Myeloid-derived suppressor cells level and MUC1 expression in de novo acute myeloid leukemia

Abstract
Background: Acute myeloid leukemia (AML) is the most common acute leukemia occurring in adults. It is an aggressive myeloid neoplasm with maturation arrest of myelopoiesis, leading to an accumulation of myeloblasts in the bone marrow and peripheral blood. Objective: To evaluate alterations in myeloid-derived suppressor cells level and MUC1 gene expression in patients with de novo acute myeloid leukemia concerning disease characteristics and response to induction chemotherapy. Patients and methods: The study was performed on 50 AML patients and 50 healthy controls. Detection of myeloid-derived suppressor cells (MDSCs) in peripheral blood was performed by mononuclear separation and flow cytometry. MUC1 gene expression was performed by RNA extraction, reverse transcription, and real-time PCR at Hematology Department Medical Research Institute, Alexandria University. Results: We have demonstrated that AML patients had both increased presence of MDSCs in peripheral blood as well as MUC1 overexpression in comparison to normal controls. MDSCs showed a significant correlation regarding response to induction chemotherapy on day 28. While MDSCs and not MUC1 are associated with inferior response to induction chemotherapy on day 28. Conclusion: The current data suggested that AML patients exhibit an increased presence of MDSCs as well as MUC1 gene overexpression in comparison with normal controls. While MDSCs showed a significant correlation regarding response to induction chemotherapy on day 28, MDSCs and not MUC1 are associated with inferior response to induction chemotherapy on the same day.

Keywords: acute myeloid leukemia, induction response, MUC1 gene, myeloid-derived suppressor cells

Introduction
Acute myeloid leukemia (AML) is a heterogeneous clonal hematopoietic stem cell malignancy in which immature hematopoietic cells proliferate and accumulate in bone marrow, peripheral blood, and other tissues. Most cases of AML have no apparent cause. Some patients may have the emergence of abnormal myeloid clones in the bone marrow, termed clonal hematopoiesis, years before diagnosis [1]. Myeloid-derived suppressor cells (MDSCs) are a critical component of the tumor microenvironment that modulates interactions between immune effector cells and malignant cells. These MDSCs are newly identified, heterogeneous population of immature myeloid cells that are characterized by the ability to suppress both innate and adaptive immune responses [2]. MDSCs play a critical role in promoting immune tolerance and disease growth. The role of MDSCs in AML has not been well described. The role of MDSCs in solid tumors has been extensively characterized as protumorigenic [2, 3, 4]. In intensive clinical studies, circulating and/or infiltrating MDSCs at the tumor site were associated with poor prognosis in patients with solid tumors [5]. Removing MDSCs might contribute to restoring immune surveillance. Meanwhile, conflicting roles have been reported in hematological malignancies [6–10]. Mucin1 (MUC1) is a cell membrane glycoprotein, and it is normally expressed at low levels on the apical surfaces of epithelial cells. MUC1 is translated as a single polypeptide that undergoes autocleavage into two subunits, which in turn form a stable noncovalent heterodimer at the cell surface. The MUC1 N-terminal subunit (MUC1-N) contains glycosylated tandem repeats, which are characteristic features of the mucin family [11, 12]. MUC1-N forms a complex with the transmembrane MUC1 C-terminal subunit (MUC1-C). MUC1-C interacts with receptor tyrosine kinases such as FMS-like tyrosine kinase 3 (FLT3) at the cell membrane [13]. In these ways, MUC1-C has been shown to mediate critical aspects of oncogenesis, including cell proliferation, autonomous self-renewal, tissue invasion, and resistance to apoptosis and cytotoxic injury [14–19]. It has been recently identified that MUC1 may play an important role in modulating the immunosuppressive milieu of the tumor microenvironment [20].

Participants and methods
This study was conducted on 100 subjects that were classified into 50 de novo adult AML patients where promyelocytic leukemia cases were excluded from the present study. All patients were recruited from the Hematology Department, Medical Research Institute, Alexandria, Egypt.
University. A total of 50 healthy controls with similar age and sex are identified as a control group. This study was performed in the period from September 2018 to October 2019. All patients enrolled in the present study received induction chemotherapy (which includes standard-dose cytarabine 100–200 mg/m² continuous infusion × 7 days with idarubicin 12 mg/m² or daunorubicin 60–90 mg/m² × 3 days) [21]. All patients in our present study were subjected to a full medical checkup, such as clinical examination, complete blood count (CBC) with blood film examination, bone marrow examination, and the World Health Organization (WHO) classification. Bone marrow examination was performed at diagnosis and on day 28 post-induction chemotherapy was performed to evaluate response to induction chemotherapy. This study was approved by the local ethics committee at the Medical Research Institute, Alexandria University, Egypt. Informed consent from the patients was obtained before sample collection and after a brief explanation of research objectives.

