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Review Article

An updated account on molecular heterogeneity of acute leukemia

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Abstract: The progress in the field of personalized therapy has been the backbone for the improved mortality and morbidity figure in cancer especially with reference to acute leukemia. The same has been supported by evolving research and development in the field of genomics. The newer discoveries of mutations and the account of already discovered mutations have been playing a pivotal role to refine management strategy. Here, in this review, we are giving an account of relevant mutations and their potential role in the pathogenesis of acute leukemia. The article discusses the old and newly discovered mutations in acute myeloid/lymphoblastic leukemia. The various pathways and cross-talks between the mutations have been briefly described to develop insight towards their contributory and consequent role in the neoplastic process. The article is to sensitize the students, clinicians, and researchers towards the recent updates and development in genomics of acute leukemia.

Keywords: AML, ALL, mutations, genomics

Introduction

Acute leukemias (AL) is clinical outcomes of clonal proliferation of myeloid and lymphoid progenitor cells [1]. In present scenario, most of the leukemias respond with the current chemotherapy. However, refractory disease and multiple relapses are also the major cause of poor prognosis [2]. Earlier, the diagnosis of acute leukemias were based mainly on the clinical & morphological characteristics of myeloid and lymphoid cells which has now changed mainly on the basis of molecular genetics [3]. The molecular genetics have become important in predicting clinical course, but a large cohort is necessary for prognostic validation [4]. The prognostic relevance was first attempted by Nowell & Hungerford in the year of 1960. They discovered a recurrent chromosomal translocation t(9;22)(q34;q11.2) in patients with Chronic Myeloid Leukemia (CML) [5]. This was the first paradigm, where molecular knowledge of specific molecular inhibitor, Imatinib was used for treatment [6]. Now, with the use of advanced high-quality genomic material and high throughput molecular techniques like next generation sequencing (NGS) helped us in characterizing acute myeloid and lymphoid malignancies into various genomic subtypes, which were illustrated by WHO and compiled in 2016 [7]. The aim of this study is to discuss how alterations of the genes that are involved in the various normal cell cycle pathways which includes cell addition, cell death, cell cycle differentiation, metabolism, motility signalling, transcription and transporters ultimately lead to leukemogenesis [8].

Molecular genetics of acute myeloid leukaemia

Acute myeloid leukaemia (AML) is neoplastic proliferation of myeloid precursors. The diagno-

