

REVIEW

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Genetic methylation and lymphoid malignancies: biomarkers of tumor progression and targeted therapy

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Abstract

Lymphoid malignancies, mainly including lymphocytic leukemia and lymphoma, are a group of heterogeneous diseases. Although the clinical outcome of patients has been significantly improved with current immuno-chemotherapy, definitive biomarkers remain to be investigated, particularly those reflecting the malignant behavior of tumor cells and those helpful for developing optimal targeted therapy. Recently, genome-wide analysis reveals that altered genetic methylations play an important role in tumor progression through regulation of multiple cellular transduction pathways. This review describes the pathogenetic effect of the aberrant genetic methylation in lymphoid malignancies, with special emphasis on potential therapeutic strategies targeting key signaling networks.

Keywords: Methylation, Leukemia, Lymphoma, Biomarker, Targeted therapy

Introduction

Lymphoid malignancies, mainly including lymphocytic leukemia and lymphoma, are a group of disorders that originate from neoplastic transformation of lymphocytes. Diseases vary in cells of origin, histologic appearances, molecular biology, clinical features and disease prognosis. Thus, searching for biomarkers closely related to tumor progression is critical to better understand the disease pathogenesis and to develop subsequent targeted therapy.

DNA methylation plays a pivotal role in transcriptional regulation. Aberrant promoter hypermethylation has been observed in cancer cells, which is responsible for the transcriptional silencing of tumor suppressor genes [1,2]. For example, tumor suppressor genes, such as *p15* (*CDKN2B*) [3], *p16* (*CDKN2A*) [4], *p57* (*CDKN1C*) [5], *p73* (*TP73*) [6], *SHP-1* [7] and *DAPK* [8], are frequently hypermethylated and related to tumor progression in lymphoid malignancies.

In this review, we described recent advances on alterations of genetic methylation profiling in lymphoid malignancies and highlighted their effects on specific signaling

pathways involved in disease progression, which may be helpful in identifying strategies of targeted therapy.

Part I: Genome-wide methylation in lymphoid malignancies

Acute lymphoblastic leukemia (ALL)

Acute lymphoblastic leukemia (ALL) is derived from malignant proliferation of immature lymphoblast cells committed to B- or T-cell lineage. They are the most common, and some of the most curable, tumors in children. ALL has lower prevalence in adults. However, patients usually have much poorer disease outcome.

In T-ALL, methylation pattern of 27 T-ALL-related genes were assessed by methylation specific-polymerase chain reaction (MS-PCR). These genes selected have crucial roles involved in cell cycle arrest (*p15*, *p16*, *p57* and *LATS-2*), apoptosis (*TMS1*, *APAF-1*, *DAPK* and *DIABLO*), differentiation regulation (*NES-1*), cell adhesion and metastasis process (*CDH1*, *CDH13*, *ADAMTS1* and *ADAMTS5*), tumor suppression (*LATS-1* and *PTEN*), WNT pathway (*DKK-3*, *WIF-1*, *sFRP-1*, *sFRP-2*, *sFRP-4* and *sFRP-5*), JAK-STAT pathway (*PTPN6* (*SHP-1*)), p53 pathway (*p14*, *p73* and *PPP1R13B* (*ASPP-1*)), ubiquitination (*PARK-2*) and tyrosine kinase (*SYK*). Most of the T-ALL patients (44/50 cases) showed hypermethylation in at least one of these analyzed genes, particularly genes

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such as *NES-1*, *ADAMTS5*, *WIF-1* and *sFRP-1* (Additional file 1) [9]. Patients were classified into two distinct groups according to the existence of CpG island methylator phenotype (CIMP): CIMP-positive, with three or more hypermethylated genes, and CIMP-negative, with two or less hypermethylated genes. Clinically, CIMP-positive patients presented significantly shorter disease-free survival (DFS) and overall survival (OS) than those of CIMP-negative counterparts.

A genome-wide study was performed on 19 *ETV6-RUNX1*-positive pediatric precursor B-ALL patients and revealed a unique DNA hypermethylation signature at diagnosis compared to remission. Associated genes were mostly implicated in cell fate commitment, gene regulation, and DNA binding where DNA methylation may have impaired gene function through transcriptional regulation. Interestingly, 15 hypermethylated genes were recurrent in B-ALL patients irrespective of the cytogenetic subtypes, including genes involved in cell cycle arrest (*MYOD1* and *BTG4*), cell development (*FOXE3*, *TCF3*, *PAX5* and *RAG1*), differentiation (*PTPRZ1*, *PPARG* and *IKZF1*) and WNT pathway (*sFRP-1*) [10].

