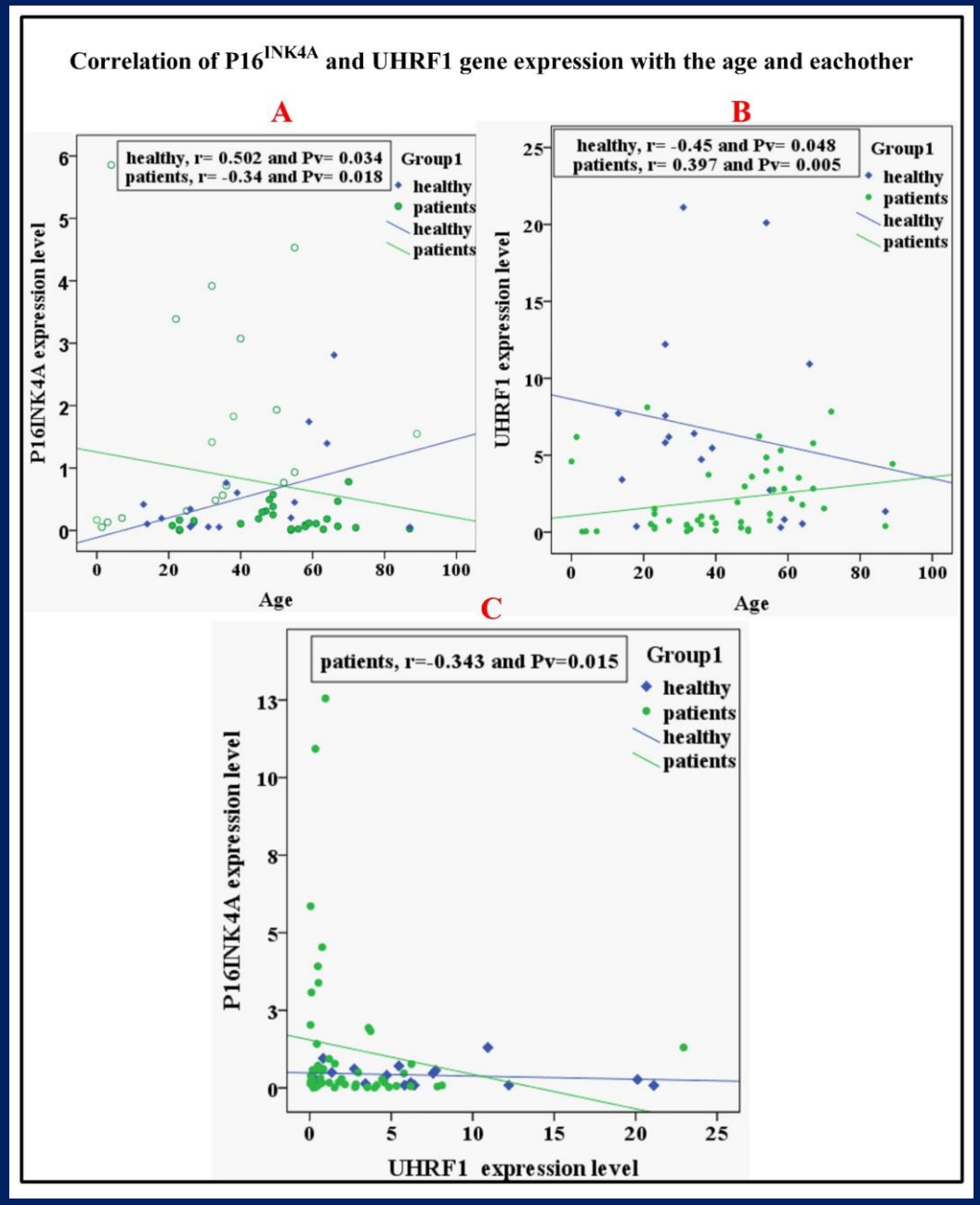
Material and method



Results


Scatter graph of P16INK4A and UHRF1 gene expression
A
Patients and Control subjects
AML patients
healthy subjects
NS
***
Log10 of normalized gene expression
P16INK4A
UHRF1
B
Gender
Male
Female
NS
NS
C
AML Subtypes
AML-M3
Non-M3 AML
NS
NS
D
Age
AML patients(<40 years)
healthy subjects (<40 years)
AML patients(>40 years)
healthy subjects (>40 years)
NS
NS
***
NS

Results


Correlation of P16INK4A and UHRF1 gene expression with the age and eachother
A
healthy, r= 0.502 and Pv= 0.034
patients, r= -0.34 and Pv= 0.018
Group1
healthy
patients
healthy
patients
P16INK4A expression level
Age
B
healthy, r= -0.45 and Pv= 0.048
patients, r= 0.397 and Pv= 0.005
Group1
healthy
patients
healthy
patients
UHRF1 expression level
Age
C
patients, r=-0.343 and Pv=0.015
Group1
healthy
patients
healthy
patients
P16INK4A expression level
UHRF1 expression level

Discussion

- The promoter of CDKN2A gene is demethylated in healthy elder patients, which causes a higher expression of this gene in these ages compare with the younger persons
- Age-associated overexpression of P16INK4A can induce apoptosis or cellular senescence in cells with genomic damages and is regarded as a protective mechanism of cells against cancer formation
- To overcome this barrier, cancer cells change P16INK4A regulator to reduce its expression and function
- For example, several types of solid tumors increase the expression of UHRF1 as an oncogene that recruits methylase enzymes to CDKN2A promoter for repressing its expression

Discussion

- Based on these observation, the overexpression of UHRF1 is useful for malignant cells, so why AML leukemic blast downregulates its expression?
- Previous report by S Mizuno et al showed that DNMTs increased in AML patients in comparison with the bone marrow normal cells. Further studies revealed that, DNMTs enzymes are marked by UHRF1 for future degradation by proteasome system
- Therefore, regarding our data UHRF1 down-regulation can be a possible mechanism, underlying DNMTs enzyme overexpression in AML patients, which is consistent with genomic hypermethylation that occurs in many TSGs region of AML blasts

Conclusion

In this article we addressed UHRF1, a critical factor in regulation of DNA methylation in normal and leukemic cells as the repressor of P16INK4A in elderly AML patients. Downregulation of P16INK4A may suppress cell physiological defense against leukomogenesis from dangerous lesion and facilitate the development of AML in elder persons.

Thank you for your time

Discussion

- In our study patients above 50 years old had a tendency to express UHRF1 in a similar fashion with healthy subjects, while younger patients had lower levels of UHRF1 in comparison with healthy counterparts
- In present study UHRF1 gene expression had a significant negative correlation with P16INK4A gene expression
- P16INK4A overexpression in younger patients can be a consequence of their positive regulator overexpression or a physiological response to keep cells from leukemogenic lesion, as well as that occurs during aging in normal people. However, this physiological barrier encounters essential defects in elderly AML patients

Discussion

- looking for a reason, we found that old patients who had down-regulation of P16INK4A, express UHRF1 similar to healthy counterpart
- We suggest that a regulated pattern of UHRF1 gene expression is need to reducing P16INK4A gene expression in AML patients
- This regulated pattern not only prevents from over degradation of DNMT enzymes that generally occurs in solid tumors (probably due to UHRF1 overexpression) but also can properly recruit DNMTs to the promoter of CDKN2A gene to suppress its expression