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Current status: Mixed lineage leukemia

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ABSTRACT

MLL associated translocations are found in 70% of infant leukaemia's less than 2 years of age. Normally, the MLL gene encodes for a SET domain histone methyltransferase that catalyzes histone H3 lysine 4 methylation at particular loci. In mixed lineage leukemia, the catalytic SET domain responsible for H3K4 methyltransferase activity is lost and the remaining MLL protein is fused to a variety of partners such as AF4, AF9, AF10 and ENL by chromosomal translocations in a balanced manner which causes the overexpression of leukemia promoting genes..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,histone methyltransferase, apoptosis, differentiation

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[2]. Normally, the MLL gene encodes for a SET domain histone methyltransferase that catalyzes the methylation of lysine 4 of histone H3 (H3K4) at particular loci [3]. In MLL, the catalytic SET domain responsible for H3K4 methyltransferase activity is lost and the remaining MLL protein is fused to a variety of partners such as AF4, AF9, AF10 and ENL by balanced chromosomal translocations and rearrangements[4]. Amino terminal portion of MLL protein is fused to 50 different binding partners[5].The fusion products retain the gene specific recognition domains even after translocation and interact directly or indirectly with other histone methyltransferaes like DOTIL[6]. 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[7].The fusion products gain the ability to recruit Dot1L to the aberrant gene locations and increase the expression of leukaemia promoting genes[8].There is still lack of good quality therapeutics for mixed lineage leukemia due to lack of small molecule inhibitors that will directly target MLL[9].The focus of the review will be on the recent published work as well as therapeutic targets from the last 10 years.

II. PI3K AS A THERAPEUTIC TARGET OF MLL

Dual inhibition PI3K/mTOR shows anticancer activity in MLL rearranged leukaemias. In vivo PI3K/mTOR inhibition reduced tumour progression and increased survival in MLL-AF9 xenograft mouse model[10].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[10].

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[11].CDK6 as a therapeutic target for mixed lineage leukemia was identified by Plakle et al., 2014[12]. 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 [12]. Current treatment of MLL is chemotherapy and allogenic stem cell transplantation in selected cases[13].

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

Inhibition of histone deacetylases by HDAC inhibitors induce apoptosis in MLL rearranged cell by autophagy inhibition[14]. Inhibition of histone deacetylase by valproic acid induced cell cycle arrest (G1-phase) and apoptosis in MLL-AF9 expressing cell lines[15].

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

MLL-AF9 expressing cell line MOLM-14 undergoes differentiation when exposed to ATRA or 1, 25-dihydroxyvitamin D3[16]. Retinoic acid in combination with 5-azacytidine inhibit growth MLL positive leukemic cells[17]

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

Glycogen Synthase kinase3 supports MLL leukemia proliferation and maintainance.GSK3 inhibition induces G1 arrest and cell death in MLL transformed cells. GSK3-β inhibition increased survival in mouse model of MLL associated leukaemic. Specific GSK-3 inhibitor SB-415286 inhibits growth and induces apoptosis in leukemic cells[18].

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

Activation of SIRT1 and inhibition of DOTIL can be an effective therapy for mixed lineage leukemia.SIRT1 mediates silencing of the MLL-AF9 leukemic program upon DOT1L inactivation by H3K9 deacetylation [19].SIRT1 activator SRT1720 in combination with DOTIL inhibitor augment apoptosis induction in mixed lineage leukemia cells[19].

VIII. β-catenin as a therapeutic target of MLL

Leukemic stem cells show more self renewal and drug résistance[20]. β-catenin establishes the growth of MLL Leukemic stem cells[21]. Reversal of LSC to PLSC significantly reduces the growth of MLL-transformed cells by suppression of β-catenin [22].

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

TET1 is significantly up-regulated in MLL-rearranged leukemia, leading to a global increase of 5-hydroxymethylcytosine level[23].TET1 is a fusion partner of MLL. TET1 is overexpressed in MLL rearranged leukemia and increases the expression of leukemia promoting genes Hoxa9, Meis1 and Pbx3[24].TET1 overexpression increases proliferation and inhibits apoptosis of MLL cells[25].TET1 knockdown or therapeutic intervention of TET prevent MLL rearranged leukemia[26].

X. BET FAMILY MEMBERS AND MLL

Bromodomain and extra terminal protein (BET) family of proteins (BRD2, BRD3, BRD4 and BRDT) recruit MLL fusion oncogene proteins to aberrant gene locations and increase the expression of leukemia promoting genes BCL2, CDK6 and C-MYC[27]. So inhibition of bromodomain proteins provide a new approach for the treatment of mixed lineage leukemia.

XI. DOTIL INHIBITORS FOR THE TREATMENT OF MLL

Small molecule inhibition of DOTIL kill mixed lineage leukemia cells by inhibiting H3K79 hypermethylation at the promoters of leukemia promoting genes[28].Small molecule inhibition of DOT1L increases apoptosis in cells carrying MLL rearrangement as well as in mouse model of MLL[29]. EPZ5676 and EPZ004777 are the currently available DOT1L inhibitors which are in research and development for the treatment of mixed lineage leukemia[30].

XII. LYSINE SPECIFIC DEMETHYLASE INHIBITORS FOR THE TREATMENT OF MLL

LSD1 is essential for proliferation of leukemic stem cells containing MLL-Fusion oncogene LSD1 (Lysine specific demethylase1) is highly up regulated in mixed lineage leukemia [31]. LSD1 inhibitors promote differentiation and apoptosis of MLL cells[32].

XIII. MENIN AND MLL INTERACTION BLOCKERS

Borkin et al. recently developed highly potent and orally bioactive small molecule inhibitors that block the interaction between menin and MLL protein[33]. These compounds inhibit the growth of leukemia cells in vitro as well as prolonged the survival MLL leukemic mice.Inhibiting the Menin-MLL Interaction Causes Hox Gene downregulation and differentiation of MLL-Rearranged Leukemia[33]. MI-463 and MI-503 block the MLL binding site on menin, resulting in downregulation of Hox genes and differentiation of leukemic blasts[33].

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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