Moreover, analysis of CpG methylation not only allowed T-ALL and B-ALL classification, but also distinguished subtypes among B-ALL patients. Methylation status of 416 methylation-involved or ALL-related genes was determined by methylation array in 401 patients with ALL [11]. Many of these genes were involved in key cellular functions like cell adhesion, apoptosis, proliferation and growth. Precursor B-ALL patients showed remarkably lower median methylation level than T-ALL patients. Methylation patterns clearly separated patients from the main cytogenetic subtypes of precursor B-ALL, such as high hyperdiploidy, t(12;21), 11q23, and t(1;19). Hypermethylation of *COBL*, *CPVL*, *EVC*, *LRP1B*, *PAX8*, *PCDHGA12* and *SPON2* were correlated with favorable prognosis.

Methylation status may also influence response to treatment in ALL. In a cohort study of initial diagnosed and relapsed matched B-ALL patients, genomic methylation level was distinctly higher in relapse than at newly diagnosis. A total of 905 genes were preferentially hypermethylated and 79 genes were hypomethylated. Integration analysis of methylation with gene expression profile and copy number abnormalities revealed six genes closely related to disease relapse. Among them, four genes (*CDKN2A*, *COL6A2*, *PTPRO* and *CSMD1*) were hypermethylated, down-regulated and focally deleted, and two genes (*NOTCH4* and *TOP1MT*) were hypomethylated, up-regulated and focally amplified [12]. Of these genes, *CDKN2A* is an important tumor suppressor which controls cell cycle by stabilizing p53. *PTPRO* encodes a receptor-type protein tyrosine phosphatase, which inhibits cell proliferation and induces apoptosis.

Chronic lymphocytic leukemia (CLL)

Chronic lymphocytic leukemia (CLL) is an indolent disease with clonal expansion of mature neoplastic B cells. Somatic mutation status of the immunoglobulin heavy-chain variable (*IGHV*) gene is an indicator of favorable prognosis [13].

Genome-wide methylation analysis was performed in 10 CLL patients. An average of 4.8% of CpGs analyzed was aberrantly methylated compared with normal neutrophils. One-hundred-and-seventy-three genes were differentially methylated [14]. This study identified a hypermethylated gene, *GRM7*, which inhibited cAMP and induced cell apoptosis. Another methylation array covering 14495 genes was performed in 23 CLL cases. Significant difference in methylation pattern was observed between *IGHV*-unmutated and *IGHV*-mutated CLL subgroups, with 64 genes differentially methylated. Hypermethylated tumor suppressor genes (*ABI3*, *SCGB2A1*, *VHL*, *GPX3*, *IGSF4* and *SERPIND5*) were identified in unmutated CLL. In mutated cases, hypermethylation genes were involved in cell proliferation and NF- κ B pathway (*ADORA3*, *AIRE*, *CARD15*, *LOC340061*, *UNC5CL* and *LDOC1*) and MAPK pathway (*PRF1*, *FABP7*) [15].

Methylation profiling is also indicative in CLL prognosis prediction. Genome-wide analysis of methylated CpG amplification, coupled with promoter microarray, identified 22 of 280 aberrantly methylated genes in 78 CLL patients, compared to normal B cells from 10 healthy volunteers. These genes were enriched in cellular functions, including cell growth and differentiation, tissue and organ development, tissue morphology, cancer, cell death and cell cycle regulation [16]. Twenty-seven genes were mapped to the neighboring genetic region of *TP53* in chromosome 17. Among these genes, *PRIMA1*, *TFAP4*, *SIRT2* and *TP53INP2* were previously reported to functionally interact with p53. Bisulfite pyrosequencing further confirmed hypermethylation status of 19 candidate genes (*SOX11*, *DLX1*, *FAM62C*, *SOX14*, *RSP01*, *ADCY5*, *HAND2*, *SPOCK*, *ING1*, *PRIMA1*, *BCL11B*, *LTBP2*, *NR2F2*, *GALGT2*, *LHX1*, *DLX4*, *KLK10*, *TFAP2* and *APP*). Survival analysis showed that *LINE*, *APP*, *SALL1* and *PRIMA1* were correlated with shorter OS.