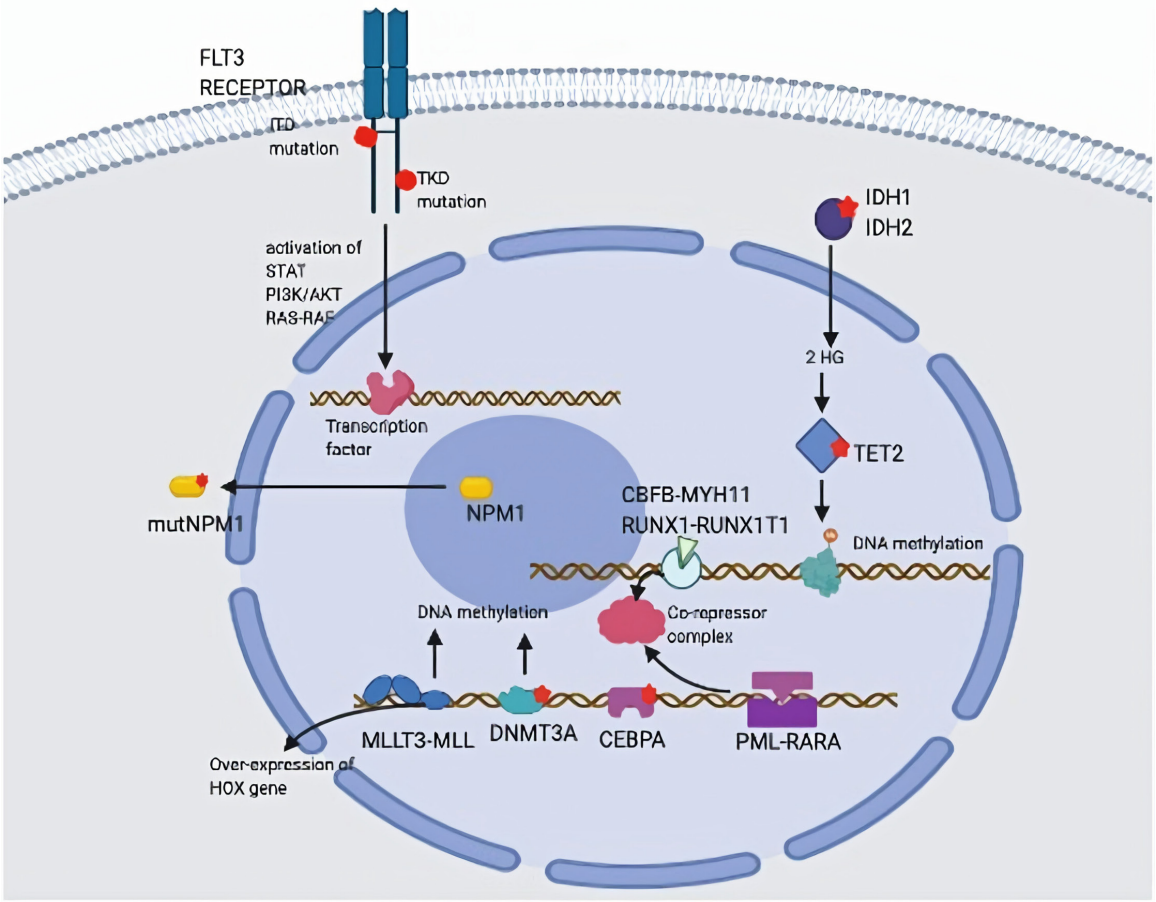

Figure 1. Genetic mutation landscape in AML; Mutations involved at the level of transcription factors are t(8;21) [RUNX1-RUNX1T1], t(15;17) [PML-RARA] and inv.16 [CBFB-MYH11], CEBPA. Mutations at the level of epigenetic modifiers are t(9;11) [MLLT3-MLL], IDH1/2, TET2 and DNMT3A. Mutations at the level of kinases are FLT3 [ITD/TKD] mutations and NPM1 mutations.

sis has gone beyond the boundaries of morphology. Now, AML is categorise in heterogeneous groups on the basis of cytogenetic and molecular mutations [9, 10]. Some of these recurrent genetic mutations are associated with specific prognosis or management strategies [11]. The most common genes involved for the development of AML are those that encode for transcription factors, epigenetic pathways modifiers, Hox pathways modifiers, cell kinases and nuclear pore proteins (**Figure 1**).

Transcription factors

Promyelocytic leukemia-retinoic acid receptor-alpha

Promyelocytic leukemia Retinoic Acid receptor Alpha fusion (PML-RARA) results from t(15,17). It has specific morphology (Hypergranular blasts with frequent Auer rods or microgranular variants with dumbbell shaped nucleus). It can be treated with Retinoic Acid. PML/RARA gene has 5' end formed by PML and 3' end formed by RARA gene. C-terminal of fusion protein has a ligand binding, dimerization and repression functions. Wild type RARA is a steroid receptor present at the nucleus that acts as a transcription factor and binds to the promoter of genes important for myeloid differentiation. RARA acts as a transcription repressor until it binds to its ligand [12]. In resting state, it binds with Retinoid X receptor protein and forms a heterodimer & acts as repressor along with other repressors like SMRT, NCOR, mSin3A & HDACs. Its target genes like GCSF, GCSFR, neutrophil protein; cell surface receptor (CD116, CD18) & regulators of BCL2 [13]. Ligand binding causes recruitment of co activator complex (SRC-1) [14]. PML acts as tumour suppressor protein [13]. RARA (wild-type) influences other genes by binding with retinoic acid response elements

(RARE). Fusion protein is not able to convert itself into a transcription activator under physiological level (10^{-8} M) but can function normally at pharmacological level (10^{-6} M) [14, 15]. Another variant is t(11;17)(ZBTB16/RARA) which does not act as transcription activator even at pharmacological levels. But they are treated with inhibitors of co-repressors of RARA (eg. Inhibitor of HDAC i.e. Trichostatin-A (TSA)) [15, 16].