Response assessment

Response assessment was performed on day 28. Where morphologic complete response (CR) was defined as an absolute neutrophil count >1,000/mL, with platelets ≥100,000/mL, bone marrow <5% blasts in an aspirate with spicules, no blasts with Auer rods, and no residual evidence of extramedullary disease were found. Partial response (PR) decreases of at least 50% in the percentage of blasts to 5–25% in the bone marrow aspirate and the normalization of blood counts. No response is defined as the failure to attain CR or PR after induction chemotherapy [21].

Detection of MDSCs by flow cytometry

The sample is a fresh EDTA anticoagulated peripheral blood sample, and peripheral blood mononuclear cells were isolated using the Ficoll mononuclear separation principle [22]. After two washes, labeled antihuman monoclonal antibodies (mAbs) were used for stainings, such as HLA-DR FITC (Immunostep, Spain), CD11b FITC (Immunostep, Spain), and CD 33 PE (Immunostep, Spain) monoclonal antibodies. The three tubes were incubated in the dark for 40 min and washed twice by adding 1–2 mL of phosphate-buffered saline (PBS) to each tube.

Samples were acquired and the frequency of the MDSCs subsets was analyzed by flow cytometry Sysmex Partec CUBE 8 using Cytflow software. Sequential gating was performed; first, AML blasts are gated out based on previously clinically defined phenotype (HLA-DR positive blasts were gated out) [23]. Second, gating of HLA-DR negative/low population of cells and then sequential gating of CD 11b and CD 33 double-positive cells [23]. The gating strategy is shown in figure 1.

**MUC1 gene expression by real-time PCR**

RNA extraction was performed via Qiagen Blood QIAamp genomic RNA extraction kit and under sterile conditions using a UV laminar flow cabinet according to manufacturer instructions. The quality and quantity of RNA samples were analyzed and controlled at the end of extraction by NanoDrop 2000 spectrophotometer (Thermo Scientific). Reverse transcription (RT) was performed using QuantiTect Reverse Transcription Kit (Qiagen). The quality and quantity of DNA samples were analyzed and controlled at the end of RT by NanoDrop 2000 spectrophotometer. SYBR Green real-time PCR preparation was performed under sterile conditions using a UV laminar flow and the reaction was performed using Rotor-Gene Q cycler from Qiagen.



| **Target gene** | **MUC1** |
|----------------|----------|
| **Catalog number** | QT00015379 |
| **Lot number** | 269867127 |
| **Forward** | 5'-CTCACCCGCGAACTAC-3' |
| **Reverse** | 5'-GTCGGCCGAAAGAAGACTAC-3' |
| **Product size** | 312 |

**Results**

With regard to the age of AML patients, it had a mean of 45.38 ± 14.35 years. The hemoglobin value of the studied group had a mean of 7.87 ± 2.05 g/dL, while the WBC count mean value was 64.34 ± 94.19 × 10^9/L, where 60% of the patients had leukocytosis, while 20% had leucopenia. Also, 90% of AML patients had thrombocytopenia. The blast percentage in peripheral blood was 40.10 ± 33.25%. All cases were diagnosed and subtyped according to WHO classification including morphology, immunophenotyping, and cytogenetic studies as shown in table II. Also, FAB classification was performed and showed the following frequencies: M1 24%, M2 26%, M4 24% (6% of which were M4eso), and M5 24%. Regarding the response to induction chemotherapy, 44% of AML cases were responsive to chemotherapy, 32% achieved CR1, and 12% achieved PR, while 12% were nonresponsive to induction chemotherapy and 42% died very early before evaluation of treatment response. The results are shown in figure 2.