Malignant lymphoma

Malignant lymphoma mainly includes non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL). Its incidence is increasing and now ranges among the tenth most frequent cancers worldwide.

Diffuse large B-cell lymphoma (DLBCL)

Diffuse large B-cell lymphoma (DLBCL) is one of the most common NHL. Two biologically distinct subtypes are identified by gene expression profiling: germinal center B-cell-like (GCB) DLBCL and activated B-cell-like (ABC) DLBCL [17].

Genome-wide methylation was analyzed in 24 GCB-DLBCL and 21 ABC-DLBCL patients. The CpGs of 12 genes showed a hypermethylation pattern in both DLBCL subtypes, including genes involved in cell cycle arrest (*CDKN1C* and *MYOD1*), apoptosis (*GDNF*), Rho pathway (*DLC1*), transcription factors (*AR*, *GATA4*, *NEUROD1*, *ONECUT2* and *TFAP2A*), receptor proteins (*DRD2* and *GRIN2B*) and metabolism process (*MTHFR*). Methylation status of genes *FLJ21062* (*C7orf63*), *ONECUT2* and *GNMT* differed between GCB-DLBCL and ABC-DLBCL. In addition, *FLJ21062*, *BNIP3*, *MGMT*, *RBPI*, *GATA4*, *IGSF4* and *CRABP1* showed significantly increased levels of DNA methylation with decreased gene expression [18].

Another study measured gene methylation status in 69 DLBCL patients treated with Rituximab combined with CHOP regimen (cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone). Supervised analysis identified 263 differentially methylated genes between GCB-DLBCL and ABC-DLBCL subtypes. These genes were mostly enriched in antigen processing-presentation pathway, cytokine and inflammatory pathway. Integrated data with expression profile further confirmed 16 genes (*LANCL1*, *KCNK12*, *SORL1*, *CXorf57*, *SOX9*, *KIAA0746*, *ASPHD2*, *ARHGAP17*, *IKZF1*, *PMM2*, *IL12A*, *JDP2*, *PAK1*, *GALNS*, *FGD2* and *LYAR*) that distinguished these two subtypes with 92%-98% accuracy [19]. Some of these genes were previously recognized in signaling pathways, such as JAK-STAT (*IL12A*) and Rho pathway (*ARHGAP17*, *PAK1* and *FDG2*).

Mantle cell lymphoma (MCL)

Mantle cell lymphoma (MCL) is an aggressive B-NHL that arises from naïve B cells in the mantle zone of the lymph nodes. It is characterized by t(11;14)(q13;q32) translocation and subsequent overexpression of *CCND1*.

Methylation study in MCL cell lines found 331 differentially expressed genes mapped to autosomal chromosomes. Pathway analysis revealed that top cellular functions represented cell death, cell cycle, cellular growth and proliferation. MassARRAY assay of 25 candidate genes in seven MCL cell lines and normal B cells showed 20 genes hypermethylated in more than one MCL cell line, encompassing cell differentiation (*SOX9*), cell adhesion (*CDH1*), cell cycle (*GOS2*) and apoptosis (*LGALS3*), p53 pathway (*CDC14B*) and PI3K pathway (*THEM4*), transcription factors (*AHR*, *HOXA9*, *NR2F2*, *FOXCl*, *TWIST1*) and others with unknown functions (*ROBO1*, *NPTX2*, *CYB1B1*, *GPX3*, *MAL*, *PAX6*, *PTPRG1*, *TFPI2*). Among them, seven genes, whose methylation was reported in different tumor models, appeared to be frequently methylated in primary cells of 38 MCL patients (*SOX9*, *HOXA9*, *AHR*, *NR2F2*, *ROBO1*, *NPTX2* and *CDH1*). MCL patients with two or more methylated genes had higher proliferation index Ki-67, increased number of chromosomal

abnormalities and shorter OS than those with none or only one methylated gene. Methylation of tumor suppressor genes *SOX9* and *HOXA9* were also associated with the above-mentioned clinicopathological parameters and poor disease outcome in MCL [20].

