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Significance of GRP78 expression in acute myeloid leukemias

Research Article

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Abstract: The GRP78 (glucose-regulated protein 78) is a major endoplasmic reticulum (ER) chaperone facilitating proper folding of the newly synthesized proteins. By the interaction with caspases, GRP78 has antiapoptotic properties allowing cells to survive under stress condition. GRP78 expression and its association with tumor proliferation, metastasis and resistance to chemotherapy were observed in solid tumors. There are limited data on the expression and impact of this protein on the clinical course and treatment response in acute myeloid leukemia (AML). The aim of this study was to evaluate the expression of *GRP78 mRNA* in patients with de novo AML. These results were compared to healthy controls, blast phenotype, molecular and cytogenetic status and clinical features of AML. 101 non-M3 AML patients and 26 healthy individuals were included in this study. The expression of *GRP78 mRNA* in bone marrow was analyzed by real-time quantitative polymerase chain reaction (RQ-PCR). We demonstrated increased *GRP78 mRNA* expression in AML patients compared to healthy controls, although this difference was statistically significant only in $CD34^+$ leukemias. There was also no significant correlation between *GRP78 mRNA* expression and complete remission rate, relapse-free survival and overall survival. These results indicate that GRP78 expression is increased in $CD34^+$ leukemias and has no prognostic impact on clinical outcome in AML.

Keywords: *Acute myeloid leukemia • GRP78 • Resistance to chemotherapy*

1. Introduction

Acute myeloid leukemias (AMLs) belong to haematological malignancies derived from the hematopoietic stem cells (HSCs), which undergo malignant transformation [1]. One of the feature of cancer stem cells is activation of the unfolded protein response (UPR), which is triggered by the accumulation of misfolded proteins in the endoplasmic reticulum (ER), leading to ER stress [2]. Key components of the UPR include three stress sensors constitutively expressed in the ER membrane: protein kinase-like endoplasmic reticulum kinase (PERK), activating transcription factor 6 (ATF6), and inositol requiring enzyme 1 (IRE1) with substrate X-box binding protein 1 (XBP-1). During homeostasis, these molecules are kept inactive by their complex with the glucose-regulated protein 78 (GRP78), which is a major modulator of UPR and ER chaperone facilitating proper folding of the newly synthesized proteins. In the pathological condition like increased glycolysis, low pH or hypoxia, GRP78 shifts away from these sensors and allows their activation. This process leads to decrease protein translation, cell cycle arrest and increased transcription of ER chaperones, including GRP78 which has antiapoptotic properties through interaction with caspases [3]. Thus by sustaining the UPR, GRP78 induction in pathological conditions can be an important protective mechanism allowing cells to survive under stress. Prolonged and increased activation of the UPR leads to programmed cell death. This apoptotic effect is mediated largely by increased expression of the transcription factor CCAAT/enhancer binding protein homologous protein (CHOP), which leads finally to apoptosis by the intrinsic mitochondrial pathway. The GRP78 overexpression reduces CHOP induction and reduces apoptosis in prolonged cellular stress condition.

The GRP78 expression and its association with tumor proliferation, metastasis and resistance to chemo-

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therapy was observed in solid tumors [4]. The role of GRP78 during leukemogenesis is not well established. There are also limited data about expression and impact of this protein on the clinical course and treatment response in AML. In this study we evaluated the expression of *GRP78 mRNA* in patients with de novo AML. These results were compared to healthy controls, the CD34 expression, classical prognostic factors, molecular and cytogenetic indicators and treatment results such as: complete remission rate, relapse free survival and overall survival.

2. Materials and methods

2.1 Patients

101 non-M3 AML patients were included in this study: 58 men and 43 women with the median age at diagnosis 49 years (range: 19-84 years). All AML patients were diagnosed between 2000-2010 at the Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Medical University in Wrocław, Poland. Bone marrow (BM) samples were evaluated prior to initiation of induction therapy. The subtypes of AML were classified based on French-American-British classification criteria [5]. According to European Leukemia Net (ELN) patients were categorized into 3 risk groups: standard, intermediate and high risk [6]. Clinical characteristic of all AML patients is summarized in Table 1.

