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Current status: Mixed lineage leukemia

Mohd Ishaq Dar[1], Mohd Saleem Dar[2],Suraya Jan[3]

[1,2,3] *CSIR IIIM Canal Road Jammu(India)*

ABSTRACT

MLL associated translocations are found in 70% of infant leukaemia's less than 2 years of age[1].Various studies have that In mixed lineage leukemia balanced chromosome translocations occurs lead to expression of leukemia promoting genes[2].Various cellular proteins like PI3K, GSK3β, mTOR, cyclin dependent kinases, histone deacetylases and histone methyltransferases are targeted for the treatment of mixed lineage leukemia.

Keywords-Mixed lineage leukemia, translocation, PI3K, mTOR, histone methyltransferase.

I. INTRODUCTION

Mixed Lineage Leukemia pathology associated with haemopoetic cells is under a hot bebate from the last two decades. MLL associated translocations are found in 70% of infant leukaemia's under the age of 2 years with a very poor prognosis[1]. Mixed lineage leukemia display co-expression of lymphoid as well as myeloid antigens hence infants with MLL translocation show both myeloid and lymphoid blast cell population[3, 4]. Normally, the MLL gene encodes for a SET domain histone methyltransferase that catalyzes the methylation of lysine 4 of histone H3 (H3K4) at particular regions [5]. In MLL, the active SET Histone 3 lysine 4 methyltransferase activity domain is lost and truncated MLL protein is fused to number of other protein partners such as AF4, AF9, AF10 and ENL by balanced chromosomal translocations and rearrangements[2, 6]. Amino terminal portion of MLL protein is fused to fifty distinct binding protein partners [7].The fusion products retain the abilty to locate gene specific recognition regions even after translocation and interact directly or indirectly with other histone methyltransferaes like DOTIL[8]. DOT1L interacts with six unique MLL fusion proteins created by chromosomal translocations i.e. MLL-AF4, MLL-AF9, MLL-ENL, MLL-AF10, SET-NUP214, CALM-AF10[9, 10].The fusion products gain the ability to recruit Dot1L to the aberrant gene regions and increase the expression of genes responsible for promotion of leukaemia [11].There is still lack of good quality therapeutics for mixed lineage leukemia due to lack of small molecule inhibitors that will directly target MLL[12].The focus of the review will be on the recent published work as well as therapeutic targets from the last 2 decades.

II. PI3K AS A THERAPEUTIC TARGET OF MLL

Recent reports have shown that Simaltaneous inhibition of PI3K/mTOR has shows anticancer activity in MLL rearranged leukaemias[13]. In vivo PI3K/mTOR inhibition has shown to reduce tumour progression and also shown to increase survival in MLL-AF9 xenograft mouse model[13].BEZ, rapamycin and MK-2206 have shown good in vitro activity as well as have shown good activity in mice tumour models by inhibiting PI3K, mTOR and AKT pathways[13].

III. CDK4/CDK6 AS A THERAPEUTIC TARGET OF MLL

In MLL there is a cell differentiation block which can be broken by using small molecules like CDK6 inhibitors[14].CDK6 as a therapeutic target for mixed lineage leukemia was identified by Plakle et al., 2014[15]. PD-0332991 is a dual inhibitor of CDK4/CDK6 which is clinical trials for treatment of breast cancers as well as

PD-0332991 have shown strong growth inhibition in MLL rearranged leukemic cells [15]. Current treatment of MLL is chemotherapy and stem cell theray[16].

IV. SMALL MOLECULE INHIBITORS OF HISTONE DEACETYLASES AS TREATMENT OF MLL

It has been shown recently that HDAC inhibitors induce apoptosis in MLL rearranged cell by autophagy [17]. Inhibition of histone deacetylase by VPA (valproic acid) in cells harbouring MLL induced cell cycle arrest (G1-phase) and apoptotic cell death in MLL-AF9 expressing cell lines[18].

V. RETINOIC ACID AND VITAMIN D AS IMPORTANT DRUGS FOR MLL

MLL-AF9 expressing leukemic cell line MOLM-14 undergoes differentiation when exposed to ATRA or 1, 25-dihydroxyvitamin D3[19]. Simultaneous treatment of MLL cells with Retinoic acid and epidrug 5-azacytidine has shown to inhibit growth of MLL positive leukemic cells[20]

VI. GLYCOGEN SYNTHASE KINASE 3 IS AN IMPORTANT TARGET TO CONTROL MLL

Glycogen Synthase kinase3 has shown to support MLL leukemia proliferation[21].GSK3 inhibition has shown to induce G1 growth arrest and cell death in MLL transformed cells[21]. GSK3-β inhibition has shown to increase survival in mouse model of MLL associated leukaemic [21]. Specific GSK-3 inhibitor SB-415286 has been repored to inhibit growth by induction of apoptosis in leukemic cells[22].