MDSCs showed a significantly higher level in peripheral blood of AML patients with a mean value of 8.02 ± 8.11% among the gated HLA-DR negative cells, to normal controls with a mean of 0.20 ± 0.42%. MDSCs showed significant correlation as regard WBCs count and blast percentage in peripheral blood as well as bone marrow (Tab. III). MDSCs showed a significant correlation regarding response to induction chemotherapy on day 28 (p = 0.002). As regards patients achieving CR, MDSCs showed a lower level with a mean value of 2.44 ± 2.58% compared with those achieving a PR (mean = 8.67 ± 8.50%). Also, patients achieving CR had...
Fig. 1. Gating of HLA-DR negative/low population of cells (A). Sequential gating of CD 11b and CD 33 double-positive cells (B)

Fig. 2. Distribution of the studied AML patients according to response to induction chemotherapy on day 28 (n = 50). Accordingly, they were divided into those achieving complete response (CR1), partial response (PR), nonresponsive patients, and those who died early before the evaluation of treatment response as well as those who refused chemotherapy.
significantly lower MDSCs level compared to nonresponsive patients (mean = 11.17 ± 11.65%) (p = 0.037) as well as patients who died (mean = 11.52 ± 7.79%). As shown in figure 3. However, there was no significant correlation between MDSCs and specific morphologic subtypes as well as blasts phenotype.

A receiver operating characteristic (ROC) curve for the level of MDSCs in peripheral blood was performed at diagnosis to distinguish AML patients achieving CR from nonresponsive patients (NR) after induction chemotherapy. A cutoff value of >10% MDSCs in peripheral blood (sensitivity of 66.67% and specificity of 62.5%) between patients achieving CR and nonresponsive patients.

As regards MUC1 gene expression using 2ΔΔCt, it showed a significantly higher level in AML patients with a median value of 8.80 (3.57–18.82) than normal controls with a median of 0.75 (0.39–1.41).

A ROC curve was performed as regards MUC1 gene expression to distinguish AML cases from normal controls showing a cutoff value of >5.38 having a sensitivity of 66% and a specificity of 90% (Fig. 4).

Where, AML cases showed positive MUC1 gene expression in 88%, while only 12% showed MUC1 gene under expression. As regards the correlation between MUC1 gene expression and the patients’ age, CBC parameters, and CRP, there was no significance (p > 0.05). Also, there was no significant correlation between MUC1 gene expression level at different laboratories, and clinical data as
well as therapeutic response on day 28 post-induction chemotherapy (Tab. IV). Also, there was no significant correlation between MDSCs and MUC1 gene expression.

### Discussion

The present work aimed at the study of MDSCs level and MUC1 gene expression in de novo AML patients. In the present study, MDSCs showed a significantly higher level in AML patients than in normal controls. This was in concordance with Pyzer et al. with a mean value of circulating MDSCs 7.94% (range: 1.70–17.0) and 0.2% (range: 0.02–0.88), respectively [23]. Moreover, similar results were reported by Alex et al. [25], Lv et al. [26], and Sun et al. [27]. Interestingly, MDSCs were elevated in peripheral blood in different hematological malignancies including lymphoma, multiple myeloma, and leukemia [26]. Also, in MDS, there was a higher MDSCs level in PB as well as in MM [28, 29, 30]. Also, CML patients showed increased PMN-MDSCs and M-MDSCs subsets at diagnosis, have been shown to return to normal levels after treatment with the tyrosine kinase inhibitor and M-MDSCs frequency has been proposed as a prognostic factor in CML patients receiving the TKI dasatinib [31]. Besides, CLL and DLBL patients showed the accumulation of myeloid-derived suppressor cells in peripheral blood [32, 33]. In the present series, there was no significant correlation between MDSCs and the age of AML patients (p = 0.208) which was consistent with Sun et al. [27]. Also, according to Alex et al. there was no significant correlation as regards patients’ age [25]. The present study MDSCs showed a significant correlation with blast percentage in peripheral blood as well as bone marrow blast percentage and WBCs count. Following Pyzer et al. [23] MDSCs are expanded in the presence of AML blasts. According to Alex et al. [25] there was a significant positive correlation of MDSC with WBC counts at diagnosis. On the contrary, Sun et al. [27] stated that there was no significant correlation between the MDSCs level with WBC counts. This difference may be explained by the different ethnic backgrounds and the difference in sample size.

In the present study, there was no significant correlation with different morphologic subtypes according to FAB classification. This was similar to Sun et al., where there was no significant difference of MDSC between AML-M4 and M3, M2 but MDSCs in AML-M5 were significantly lower than that in AML-M2, M3, and M4 [27].

In this study, there was no significant correlation between MDSCs and CD34 expression on blast cells. However, according to Alex et al., there was a significant negative correlation with CD34 expression on blast cells at diagnosis [25]. This difference is related to the fact that CD34 expression was enrolled in this study as a qualitative value but as regards Alex et al. work it was quantitative.