Patients ≤60 yrs (n= 76) were treated according to the Polish Adult Leukemia Group (PALG) induction protocols based on daunorubicin and conventional dose of cytarabine arabinoside (Ara-C) [7-9]: Patients >60 yrs (n=25) were treated according to the PALG or Cancer and Leukemia Group B (CALGB) protocols [10,11]. In three patients older than 60 yrs we applied a low dose of Ara-C and in two patients decitabine. 7 of 76 patients ≤60 yrs and 3 of 25 patients >60 yrs received only palliative therapy due to poor performance status and comorbidities. Response criteria were assessed based on European Leukemia Net recommendations [6].

2.2 Control group

The control group consisted of 26 healthy individuals: 17 men and 9 women with the median age 46 years (range: 22-74 years).

2.3 Methods

BM specimens from 101 patients and 26 healthy individuals were obtained. Mononuclear cells from BM were isolated by gradient separation using Gradisol L (Aqua Medica, Łódź). RNA was extracted using TriReagent® kit (Ambion/Applied Biosystems, Warszawa).

Table 1. Clinical characteristic of AML patients.

Number of patients	101
Age	49 (19-84)
Sex	F- 43, M -58
FAB, *n*	
M0	8
M1	20
M2	23
M4	31
M5	16
M6	3
AML *de novo*, *n*	96
AML secondary to MDS, *n*	5
Risk, *n*	
SR	21
IR	48
HR	32
Molecular changes, *n*	
FLT3-ITD	22
NPM1-mut	31
Median white blood cells count (10^9/L)	30 (0.52- 509)
Median platelet count (10^9/L)	52 (5-433)
Median hemoglobin level (g/dL)	9 (5.5- 15.1)
LDH (U/l)	709 (180-13534)
Blast cells in bone marrow (%)	75 (20,5-97)
CD 34^+, *n*	61
Treatment, *n*	
a) ≤ 60 yrs (*n*= 76)	
DA	35
DAC	25
DAF	9
Palliative treatment	7
b) > 60 yrs (*n*= 25)	
DA	15
Ara-C + mitoxantron	2
Low dose of Ara-C	3
Low dose of decitabine	2
Palliative treatment	3
Response to treatment, *n*	
CR	57
NR	44

F-female; M-male; LDH-lactic acid dehydrogenase; SR-standard risk; IR-intermediate risk; HR–high risk; MDS-myelodysplastic syndrome, FAB- French, American, British Co-operative group; CR-complete remission; NR-non response; Ara-C- cytarabine arabinoside; DA-daunorubicin+cytarabine arabinoside; DAF-daunorubicin + cytarabine arabinoside + fludarabine; DAC- daunorubicin + cytarabine arabinoside+ cladribine.

In a 20 µl reaction, 2 µl of total RNA was reverse transcribed using High Capacity cDNA Revese Transcription Kit (Applied Biosystems, Warszawa). The mRNA levels of GRP78 and beta-glucuronidase-GUS (control gene) were measured by real-time quantitative polymerase chain reaction (RQ-PCR) based on TaqMan Gen Expression Assay (Applied Biosystems): Hs99999174_m1 respectively for GRP78 and Hs99999908_m1 for GUS. RQ-PCR was performed in duplicate and carried out on the 7500 Real Time PCR System (Applied Biosystems) using TaqMan Gene Expession Master Mix (Applied Biosystems). The amount of complementary DNA (cDNA) used in the reaction corresponded to 50 ng of isolated RNA. The relative quantitation was indicated by threshold cycle (C_T) values, determined based on reaction for target and control gene. The measure of mRNA expression was the difference (ΔC_T) between C_T for GRP78 gene and C_T for reference gene GUS ($\Delta C_T = C_{T\ GRP78} - C_{T\ GUS}$). The relative expression level was determined as $2^{-\Delta CT}$ according to Applied Biosystems.

2.4 Statistical analysis

Statistical analysis was performed using STATISTICA version 9.0 software. To study the relationship between two categorical variables, the chi-squared test of independence was used. In the case of small number of groups exact Fisher's test and Yates's correction test were used. Pearson's correlation was used to evaluate correlation between paired values. Due to the presence of outliers, in some cases the Spearman rank correlation coefficient was used. Statistical comparisons between groups were performed also by means of the Mann-Whitney U-test (non-parametric analysis) and ANOVA rank Kruskal-Wallis test. A p-value <0.05 indicated a statistically significant difference.