Another genome-wide methylation analysis was performed in primary MCL samples and found significant aberrations in promoter methylation pattern compared with normal B cells. DNA methylation was quantified for over 14000 gene promoter regions. Integration of methylation and expression profiling data revealed 4 hypermethylated genes (*CDKN2B*, *HOXD8*, *MLF-1* and *PCDH8*) and 4 hypomethylated genes (*CD37*, *HDAC1*, *NOTCH1* and *CDK5*). Among these genes, *CDKN2B* and *CDK5* are involved in cell cycle control. *HDAC1* and *NOTCH1* are known targets for treating lymphoid malignancies. *HOXD8*, *MLF-1* and *PCDH8* are implicated in multiple tumor types. *CD37* belongs to tetraspanin transmembrane family and is expressed mainly in B cells [21].

Hodgkin's lymphoma (HL)

Screening of methylated genes was performed in HL KM-H2 cell line by microarray analysis before and after treatment with 5-aza-2'-deoxycytidine. Thirty tumor suppressive genes were identified, including genes in cellular adhesion (*CADM1* (*IGSF4*), *CD44* and *THBS1*), growth arrest (*GADD45*), p53 pathway (*ZMAT3*) and two transcription factors (*IRF7* and *KLF6*). Among them, *CADM1* was further confirmed methylated and down-regulated in primary HL cells. Restoration of *CADM1* expression in HL cells decreased cell survival and increased their sensitivity to apoptosis, demonstrating that *IGSF4* silencing by CpG methylation inhibited apoptosis in Reed-Sternberg cells, which was an important process in HL pathogenesis [22].

Another genome-wide methylation study of 13088 genes compared five HL cell lines (L-1236, L-428, KM-H2, HDLM-2 and U-HO1) to normal B cells and 20 germinal center derived B-cell lymphoma (gcbBCL). HL and gcbBCL showed 329 commonly hypermethylated genes, mainly involved in development and morphogenesis, WNT pathway and regulation of adenylated cyclase activity. Two-hundred-and-nine genes were distinctly hypermethylated in HL cell lines, compared to gcbBCL or normal B cells. Gene Ontology analysis indicated that genes were enriched for positive regulation of B-cell activation and T-cell differentiation, suggesting that hypermethylated genes in HL targeted the B-cell program [23].

PART II: Signaling pathways involved in alterations of methylation status

Epigenetic profiling showed different genomic DNA methylation patterns among diseases. Several signaling pathways,

such as WNT pathway, JAK-STAT pathway and p53 pathway, are recurrently involved in lymphoid malignancies (Figure 1).