VII.COMBINATION OF SIRT1 ACTIVATORS AND DOT1L INHIBITOR FOR THE TREATMENT OF MIXED LINEAGE LEUKEMIA

Activation of SIRT1 and at same time inhibition of DOTIL has been shown be an effective therapy for mixed lineage leukemia[23].SIRT1 activation mediated silencing of the MLL-AF9 leukemia has been shown to be enhanced by simultaneous DOT1L inhibition[23]. SIRT1 activation by SIRT1 activator SRT1720 in combination with DOTIL inhibitor has been reported to augment apoptosis induction in mixed lineage leukemia cells[23].

VIII. β-CATENIN AS A THERAPEUTIC TARGET OF MLL

It has been reported that Leukemic stem cells have a more self renewal and drug résistance property [24]. β-catenin establishes the growth of mixed lineage leukemia Leukemic stem cells[25]. Reversal of LSC to PLSC has shown to significantly reduces the growth of mixed lineage leukemia cells by β-catenin downregulation or suppression [26].

IX. TET1 IS A DIRECT TARGET OF MLL-FUSION PROTEINS AND IS AN IMPORTANT THERAPEUTIC TARGET

TET1 has shown to be highly expressed in MLL-rearranged leukemia cells with leads to drastic increase of 5-hydroxymethylcytosine levels[27].TET1 has shown to be an associated parter of MLL which is leads to increased growth [27]. Overexpressed of TET1 in MLL rearranged leukemia has shown to be responsible for overexpression of leukemia promoting genes Hoxa9 Pbx3 and Meis1 [28].TET1 overexpression has shown

increases proliferation and inhibit cell death of MLL cells[29].Recent report suggested that TET1 knockdown or therapeutic intervention of TET subside MLL rearranged leukemia [30].

X. BET FAMILY MEMBERS AND MLL

It has been shown that BET family members i.eBromodomainT,Bromodomain2,Bromodomain 3 and Bromodomain 4 recruit MLL fusion oncogene proteins to diverged genic regions and increase the expression of leukemia inducing genes BCL2, CDK6 and C-MYC[31]. It has been shown that inhibition of bromodomain proteins could provide a new novel approach for the treatment of mixed lineage leukemia[31] .

XI. DOTIL INHIBITORS FOR THE TREATMENT OF MLL

It has been shown that inhibition of DOTIL by small molecules kill mixed lineage leukemia cells by inhibiting H3K79 hypermethylation at the promoters of leukemia promoting genes[32]. Inhibition of DOT1L has shown to increase apoptosis in cells carrying MLL rearrangement cells as well as in mouse model of MLL[33]. EPZ5676 and EPZ004777 are the currently available DOT1L inhibitors which are in research and development for the treatment of mixed lineage leukemia[34].

XII. LYSINE SPECIFIC DEMETHYLASE INHIBITORS FOR THE TREATMENT OF MLL

LSD1 is shown to be essential for proliferation and growth of leukemic stem cells containing MLL-Fused oncogenes[35] LSD1 (Lysine specific demethylase1) is shown to be highly up regulated in mixed lineage leukemia [35]. It has been shown that Lysine specific demethylase inhibitors promote differentiation and apoptotic cell death of MLL cells[36].

XIII. MENIN AND MLL INTERACTION BLOCKERS

Borkin et al. recently developed potent inhibitors blocking interaction of leukemia associated protein MLL and menin [37]. These compounds showed to inhibit the growth of leukemia cells in vitro as well as prolonged the survival of MLL leukemic mice[37]. Inhibiting the interaction between Menin and MLL has shown to cause downregulation of Hox A genes and differentiation of MLL-Rearranged Leukemic cells[37]. Borkin et al. Showed that MI-463 and MI-503 blocked the MLL Menin interaction, resulted in increased cell death and differentiation [37].

XIV. CONCLUSION

Various small molecule inhibitors are in research and development for the treatment of mixed lineage leukemia. All Currently available treatments for mixed lineage leukemia have low efficacy as well as high toxicity. So there is a need to develop new drugs as well as to identify new therapeutic targets for mixed lineage leukemia.

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