3. Results

3.1 Expression of *GRP78 mRNA* in all AML patients, AML CD34$^+$, AML CD34$^-$ and in control group

We analyzed expression of *GRP78 mRNA* in all 101 AML patients and in 26 volunteers. CD34 antigen on the surface of blast cells was evaluated by flow cytometry during the routine diagnosis of leukemia. Expression of CD34 antigen in more than 20% of cells were considered as positive (CD34$^+$). Expression of *GRP78 mRNA* was higher in AML patients compared to control group, but the difference was not statistically significant. On the other hand, we observed that the expression level of *GRP78 mRNA* was significantly higher in AML CD34$^+$ patients compared to the healthy control group. Moreover the expression of *GRP78 mRNA* in CD34$^+$ leukemias was significantly higher than in CD34$^-$ leukemias. Results are presented in Table 2.

Table 2. Expression of *GRP78 mRNA* in AML, AML CD34$^+$, AML CD34$^-$ and in control group.

	n	*GRP78 mRNA* (x ± SD)	p-value
AML	101	5.670 ± 3.780	0.1507
control	26	4.359 ± 1.533	0.014
AML CD34$^+$	61	6.249 ± 3.936	0.005
AML CD34$^-$	39	4.730 ± 3.431	

AML-acute myeloid leukemia; x- mean; SD- standard deviation.

3.2 *GRP78 mRNA* expression and clinical characteristic of AML patients

The analysis includes: age, white blood cells (WBC) count, lactate acid dehydrogenase (LDH) activity and percentage of blast cells in bone marrow (Table 3). We found that higher expression of *GRP78 mRNA* correlates with lower WBC count (p ≤0.05). There was no correlation between *GRP78 mRNA* expression and other parameters. Further, patients were divided into 4 groups using morphological features according to the FAB criteria: Group 1 – AML M0 + M1; Group 2 – AML M2, Group 3 - AML M4 + M5, Group 4 – AML M6. The statistical analysis does not include patients with subtype M6 (group 4) due to the limited number of patients (n=3). The average level of *GRP78 mRNA* was the lowest in AML with monocytic fenotype, while the highest in AML with minimal or without maturation. The results are shown in Table 4.

Table 3. Expression of *GRP78 mRNA* depends on clinical characteristic of AML patients.

	GRP78 mRNA	
	r	p-value
WBC	-0.200	p≤0.05
LDH	0.064	NS
Blast cells	-0.091	NS
Age		

WBC-white blood cells; LDH- lactic acid dehydrogenase; r- Spearman's rank correlation; NS-not significant.

Table 4. GRP78 mRNA expression according to FAB classification.

	n	*GRP78 mRNA* (x ± SD)	p-value
Group 1	28	6.7607 ± 4.4735	1.0000
Group 2	23	6.0142 ± 3.9647	0.0291
			0.4669
Group 3	47	4.8931 ± 3.1969	

x- mean; SD- standard deviation; Group 1- M0 + M1; Group 2- M2; Group 3 – M4 + M5.

3.3 Correlation between *GRP78 mRNA* expression and cytogenetic and molecular features

Expression of *GRP78 mRNA* was evaluated in relation to cytogenetic status according to the ELN criteria [6]. All 101 patients were classified into 3 groups: standard risk (n=21), intermediate risk (n=48) and high risk (n=32). There was no statistical significant difference in expression of *GRP78 mRNA* between cytogenetic risk group. Then, all patients were analyzed for mutations in nucleophosmin 1 gene (NPM1) and for internal tandem duplications of the *fms*-like tyrosine kinase 3 (FLT3-ITD). Expression of *GRP78 mRNA* was significantly lower in AML patients with NPM1 mutation compared to patients with wild-type form of this gene. No difference was observed between wild-type and *ITD* form of *FLT3*. Data are summarized in Table 5 and 6.

Table 5. Expression of GRP78 mRNA and AML cytogenetic risk groups.