In this study, patients with low MDSCs showed better outcomes as regards the response to induction chemotherapy on day 28. Although in this study, the patient’s survival could not be detected, according to Cheong et al. [34] patients with higher MDSCs group had worse outcomes with a significantly shorter overall survival and leukemia-free survival. Besides, Sun et al. [27] observed a significantly lower number of MDSCs in the blood of patients at complete remission. The higher proportion of early deaths in this study was related to

### Table IV. Comparison between high and low MUC1 gene expression in AML cases as regards different clinical and laboratory parameters

| Clinical parameters       | MUC1 low ≤ 5.38 (n = 7) | MUC1 high > 5.38 (n = 21) | p       |
|---------------------------|--------------------------|---------------------------|---------|
| Bone marrow blast (%)     | (n = 17)                 | (n = 33)                  |         |
| Min.–Max.                 | 3.0–90.0                 | 0.0–98.0                  | 0.126   |
| Mean ± SD                 | 47.94 ± 30.47            | 36.06 ± 34.34             |         |
| Median (IQR)              | 40.0                     | 26.0                      |         |
| Complete response         | (n = 7)                  | (n = 21)                  | 1.000   |
| Partial response          | 12 (57.1%)               | 4 (19.0%)                 |         |
| Non-responsive            | 1 (14.3%)                | 5 (23.8%)                 |         |
| Blast (%) in peripheral blood | (n = 7)                 | (n = 21)                  |         |
| Min.–Max.                 | 16.0–91.0                | 20.0–95.0                 | 0.367   |
| Mean ± SD                 | 61.41 ± 23.75            | 53.36 ± 25.06             |         |
| Median (IQR)              | 65.0                     | 48.0                      |         |
| CD 19                     | (n = 17)                 | (n = 33)                  |         |
| Negative                  | 15 (88.2%)               | 31 (93.9%)                | 0.597   |
| Positive                  | 2 (11.8%)                | 2 (6.1%)                  |         |
| CD 4                      | (n = 17)                 | (n = 33)                  |         |
| Negative                  | 16 (94.1%)               | 27 (81.8%)                | 0.398   |
| Positive                  | 1 (5.9%)                 | 6 (18.2%)                 |         |
| CD 34                     | (n = 17)                 | (n = 33)                  |         |
| Negative                  | 15 (88.2%)               | 27 (81.8%)                | 0.699   |
| Positive                  | 2 (11.8%)                | 6 (18.2%)                 |         |
| FAB classification        | (n = 17)                 | (n = 33)                  |         |
| M1                        | 5 (29.4%)                | 7 (21.2%)                 | 0.616   |
| M2                        | 3 (17.6%)                | 10 (30.3%)                |         |
| M4                        | 4 (23.5%)                | 5 (15.2%)                 |         |
| M4 ESO                    | 2 (11.8%)                | 1 (3.0%)                  |         |
| M5                        | 3 (17.6%)                | 9 (27.3%)                 |         |
| M6                        | 0 (0.0%)                 | 1 (3.0%)                  |         |
| Splenomegaly              | (n = 17)                 | (n = 33)                  |         |
| Absent                    | 14 (82.4%)               | 25 (75.8%)                | 0.728   |
| Present                   | 3 (17.6%)                | 8 (24.2%)                 |         |
| Lymphadenopathy           | (n = 17)                 | (n = 33)                  |         |
| Absent                    | 14 (82.4%)               | 23 (69.7%)                | 0.499   |
| Present                   | 3 (17.6%)                | 10 (30.3%)                |         |
infection and febrile neutropenia, which were the major causes of early mortality.

In this study, \( MUC1 \) gene expression showed a significantly higher level in AML patients than in normal controls. This was in accordance with Tagde et al’s. work which stated that \( MUC1 \) expression was significantly elevated in AML cells as compared to that in normal bone marrow cells [35]. Moreover, \( MUC1 \) is overexpressed in human cell lines and a majority of primary samples obtained from AML patients at the time of presentation and relapse [36, 37, 38].

**Conclusion**

We have demonstrated that MDSCs are expanded in AML patients and they appear to impact the clinical course and prognosis of AML cases. Also, the \( MUC1 \) gene is overexpressed in AML patients compared to normal controls. Additionally, using specific MDSC inhibitors or via \( MUC1 \) inhibition, could pave the way for improved responses to immune therapies in AML.

**Conflicts of interest**

There are no conflicts of interest.

**Financial support**

None.