RUNX1-RUNX1T1/(RUNX1-ETO)

Chromosome 19 when positive in t(8,21) is associated with good prognosis but may cause bad prognosis when co-expressed with CD34. When AML with maturation (AML-M2) shows t(8,21), they are positive for CD19 & CD56. RUNX-RUNX1T1 fusion gene is present on Chr-8 [17]. Core binding factor translocation seen in 15% of all AML [18]. RUNX-1 is a part of the core binding factor which binds to a core enhancer sequence of moloney murine leukemia virus as described by Golemis et al. [19]. Core Binding Factor (CBF) has a non-DNA binding CBFβ unit associated with inv.16 in AML [20]. Fusion partner of RUNX-1 is RUNX1T1. Another fusion partner is CBFA2T3 {t(16;21)} [21]. N-terminal of RUNX contains the Runt homology domain (RHD) (DNA binding domain). This domain is mutated in AML and familial platelet disorders [22, 23]. The non-DNA binding CBFB of CBF interacts with the N terminal of RUNX-1 which will change the conformation of RUNX-1 to increase DNA binding affinity [24]. C-terminal of the RHD are potential MAP kinase phosphorylation sites [25]. C-terminal's other weak activation domains are, nuclear matrix target signal, dimerization domain and sequences that are recognized by co-repressor proteins.

RUNX-1 is essential in hematopoietic development. It regulates B-cell tyrosine kinase, TCR α & β, CK (1L-3, GMCSF) & granulocyte proteins (e.g. MPO & elastase) [26-29]. RUNX-1T1 acts as a co-repressor associated with NCOR, mSin3A which is Class I HDAC fusion protein has a DNA binding domain but C terminals are absent [25]. Thus, act as a negative regulator of wild type RUNX-1 [30]. The fusion protein acts as a transcriptional repressor. But, its action depends upon its association with HDACs. HDACs inhibitor such as Trichostatin A (TSA) inhibits the effect of RUNX-1 RUNX1T1 [31]. It also inhibits cell cycle progression of myeloid progenitor cells. The homozygous lack of *RUNX1* is lethal, it leads to death of embryos due to haemorrhagic necrosis of central nervous system and abnormal haematopoiesis [32]. In a study done by Gaidzik et al. *RUNX1* mutations were associated with resistance to routine chemotherapy in about 30% cases with low survival outcomes [33]. In these patients allogeneic SCT was considered as the best option for improving survival rates [33].

Inversion 16 (CBFB-MYH11)

Inversion 16 with co-expressed CD34 is present in 8% of AML cases. It involves CBF-B & responsible for differentiation of AML M4 with Eosinophilia in morphology (myelo-monocytic leukaemia with eosinophils that has dark purple as well as orange granules) [34]. This inversion leads to fusion of CBFB with C terminal of smooth muscle myosin heavy chain protein gene (MYH11) [20]. Fusion protein acts as a co-repressor associated with mSin3A & HDAC8. This fusion protein needs RUNX-1 for its action [35]. CBF translocation in inv.16 & RUNX-1-RUNX1T1 translocation is not sufficient to produce leukaemia. Multiple genetic hits are necessary for development of AML [36]. They are usually associated with good prognosis [37] and have excellent response when Gemtuzumab ozogamicin is added to normal induction chemotherapy used for other AML [38].

CCAAT/Enhancer binding protein α (CEBPA)

CEBPA is a transcription factor that regulates granulocytic differentiation [39]. Cytogenetically silent mutations of CEBPA are seen in 10% of AML [40]. Other genetic mutations in AML often down regulate CEBPA [41]. RUNX1-RUNX1T1 represses CEBPA promoters. FLT3-ITD activation leads to reduced activity of CEBPA [41, 42]. Granulocytic maturation is lost in CEBPA knockout mouse [43].