	GRP78 mRNA			
	n=101	(x ± SD) statistic value	H-statistic	p-value
Standard risk (SR)	21	4.447 ± 1.891		
Intermediate risk (IR)	48	5.254 ± 3.194	3.95535	0.1384
High risk (HR)	32	7.025 ± 5.026		

x- mean; SD- standard deviation.

Table 6. Expression of *GRP78 mRNA* in *NPM1* and *FLT3* AML.

	GRP78 mRNA, x ± SD		
	n=101		p-value
FLT3 wild-type	79	5.860 ± 4.086	0.8466
FLT3-ITD	22	4.983 ± 2.308	
NPM1 wild-type	70	6.1688 ± 4.1362	0.0284
NPM1 mutation	31	4.5403 ± 2.5163	

x- mean; SD- standard deviation.

3.2 Correlation between *GRP78 mRNA* expression and clinical outcome

We correlated expression of *GRP78 mRNA* and clinical outcome such as: response to induction chemotherapy, relapse-free survival (RFS) and overall survival (OS). A first complete remission (CR_1) was achieved in 57 of 101 patients. The expression level of *GRP78 mRNA* was lower in CR_1 group than in non response patients (NR, n=44), but this difference was not statistically significant (5.279 ± 2.818 vs. 6.174 ± 4.732, p=0.8246). Next, we analyzed the relationship between *GRP78 mRNA* expression and risk of leukemia relapse. Relapsed disease was diagnosed in 26 patients who initially achieved CR_1. Median time to relapse was 5 months. The average level of *GRP78 mRNA* between patients who remained CR_1 and those with relapse was insignificant (5.44 ± 5.34, p=0.992). At median follow-up 37 months we did not observe any correlation between *GRP78 mRNA* expression and RFS and OS in AML patients.

4. Discussion

Standard chemotherapy achieves CR in a significant proportion of AML patients. However, the relapse rate is still high [12,13]. Drug resistance is the main cause of therapy failure. It is a multifactor phenomenon which includes different mechanisms leading to evasion of apoptosis [14]. One of the proteins involved in this process is GRP78. GRP78 is a major modulator of UPR response with antiapoptotic properties and is activated in many types of solid tumors. Increased glycolytic activity, hypoxia and secondary metabolic acidosis in tumor tissue, stimulate the activation of the UPR. Expression of GRP78 and its association with resistance to chemotherapy was observed in solid tumors [15-18], while the impact of this protein on leukemogenesis and the AML clinical course remains unexplained. A. Tanimura et al. observed that patients with AML show significantly higher expression of *GRP78 mRNA* in bone marrow than healthy controls [19]. Analogous data obtained by PJ Valk, who studied 285 AML patients [20]. We have made similar observations. In patients with AML *GRP78 mRNA* expression was higher in bone marrow compared to healthy controls, although this difference was not statistically significant. However in poorly differentiated leukemia $CD34^+$, *GRP78 mRNA* level was significantly higher relative to the control group. These data may indicate that the increased expression of GRP78 protein, which modulates the UPR response occurs not only in solid tumors, but also in AML. Such observations were confirmed by Schardt JA et al., who analyzed bone marrow samples using RQ-PCR of 105 patients with AML. UPR response with increased expression of chaperone proteins like GRP78 and calreticulin was observed in 16.2% of patients [21]. These data indicates that stress activation, disturbing ER homeostasis occurs in leukemic cells under specific factors [22]. GRP78 has protective properties necessary for the survival of cells in pathological conditions, so increased expression of *GRP78 mRNA* in AML patients is probably due to stress induction.

One of the cell surface antigens associated with the maturation of hematopoietic cells is CD34 (cluster of differentation-CD). This antigen is highly expressed on

the surface of stem cells. $CD34^+$ cells HSCs are located in healthy bone marrow. In the bone marrow of a patient with acute leukemia a fraction of $CD34^+$ cells was shown to contain LSCs [23].

J. Ota et al., based on proteomic studies demonstrated the expression of GRP78 in HSCs in patients with acute leukemia [24]. We observed that patients with AML $CD34^+$ have significantly higher expression of *GRP78 mRNA* compared to patients with AML $CD34^-$. In addition, *GRP78 mRNA* level positively correlated with expression of CD34 on the blast cells. Thus, increased expression of GRP78 may be a result of UPR activation and evasion of apoptosis in leukemic stem cells.