WNT pathway

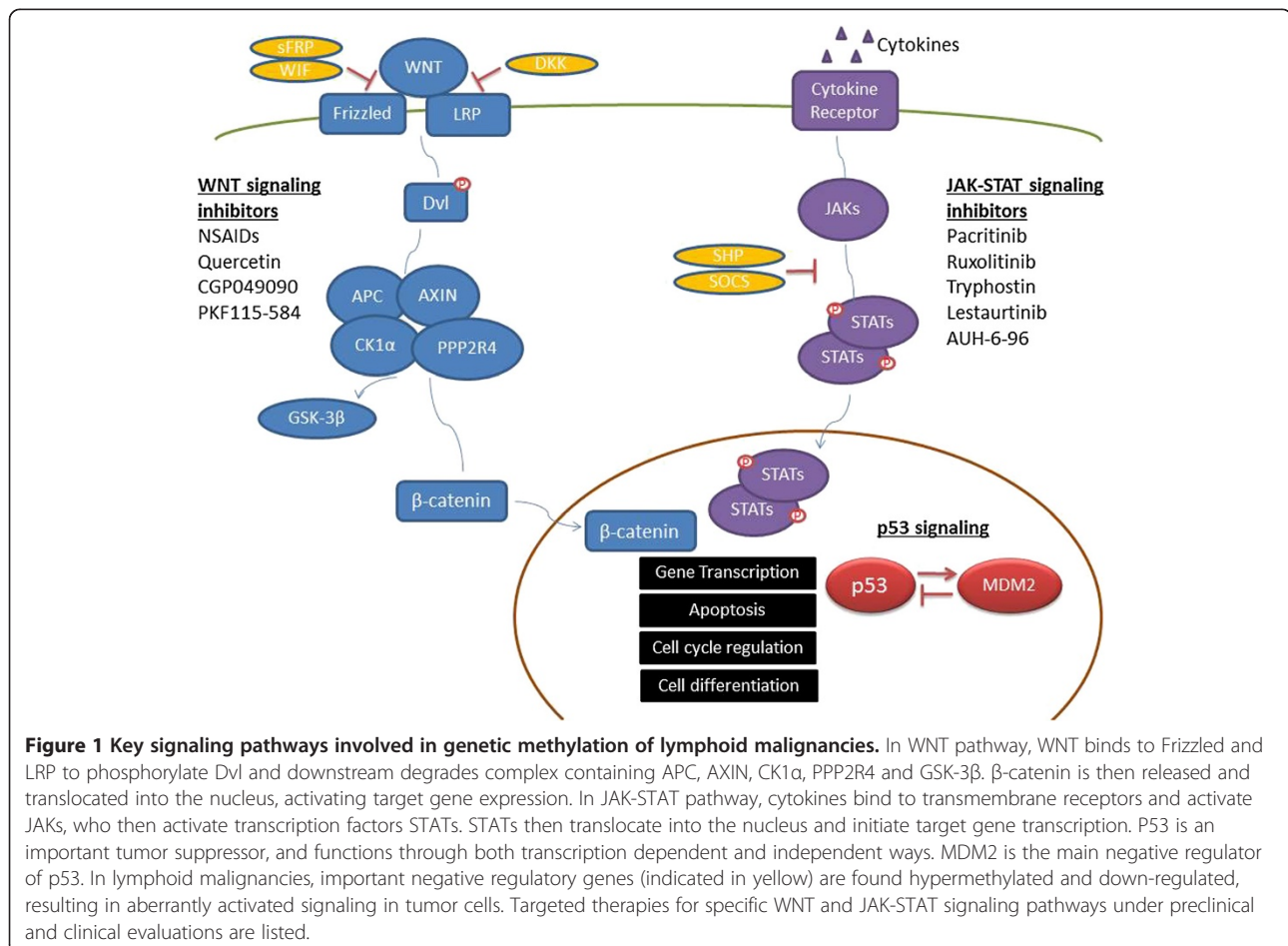
WNT pathway is essential in hematopoiesis and plays an important role in controlling cell proliferation, differentiation and survival [24]. *WNT* encodes a family of secreted cysteine-rich glycoproteins. The ligand receptor of WNT contains transmembrane protein Frizzled and LRP5/6. The main downstream target of WNT pathway is β -catenin. In the absence of WNT binding to its receptor, β -catenin is stabilized and bound to E-cadherin. The excess β -catenin protein is phosphorylated and degraded by destruction complex containing APC, AXIN, CK1 α , PPP2R4 and GSK-3 β . Upon activation, the WNT ligand binds to its membrane receptors and cytoplasmic protein Dvl is accordingly recruited and activated by phosphorylation. Activated Dvl induces dissociation and subsequent inhibition of GSK-3 β from the complex. β -catenin is then released and translocated into the nucleus, where it up-regulates target gene expression. There are

also several antagonist proteins of WNT-Frizzled interaction, including DKK, WIF and sFRP family members.

Increasing evidence showed dysregulation of WNT signaling in lymphoid malignancies. Pediatric precursor B-ALLs present hypermethylation of WNT inhibitors (*WIF-1*, *PTPRO*, *sFRP2*, *sFRP4*, *sFRP5*, *FZD10*, *DKK2* and *DKK3*), β -catenin/TCF/LEF complex inhibitors (*APC* and *WT1*), cadherin genes (*CDH1*, *CDH11* and *CD13*) and SOX genes (*SOX2*, *SOX3*, *SOX8*, *SOX9*, *SOX14* and *SOX21*). Moreover, in Ph-positive ALLs, the silencing of *sFRP1*, *sFRP2*, *sFRP4*, *sFRP5*, *WIF1*, *DKK3*, *HDPR1* and *WNT5A* by methylation predicts longer DFS and OS [25]. Primary CLL samples show hypermethylation pattern of *sFRP* gene family, especially *sFRP1* and *sFRP4*, [26]. Other WNT inhibitors, such as *WIF1* and *DKK3*, are also methylated in CLL [27].