**Ethics**

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

**Authors’ contributions**

SN – manuscript writing. All authors – revision of manuscript and paper design.
References

[1] Stein EM, Shukla N, Altman JK. Acute myeloid leukemia. In: ASH SAP text book. 7th ed. Washington: American Society of Hematology; 2019. p.580–92.

[2] Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391–405.

[3] Giese MA, Hind LE, Huttenlocher A. Neutrophil plasticity in the tumor microenvironment. Blood 2019;133:2159–67.

[4] Tesi RJ. MDSC; the most important cell you have never heard of. Trends Pharmacol Sci 2019;40:4–7.

[5] Wang PF, Song SY, Wang TJ, et al. Prognostic role of pretreatment circulating MDSCs in patients with solid malignancies: a meta-analysis of 40 studies. Oncoimmunology 2018;7:e1494113.

[6] Höpken UE, Rehm A. Targeting the tumor microenvironment of leukemia and lymphoma. Trends Cancer 2019;5:351–64.

[7] Malek E, de Lima M, Letterio JJ, et al. Myeloid-derived suppressor cells: the green light for myeloma immune escape. Blood Rev 2016;30:341–8.

[8] Betsch A, Rutgeerts O, Fever SY, et al. Myeloid-derived suppressor cells in lymphoma: the good, the bad and the ugly. Blood Rev 2018;32:490–8.

[9] Curran EK, Godfrey J, Kline J. Mechanisms of immune tolerance in acute myeloid leukemia and lymphoma. Trends Immunol 2017;38:513–25.

[10] Vetro C, Romano A, Ancora F, et al. Clinical impact of the immunome in lymphoid malignancies: the role of myeloid-derived suppressor cells. Front Oncol 2015;5:104.

[11] Kufe DW. Mucins in cancer: function, prognosis and therapy. Nat Rev Cancer 2009;9:874–85.

[12] Kufe DW. Functional targeting of the MUC1 oncogene in human cancers. Cancer Biol Ther 2009;8:1197–203.

[13] Li S, Yin L, Stroopinsky D, et al. MUC1-C oncproteon promotes FLT3 receptor activation in acute myeloid leukemia cells. Blood 2014;123:734–42.

[14] Alam M, Rajabi H, Ahmad R, Jin C, Kufe D. Targeting the MUC1-C oncoprotein inhibits self-renewal capacity of breast cancer cells. Oncotarget 2014;5:2622–34.

[15] Schroeder JA, Adriance MC, Thompson MC, Camenisch TD, Gendler SJ. MUC1 alters b-catenin-dependent tumor formation and promotes cellular invulsion. Oncogene 2003;22:1324–32.

[16] Ren J, Agata N, Chen D, et al. Human MUC1 carcinoma-associated protein confers resistance to genotoxic anticancer agents. Cancer Cell 2004;5:163–75.

[17] Sahraei M, Roj LD, Curry JM, et al. MUC1 regulates PDGFA expression during pancreatic cancer progression. Oncogene 2012;31:4935–45.

[18] Nath S, Daneshvar K, Roj LD, et al. MUC1 induces drug resistance in pancreatic cancer cells via upregulation of multidrug resistance genes. Oncogenesis 2013;2:e51.

[19] Raina D, Uchida Y, Kharbanda A, et al. Targeting the MUC1 oncprotein downregulates HER2 activation and abrogates trastuzumab resistance in breast cancer cells. Oncogene 2014;33:3422–31.

[20] Stroopinsky D, Kufe D, Avigan D. MUC1 in hematological malignancies. Leuk Lymphoma 2016;57:2489–98.

[21] O’Donnell MR, Tallman MS, Abboud CN, et al. Acute myeloid leukemia, version 3.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw; 2020:360–83. https://www.nccn.org/professionals/physician_gls/default.aspx#site [accessed 12 March 2020].

[22] Healthcare Bio-Sciences. Isolation of mononuclear cells: Methodology and applications. Sweden: GE Healthcare Bio-Sciences AB; 2014;1–20.

[23] Pyzer AR, Stroopinsky D, Rajabi H, et al. MUC1-mediated induction of myeloid-derived suppressor cells in patients with acute myeloid leukemia. Blood 2017;129:1791–801.

[24] Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2-DDCT method. Methods 2001;25:402–8.

[25] Alex AA, Tartour E, Gey A, et al. Myeloid derived suppressor cells in acute leukemia and its association with conventional cytogenetic and molecular risk factors. Blood 2012;120:1446.