Some authors suggest that UPR response in leukemic cells may occur under the influence of the specific translocation products and genetic changes [24]. Therefore, gene mutations and changes in the karyotype of leukemic cells may significantly affect the activation of the UPR, including GRP78 expression. Schardt et al. found that the *mRNA* expression of proteins involved in the UPR occurs in all cytogenetic risk groups in patients with AML. In addition, the author observed association between deletion of chromosome 7 and activation of the UPR [23]. We observed GRP78 expression in all cytogenetic risk group. There was no significant difference in *GRP78 mRNA* among cytogenetic risk group. *NPM1* gene mutation is considered to be a favorable prognostic factor, while the tandem duplication of *FLT3* gene (*FLT3-ITD*) adversely affects the prognosis and is associated with frequent relapses of AML. UPR activation with expression of *GRP78 mRNA* in bone marrow of AML patients was associated with less frequent incidence of *FLT3* and *NPM1* mutation [21]. In our study, *NPM1* mutation was correlated with lower expression of *GRP78 mRNA*. In addition, the *GRP78 mRNA* level was no statistically different between wild-type and mutation form of *FLT3* gene.

Our results were finally related to the classical prognostic factors such as age at the time of diagnosis and WBC counts. There are limited data about correlation between patient-related risk factors in AML and GRP78 expression. Activation of the UPR response with *GRP78 mRNA* expression was observed in patients with lower levels of white blood cells (median 4.3 x 10^9/L). It was a good prognostic factor in this group. Patients without induction of UPR demonstrated significantly higher WBC count (median 27.05 x 10^9/L). Median age was not significantly different between these groups and it was not a prognostic factor in this study [21]. We did not observe any statistical significant correlation between *GRP78 mRNA* expression and clinical course of AML.

It is known that the expression of GRP78 regulates cell proliferation, tumor cell survival and resistance to chemotherapy in both solid tumors and hematological malignancies. Bagratuni et al. demonstrated that UPR activation correlates with poor prognosis in patients with multiple myeloma [25]. Moreover, D. Bhojwani et al. analyzed the bone marrow of 60 patients with ALL and found significantly higher levels of GRP78 expression among patients with early relapse (<36 months) relative to patients with late recurrent disease (≥36 months) [26]. In opposite to these studies, there are confusing data about prognostic impact of UPR activation and GRP78 expression in AML [19,21,27]. Our results revealed that there was no significant differences in the *GRP78 mRNA* expression level between patients who achieved complete remission after induction therapy and no response patients. Moreover, *GRP78 mRNA* level had no significant effect on the relapse-free survival and overall survival.

In conclusions, our results indicate that GRP78 expression is increased in $CD34^+$ leukemias and has no prognostic impact on clinical outcome in AML.

References

[1] Christ O, Feuring-Buske M, Hiddemann W et al. Pathobiology of acute myeloid leukemia. Med Clin. 2007; 102:290-295
[2] Schroder M, Kauffman RJ. ER stress and the unfolded protein response. Mutat Res 2005; 569:29-63
[3] Ron D, Walter P. Signal integration in the endoplasmic reticulum unfolded protein response. Nat Rev Mol Cell Biol. 2007; 8:519-529
[4] Fu Y, Lee AS. Glucose regulated proteins in cancer progression, drug resistance and immunotherapy. Cancer Biol Ther. 2006; 5:741-744
[5] Bennett JM, Catovsky D, Daniel MT et al. Proposals for the classification of the acute leukaemias. A report of the French-American-British (FAB) cooperative group. Ann Intern Med. 1985;103:620-625
[6] Döhner H, Estey EH, Amadori S et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European Leukemia Net. Blood. 2010; 115: 453-474
[7] Hołowiecki J, Grosicki S, Robak T et al. Polish Adult Leukemia Group (PALG). Addition of cladribine to daunorubicin and cytarabine increases complete remission rate after a single course of induction treatment in acute myeloid leukemia. Multicenter, phase III Study. Leukemia. 2004; 18:989-997