JAK-STAT pathway

JAK-STAT pathway plays an essential role in the transduction of extracellular cytokine signals into intracellular process during hematopoietic ontogeny. The JAK family contains four cytoplasmic tyrosine kinases (JAK1-3 and TYK2) which are activated after cytokine receptor



activation. Downstream of JAKs activation is phosphorylation of STATs transcription factor family (STAT1-4, STAT5A, STAT5B and STAT6). The phosphorylated STATs form homo- or heterodimers and translocate into the nucleus, initiating target gene transcription [28]. Constitutive STAT activation leads to increased cell proliferation, tumorigenesis and decreased apoptosis.

SHPI is an important tumor suppressor gene which blocks the JAK-STAT pathway by dephosphorylating the receptors and receptor-associated kinases. Frequent methylation of *SHPI* was observed in MCL, as compared to normal B cells [29]. In another study, *SHPI* methylation was observed in 100% NHL and 94% leukemia patients, with mRNA expression accordingly decreased [30]. This study also found recurrent methylation of *SOCS1* gene, inhibitor of the JAK-STAT pathway through blocking JAK activation, in about 30% of NHL and leukemia patients.

P53 pathway

TP53 is one of the most frequently altered tumor suppressor genes in cancer. The encoded p53 protein, which is ubiquitously expressed in tissue, keeps genome stability under stress, and is involved in multiple cellular activities such as development, differentiation, aging and disease [31]. In normal state, p53 is inhibited and degraded by MDM2. When activated, p53 exerts its function through transcription-dependent and -independent activities.

Methylation in promoter CpG or in CCWGG motif of *TP53* was observed in 32% of ALL patients and correlated with decreased mRNA expression [32]. In CLL and DLBCL cases, methylation of *TP53* was also observed, but with less methylation rate (18.5% and 3.7%, respectively) [33,34]. A recent study analyzed 24 genes involved in the p53 pathway in six ALL cell lines and found 13 genes to be aberrantly hypermethylated. These genes are involved in the regulation of p53-dependent apoptosis (*DBC1*, *POU4F2*, *AMID*, *APAF1*, *ASPP1*, *TP73*, *NOXA*, *has-miR-34b* and *has-miR-34c*), cell cycle regulation (*POU4F1* and *CDKN1C*) and regulation of p53 itself (*LATS2* and *DAPK1*). Further confirmation analysis on independent cohort of 200 ALL cases showed that 78% of them present methylation in at least one of these 13 genes. These patients are characterized by lower complete remission (CR) rate (84% versus 91% in non-methylated group), higher relapse rate (46% versus 21%) and higher mortality rate (56% versus 19%). Survival analysis further indicated that hypermethylation of these genes is an independent prognostic factor both for DFS and OS [35].

PART III: Targeted therapy on genetic methylation and involved signaling pathways

Different from genetic abnormalities, epigenetic aberrations are possibly reversible. Great efforts have been made

on the development of epigenetic modulators, mainly focusing on the inhibition of DNA methyltransferase (DNMT) and histone deacetylase (HDAC). Also, specific targeted therapies on involved signaling pathways are under active preclinical investigation.

DNMT inhibitors

DNMT inhibitors are small molecules that effectively inhibit DNA methylation. 5'-azacytidine (Azacytidine, Vidaza) and 5-aza-2'-deoxycytidine (Decitabine, Dacogen) have been approved by Food and Drug Administration (FDA) for treating hematological malignancies [36].

Successful treatment with 5'-azacytidine was first reported in a 74-year-old female patient with myelodysplastic syndrome transformed pre-B ALL. At the time of transformation, bone marrow examination demonstrated pre-B blasts with del(20)(q11.2). The patient received 5'-azacytidine monotherapy (75mg/m² subcutaneously, for 7 consecutive days every 28 days, 6 cycles) and attained CR for over 6 months [37]. Induction of 5-aza-2'-deoxycytidine in childhood refractory ALL was also reported [38]. A four-year-old girl with relapsed B-ALL from hematopoietic stem cell transplantation (HSCT) received 5-aza-2'-deoxycytidine (15mg/m² i.v., three times a day for 3 days) combined with dexamethasone. The patient achieved CR and received a second allogeneic HSCT.