CEBPA produces two proteins, first large protein (42-kD) which has N terminal that has a trans-activating domain and a C terminal that has b-ZIP domain that mediates dimerization. A second smaller protein (30-kD) whose transactivating domain is absent but has b-ZIP domain. Two types of mutations are seen in CEBPA [44-46]. N terminal truncation mutation leads to increased production of 30-kD protein and a C terminal ZIP domain mutation that inhibits

dimerization & DNA binding. N terminal mutation leads to dimerization with long form but inhibits trans-activation by the dimer. All these mutations of CEBPA falls in intermediate risk AML [46]. CEBPA mutation at both alleles is associated with better survival than mutation at single allele [47]. Patients with CEBPA biallelic mutation concurrent with epigenetic modifiers such as TET2 or RNA-splicing genes appear to have a significantly worse prognosis, similar to that seen in the mono-allelic group (Konstandin et al., 2018) [48].

GATA-1

A Zinc finger transcription factor-regulates erythrocyte & megakaryocytic differentiation. Mutations of GATA1 are always present in acute megakaryoblastic leukaemia (AML-M7) that occurs in children with Down Syndrome (DS) [49-51]. Missense mutations in GATA-1 results in syndrome of dys-erythropoietic anaemia & thrombocytopenia. Approximately 10% of DS have GATA-1 mutation patient develops transient myeloproliferative disorder (TMD) in neonatal period [49, 52]. A one/third of patients with TMD develops AML-M7 within 5 years. AML-M-7 in DS is sensitive to cytosine arabinosite or anthracycline based chemotherapy with evidence free survival (EFS) rate of 80-100% [53].

Epigenetic factors modifying chromatin & DNA

IDH1/2 and TET2 mutations

IDH1/2 and TET2 mutations are found in 16% of AML with normal karyotype [54]. IDH1/2 mutations are mutually exclusive with mutation in TET-2 in de-novo AML [55]. Wild type IDH1/2 catalyses production of αKG but mutant form produces 2-hydroxyglutarate (2HG). αKG dependent enzymes e.g. Histone demethylase & TET-1/Q are inhibited by 2HG [56]. TET protein is responsible for demethylation of cytosine (5 mc to 5 hmc) [57]. Therefore, mutation in both IDH and TET leads to increased DNA methylation [55-57]. Increased DNA methylation leads to inhibition of myeloid differentiation & promotes development of AML. Drugs mimicking αKG analogues can be used for treatment [56]. Mutations in IDH1 and TET2 have not been shown to have a significant impact on survival [47]. In a study by Feng et al. of 8121 patients it was seen that patients with IDH1 mutation had inferior overall survival (OS), and some patients also had resistance to induction chemotherapy resulting in a lower complete response (CR) rate [58]. Many IDH inhibitors are in preclinical trials. According to a study by Stein et al., the effect of Enasidenib, a IDH1 inhibitor induced hematologic response in patients with refractory AML [59]. In August 2017 FDA approved the use of enasidenib for IDH2 mutated relapsed/refractory AMLs [60].

DNMT3A

It is a methyltranferase family member that catalyses addition of methyl group to cytosine in CpG dinucleotide. Increased methylation of CpG Island results in silencing of many genes [61]. Ley TJ et al. have observed occurance of DNMT3A mutations in 12 to 22% of adult AML patients [62] associated with higher WBC count and old age. Higher frequency has been reported in cases with normal cytogenetics. Role of these mutations as an early leukemic event has also been recognized [63, 64]. In meta-analysis conducted by Tie R et al. and Yuan XQ et al., DNMT3A mutations are found to be associated with poor prognosis in de novo adult patients [65, 66]. But it is observed that cases with DNMT3A mutations show higher responsiveness and overall survival with use of DNA methyltransferase inhibitor decitabine [67, 68].