[8] Hołowiecki J, Grosicki S, Kyrcz-Krzemien S et al. Daunorubicin, cytarabine and fludarabine (DAF) for remission induction in relapsed or refractory acute myeloid leukemia. Evaluation of safety, tolerance and early outcome--Polish Adult Leukemia Group (PALG) pilot study. Ann Hematol. 2008; 81:361-367
[9] Hołowiecki J, Grosicki S, Robak T et al. Daunorubicin, Cytarabine, and 2CdA (DAC-7) for remission indiction in "de novo" Adult Acute Myeloid Leukemia Patients. Acta Haematol Pol. 2001; 2002:839-847
[10] Yates J, Glidewell O, Wiernik P et al. Cytosine arabinoside with daunorubicin or adriamycin for therapy of acute myelocytic leukemia: a CALGB study. Blood. 1982; 60:454-462
[11] Wrzesień-Kus A, Robak T, Jamroziak K et al. The treatment of acute myeloid leukemia with mitoxantrone, etoposide and low-dose cytarabine in elderly patients - a report of Polish Acute Leukemia Group (PALG) phase II study. Neoplasma. 2002; 49:405-411
[12] Byrd JC, Mrózek K, Dodge RK et al. Cancer and Leukemia Group B(CALGB 8461). Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). Blood. 2002; 100: 4325-4336
[13] Castaigne S, Chevret S, Archimbaud E et al. Randomized comparison of double induction and timed- sequential induction to a " 3+7" induction in adults with AML; long term analysis of the Acute Leukemia French Association (ALFA) 9000 study. Blood. 2004; 104: 2467-2474
[14] Jurisic V, Srdic-Rajic T, Konjevic G et al. TNF-α induced apoptosis is accompanied with rapid CD30 and slower CD45 shedding from K-562 cells. J Membr Biol. 2011; 239:115-122
[15] Xing X, Lai M, Wang Y et al. Overexpression of glucose-regulated protein 78 in colon cancer. Clin Chim Acta. 2006; 364:308-315.
[16] Fernandez PM, Tabbara SO, Jacobs LK et al. Overexpression of the glucose-regulated stress gene GRP78 in malignant but not benign human breast lesions. Breast Cancer Res Treat. 2000; 59:15-26
[17] Arap MA, Lahdenranta J, Mintz PJ et al. Cell surface expression of the stress response chaperone GRP78 enables tumor targeting by circulating ligands. Cancer Cell. 2004; 6:275-284
[18] Uramoto H, Sugio K, Oyama T et al. Expression of endoplasmic reticulum molecular chaperone Grp78 in human lung cancer and its clinical significance. Lung Cancer. 2005; 49: 55-62
[19] Tanimura A, Yujiri T, Tanaka Y et al. Activation of the unfolded protein response in primary acute myeloid leukemia cells. Int J Hematol. 2011; 94:300-302
[20] Valk PJ, Verhaak RG, Beijen MA et al. Prognostically useful gene-expression profiles in acute myeloid leukemia. N Engl J Med. 2004; 350:1617-1628
[21] Schardt JA, Weber A, Eyholzer M et al. Activation of the unfolded protein response is associated with favorable prognosis in acute myeloid leukemia. Clin Cancer Res. 2009; 15:3834-3841
[22] Khan MM, Nomura T, Chiba T et al. The fusion oncoprotein PML-RARalpha induces endoplasmic reticulum (ER)-associated degradation of N-CoR and ER stress. J Biol Chem. 2004; 279:11814–11824
[23] Jordan CT. The leukemic stem cell. Best Pract Res Clin Haematol 2007; 20:13-18
[24] Ota J, Yamashita Y, Okawa K et al. Proteomic analysis of hematopoietic stem cell-like fractions in leukemic disorders. Oncogene. 2003; 22:5720-5728
[25] Bagratuni T, Wu P, Gonzalez de Castro D et al. XBP1s levels are implicated in the biology and outcome of myeloma mediating different clinical outcomes to thalidomide-based treatments. Blood. 2010; 116:250-253
[26] Bhojwani D, Kang H, Moskowitz NP et al. Biologic pathways associated with relapse in childhood acute lymphoblastic leukemia: a Children's Oncology Group study. Blood. 2006; 108:711-717
[27] Schardt JA, Mueller BU, Pabst T et al. Activation of unfolded protein response in human acute myeloid leukemia. Methods Enzymol. 2011; 489:227-243