A Phase II trial of 5'-azacytidine was carried out in nine patients with recurrent fludarabine-refractory CLL. All cases received 1 to 6 cycles of 5'-azacytidine (75 mg/m² subcutaneously, for 7 consecutive days every 3 to 8 weeks). Although this trial was discontinued because of lack of response and treatment tolerance, one patient responded to treatment after four cycles with clinical improvement and was alive at last follow-up [39]. Another Phase I trial of 5-aza-2'-deoxycytidine in 16 relapsed/refractory CLL and four NHL patients aimed to determine the minimum effective dose of 5-aza-2'-deoxycytidine. Three different escalating dose schedules were examined. All patients tolerated well the first dose group (10 mg/m²/day for 10 days). In the other two dose groups (15 mg/m²/day for 10 days or 15 mg/m²/day for 5 days), dose-limiting toxicity occurred in 67% (4 out of 6 patients) and 50% (4 out of 8 patients) patients, respectively. Main adverse effects consisted of grade 3 to 4 neutropenia, thrombocytopenia and hyperbilirubinemia. Among twenty patients treated, eight had stable disease (SD) [40]. *In vitro*, 5'-azacytidine also showed cytotoxic activity in primary samples of high-risk (11q-/17p-) and low-risk (13q-) CLL [41].

HDAC inhibitors

HDAC inhibitors can open chromatin status and suppress histone deacetylase, thus inducing transcriptional reactivation of silenced genes. Major HDAC inhibitors

approved by FDA include Romidepsin (Depsipeptide), Panobinostat and Suberoylanilide hydroxamic acid (SAHA, vorinostat).

Romidepsin was used in a Phase I clinical trial for treating 10 CLL patients. 13 mg/m² Romidepsin was given intravenously on days 1, 8 and 15. No patient met the response criteria. However, seven had improved peripheral leukocyte counts and one had lymphadenopathy reduction [42]. Another Phase II study enrolled 25 patients with relapsed/refractory HL treated with 200 mg SAHA (twice daily 14 days every 3 weeks or 3 days per week). One patient achieved partial response (PR) and seven other patients had SD over 1 year [43]. Panobinostat was also effective in treating refractory HL. In a cohort of 129 HL patients relapse/refractory to HSCT, Panobinostat (40 mg 3 times per week) was well tolerated and achieved an overall response rate (ORR) of 27%, including 23% PR and 4% CR. Median PFS was 6.1 months and estimated 1-year OS rate was 78% [44].

In vitro, ALLs with MLL-rearrangement present particular hypomethylation pattern of proto-oncogenes, such as *MYC*, *SET*, *RUNX1*, *RAN*. HDAC inhibitors (Romidepsin, Panobinostat, SAHA, and Valproic acid) can reverse such unfavorable epigenetic pattern and effectively induce leukemic cell death [45]. Moreover, HDAC inhibitors synergistically interacted with 5-aza-2'-deoxycytidine in ALL, DLBCL and MCL cell lines [21,46,47].

Targeting WNT signaling pathway

Targeted therapies circumventing the WNT signaling pathway were in the preclinical stage. Their functions include inhibition of WNT-mediated transcription and inactivation of WNT target genes.

Non-steroid anti-inflammatory drugs (NSAIDs) inhibit the WNT signaling pathway through preventing β -catenin transcription complex formation. In T-cell leukemia Jurkat cell line, para-nitric oxide-donating acetylsalicylic acid (para-NO-ASA) induces β -catenin degradation, along with an increase of caspase-3 expression and induction of apoptosis [48]. Similar apoptosis-inducing effect is observed in primary CLL cells and in a xenograft murine model, while sparing normal hematopoiesis *in vitro* [49].

Quercetin is an inhibitor of β -catenin through GSK-3 β inactivation [50]. In cell lines of T-ALL, DLBCL and MCL [51], quercetin inhibits WNT signaling and induces cell growth arrest and apoptosis. Importantly, *CCND1*, as well as anti-apoptotic *BCL-XL* and *BCL-2*, are significantly down-regulated after quercetin treatment [52].

Small molecule inhibitors of WNT cascade (CGP049090 and PKF115-584) were tested in CLL. These inhibitors efficiently induce CLL cell apoptosis, while normal B cells are not affected. Both agents suppressed

tumor growth in a JVM-3 subcutaneous xenograft murine model [53].

Although not tested in lymphoid malignancies, several antibodies have been proved to inhibit proliferation and induce apoptosis in solid tumors, including antagonists of WNT [54,55] and of WNT receptors [56,57]. In addition, peptide mimetics are identified in modulating the WNT signaling. For example, the sFRP1-derived peptides inhibit colorectal cancer xenograft formation in mice [58].