Mixed lineage leukemia (MLL); 11q23 translocation

MLL is the mammalian homolog of trithorax, a drosophila transcriptional regulator that positively regulates homeobox genes [69]. Homeobox genes are a large family of genes which are developmental regulators essential for growth and differentiation of haematopoietic cells [70]. Wild-type MLL regulates HOX gene expression by methylation of histone H3 lysine (H3K4) [71]. MLL rearrangements involve approximately 10% of chromosomal rearrangements overall in patients with ALL, AML, and MDS [72]. In paediatric and adult ALL, the most common translocation partners are the AFF1 gene (previously known as AF4) at 4q21.3 in t(4;11). However, in AML the most common partner is MLLT3 at 9p23 in t(9;11) [73]. It is most commonly seen in infants, associated with therapy related acute leukemia and associated with poor prognosis [74-76].

Kinases

FLT3 mutation

It encodes a type-III receptor tyrosine kinase. Its ligand is a type I transmembrane protein expressed on hematopoietic and other cells of bone marrow. It normally stimulates growth of myeloid & stem cells [77]. When it binds with ligand FLT3 undergoes dimerization and phosphorylation & leads to activation of signal transduction pathways i.e. PI3K/AKT, MAPK/ERK & STAT pathways [78, 79]. Two types of FLT3 mutations are seen, most common is Internal Tandem repeats (ITD) mutations which leads to duplication of juxta-membrane (JM) portion of molecule and it has inhibitory function; when receptor binds with its ligand the inhibitory function is lost [80]. Another less common mutation is Asp825Tyr which leads to activation of FLT3 [81]. The prognostic value of FLT3-TKD is still controversial [82]. FLT3-ITD is detected in most patients with APML (also associated with hyperleukocytosis). FLT3 causes proliferation signals in AML by concomitant balanced translocation or other genetic defects which blocks differentiation is necessary for development of leukemia [81]. It is associated with poor prognosis [83]. In a study by Stirewalt et al. with 140 AML patients aged >55 years the incidence of FLT3-ITD was similar to that of younger patients, and was associated to disease resistance but did not have impact on OS [84]. In a study by Schlenk et al. patients with a high allelic ratio (≥ 0.51) were responded better with allogeneic stem cell transplantation [85] and may be treated with specific FLT-Tyrosine kinase inhibitors [86, 87]. Sorafenib and Midostaurin are examples of first generation FLT3 inhibitors, among all the first generation Midostaurin is the only FLT3 inhibitor approved in the US for the treatment of adult, FLT3 mutated AMLs in combination with standard chemotherapy [88].

Nuclear pore protein-nucleophosmin (NPM)

It is a molecular chaperone that shuttles between cytoplasm and nucleus with particular nucleolar concentration [89]. There are several functions of Nucleophosmin [90] like, transport of Pre-ribosomal particles from nucleus to cytoplasm, regulation of centrosome duplication, regulation of P53 and stabilization of P19ARF. NPM1 mutation is expressed in leukemic blasts at relapse [91]. Mutation leads to unfolding of C terminal domain and disruption of binding to nucleolus [91, 92]. It leads to abnormal subcellular localization of NPM which is normally nucleolar in location, comes to cytoplasm. Homozygous mutation is lethal at embryonic stage [93]. Mutant NPM-1 destabilises tumour suppressor gene protein P14ARF which regulates P53 response. P14ARF is normally localized to nucleolus and escapes cytoplasmic degradation by interaction with NPM [91]. When associated with poor prognostic mutation like FLT3 then it improves the response [83]. According to Angenendt et al. abnormalities in karyotype may nullify the effect of NPM1 mutation on patient outcome [94]. Many drugs have been tried which have their effect inhibiting the action of mutant NPM1 for example *NSC34884* inhibits the action of hydrophobic region of NPM1 required for oligomerization resulting in apoptosis of leukemic cells [95].

Novel genetic mutations in AML

KIT

The stem cell factor receptor (c-kit, CD117) is part of type III receptor TK family. CD-117 is expressed in 70% of CD34 positive cells and also on megakaryocytes. KIT mutations are found in 5% of adult AML cases and 16-46% in CBF subgroup [96, 97]. Point mutation at exon 17 with a gain of function is most common [98]. Prognostic impact of KIT mutations has been studied by Chen et al. in a meta-analysis of 2933 patients which found that KIT mutations adversely affects relapse risk but not CR rate and OS [99]. Screening for KIT mutations might also be useful for targeted therapy using TKIs.