[26] Lv M, Wang K, Huang XJ. Myeloid-derived suppressor cells in hematological malignancies: friends or foes. J Hematol Oncol 2019;12:105.

[27] Sun H, Li Y, Zhang ZF, et al. Increase in myeloid-derived suppressor cells (MDSCs) associated with minimal residual disease (MRD) detection in adult acute myeloid leukemia. Int J Hematol 2015;102:579–86.

[28] Chen X, Eksioglu EA, Zhou J, et al. Induction of myelodysplasia by myeloid-derived suppressor cells. J Clin Invest 2013;123:4595–611.

[29] Ramachandran IR, Martner A, Pisklakova A, et al. Myeloid-derived suppressor cells regulate growth of multiple myeloma by inhibiting T cells in bone marrow. J Immunol 2013;190:3815–23.

[30] Wang Z, Zhang L, Wang H, et al. Tumor-induced CD14+HLA-DR−/low myeloid-derived suppressor cells correlate with tumor progression and outcome of therapy in multiple myeloma patients. Cancer Immunol Immunother 2015;64:389–99.

[31] Giallongo C, Parrinello N, Tibullo D, et al. Myeloid derived suppressor cells (MDSCs) are increased and exert immunosuppressive activity together with polymorphonuclear leukocytes (PMNs) in chronic myeloid leukemia patients. PLoS One 2014;9:e101848.

[32] Jitschin R, Braun M, Büttner M, et al. CLL-cells induce IDOhi methyltransferase 1 and represses tumor suppressor genes in acute myeloid leukemia patients. PLoS One 2014;9:e101848.

[33] Jitschin R, Braun M, Büttner M, et al. CLL-cells induce IDOhi methyltransferase 1 and represses tumor suppressor genes in acute myeloid leukemia patients. PLoS One 2014;9:e101848.

[34] Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2-DDCT method. Methods 2001;25:402–8.

[35] Pyzer AR, Stroopinsky D, Rajabi H, et al. MUC1-mediated induction of myeloid-derived suppressor cells in patients with acute myeloid leukemia. Blood 2017;129:1791–801.

[36] Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2-DDCT method. Methods 2001;25:402–8.

[37] Alex AA, Tartour E, Gey A, et al. Myeloid derived suppressor cells in acute leukemia and its association with conventional cytogenetic and molecular risk factors. Blood 2012;120:1446.

[38] Lv M, Wang K, Huang XJ. Myeloid-derived suppressor cells in hematological malignancies: friends or foes. J Hematol Oncol 2019;12:105.

[39] Ramachandran IR, Martner A, Pisklakova A, et al. Myeloid-derived suppressor cells regulate growth of multiple myeloma by inhibiting T cells in bone marrow. J Immunol 2013;190:3815–23.

[40] Wang Z, Zhang L, Wang H, et al. Tumor-induced CD14+HLA-DR−/low myeloid-derived suppressor cells correlate with tumor progression and outcome of therapy in multiple myeloma patients. Cancer Immunol Immunother 2015;64:389–99.

[41] Giallongo C, Parrinello N, Tibullo D, et al. Myeloid derived suppressor cells (MDSCs) are increased and exert immunosuppressive activity together with polymorphonuclear leukocytes (PMNs) in chronic myeloid leukemia patients. PLoS One 2014;9:e101848.

[42] Jitschin R, Braun M, Büttner M, et al. CLL-cells induce IDOhi methyltransferase 1 and represses tumor suppressor genes in acute myeloid leukemia patients. PLoS One 2014;9:e101848.

[43] Jitschin R, Braun M, Büttner M, et al. CLL-cells induce IDOhi methyltransferase 1 and represses tumor suppressor genes in acute myeloid leukemia patients. PLoS One 2014;9:e101848.

[44] Jitschin R, Braun M, Büttner M, et al. CLL-cells induce IDOhi methyltransferase 1 and represses tumor suppressor genes in acute myeloid leukemia patients. PLoS One 2014;9:e101848.
[37] Fatrai S, Schepers H, Tadema H, Vellenga E, Daenen SMGJ, Schuringa JJ. Mucin1 expression is enriched in the human stem cell fraction of cord blood and is upregulated in majority of the AML cases. Exp Hematol 2008;36:1254–65.

[38] Yin L, Wu Z, Avigan D, et al. MUC1-C oncoprotein suppresses reactive oxygen species-induced terminal differentiation of acute myelogenous leukemia cells. Blood 2011;117:4863–70.