Targeting JAK-STAT signaling pathway

Pacritinib (SB1518) is an inhibitor of JAK2. A Phase I trial on Pacritinib in 34 relapsed/refractory HL or NHL patients show well tolerance. Three PRs are observed at a dose of 300 mg/day. Fifteen patients achieved SD, 13 of which had 4%-46% tumor reductions. Most common adverse events are gastrointestinal toxicities [59].

Ruxolitinib is a JAK1/JAK2 inhibitor and a FDA approved drug for treatment of myeloproliferative neoplasm. Recently its anti-proliferative effect was reported in cell lines of HL and primary mediastinal B-cell lymphoma. Expression of anti-apoptotic gene *BCL-XL* and *MCL-1* decreased in a dose-dependent manner [60]. Also *in vitro*, Pacritinib induces cell apoptosis, cell cycle arrest and inhibits proliferation in lymphoid cell lines, including Jurkat and MOLT-4 [61]. Other JAK2 inhibitors include Tryphostin (AG-490) and Lestaurtinib. Tryphostin enhances the cytotoxicity effect of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in primary T-ALL cells and in Jurkat and SUPT1 T cell lines [62]. Lestaurtinib induces dose-dependent cell growth inhibition and apoptosis in five HL cell lines derived from refractory patients and primary cells obtained from four HL patients [63].

AUH-6-96 is firstly identified in *Drosophila*. In HL cell line L540, AUH-6-96 treatment abrogates the signaling pathway by reducing the level of JAK3 and STAT3 phosphorylation, thus down-regulating *BCL-XL* expression. Cell viability assay showed that this drug selectively induces apoptosis in the cancer cell line, while normal cells are not affected [64].

Conclusions

Genetic methylation plays an important role in tumor transformation and progression in lymphoid malignancies. Accumulating data of DNA methylation study not only lead to disease classification and risk stratification, but also revealed multiple signaling pathways for targeted therapy development. Although preclinical and clinical investigations indicated their beneficial effects on patients, further study should be focused on the bio-therapeutic agents targeting the specific methylated genes and the methylation status of involved signaling pathways.

Additional file

Additional file 1: Identified gene hypermethylation in lymphoid malignancies.

Abbreviations

ALL: Acute lymphoblastic leukemia; MS-PCR: Methylation specific-polymerase chain reaction; CIMP: CpG island methylator phenotype; DFS: Disease-free survival; OS: Overall survival; CLL: Chronic lymphocytic leukemia; *IGHV*: Immunoglobulin heavy-chain variable; NHL: Non-Hodgkin's lymphoma; HL: Hodgkin's lymphoma; DLBCL: Diffuse large B-cell lymphoma; GCB: Germinal center B-cell-like; ABC: Activated B-cell-like; MCL: Mantle cell lymphoma; gcbBCL: Germinal center derived B-cell lymphoma; CR: Complete remission; DNMT: DNA methyltransferase; HDAC: Histone deacetylase; FDA: Food and Drug Administration; HSCT: Hematopoietic stem cell transplantation; SD: Stable disease; PR: Partial response; ORR: Overall response rate; NSAIDs: Non-steroid anti-inflammatory drugs; para-NO-ASA: Para-nitric oxide-donating acetylsalicylic acid; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand.

Competing interests

The authors declared that they have no competing interest.

Authors' contributions

WLZ had the idea of conducting this review, XZ and WLZ wrote the manuscript, WZ and LW gave suggestions on modifications. All authors read and approved the final manuscript.

Acknowledgements

This work was supported, in part, by the National Natural Science Foundation of China (81172254 and 81101793), the Shanghai Commission of Science and Technology (11JC1407300), the Program of Shanghai Subject Chief Scientist (13XD1402700), and the "Shu Guang" project supported by Shanghai Municipal Education Commission and Shanghai Education Development Foundation (09SG21).

Received: 3 June 2013 Accepted: 6 August 2013
Published: 14 August 2013

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doi:10.1186/2050-7771-1-24

Cite this article as: Zhao et al.: Genetic methylation and lymphoid malignancies: biomarkers of tumor progression and targeted therapy. *Biomarker Research* 2013 **1**:24.

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