RAS

NRAS mutations are observed in 8-13% of AML patients while KRAS mutations are observed in 2% of such patients. Common sites of mutations are codons 12, 13 or 61. Large scale studies did not find any negative impact of RAS mutations on outcome [100, 101].

Tp53

Tumour suppressor gene Tp53 promotes cell cycle arrest, apoptosis and DNA repair [102] and is mutated in 8-14% of all AML cases.

Alterations are more frequent (69-73%) in patients with complex karyotypes [103]. Tp53 mutations independently indicate poorer prognosis, higher relapse rate and inferior event free survival (EFS) and OS [104-106].

WT1

WT1 gene encodes for a transcription factor involved in cell growth and metabolism [107]. WT1 expression in AML patients is commonly detected and is associated with poor prognosis, resistance to therapy, higher relapse and poor survival rates [108]. Recurrent somatic loss of function mutations is also described in 6-13% AML patients. They include point mutations at exon 1, 7, and 9, leading to formation of protein lacking zinc finger domain. It's role in AML pathogenesis is not completely clear, but is hypothesized to act as epigenetic modifier [109] and epigenetic targeted therapies may be employed.

ASXL1

It is mammalian homolog of additional sex comb like gene, a gene family with dual functions in both epigenetic activation and repression of gene transcription [110].

Mutations in ASXL1 gene are observed in 3-5% of AML cases and 11-17% in patients with intermediate risk (age ≥ 60 years) and secondary AML [111, 112]. In elderly patients, ASXL1 mutations are associated with reduced CR and shorter OS [113].

EZH2

EZH2 catalyses progressive tri-methylation of H3K27 to induce the repression of target genes. Although, it is rarely seen in AML [114], *EZH2* is frequently found genes mutation in childhood AML-M7; seen in 33% DS-AML-M7 & and in 16% of non-DS-AML-M7 cases [115].

Molecular genetics of acute lymphoblastic leukaemia

Acute lymphoblastic leukemia (ALL) is monoclonal neoplastic proliferation of lymphoid progenitor cells. These genetic mutations discussed below may be used for diagnostic prognostic purposes [116]. They can be divided into two main categories either B-ALL or T-ALL depending on the basis of antigen receptor rearrangements (**Figure 2**).

B-cell-acute lymphoblastic leukaemia

They are derived from B lymphocytes and show B cell receptor rearrangement. As seen in AML, the ALLs also show mutations in genes that are involved in various cell cycle pathways and have their prognostic values.

Transcription factor

PAX-5: This is most common mutation seen in 31.7% cases of B-ALL [117]. It is a paired box domain (PRD) transcription factor. In all mutations, DNA binding region and nuclear localization region are retained but C-terminal transactivation domain is deleted [118]. Therefore, these mutations facilitates C-terminal to act as transcription repressor. PAX-5 translocation correlates with normal karyotype. PAX-5 deletion is associated with complex karyotype [119].

Core binding factors (CBF) t(12;21) ETV6/RUNX1 fusion: RUNX-1 translocation present in 25% of paediatrics ALL {t(12;21)} [120]. In this translocation N-terminal of ETV6 (also called TEL) fuses with the coding region of RUNX-1 [121]. It is associated with good prognosis [122]. ETV6 is a transcription repressor & interacts with mSin3A, NCOR & HDAC-3 [123]. HDAC-3 inhibitor TSA inhibits two properties of fibroblasts cells [123], expression of Stromelysin 1 gene, and aggregation. It is the most common mutation in paediatric B-ALL [122]. Another mutation involving the RUNX1 gene leading to ALL is intra-chromosomal amplification of Chromosome 21 (iAMP21). There is a common region of amplification (CRA) on chromosome 21. CRA is associated with complex karyotype and multiple mutations associated with poor prognosis [124]. FISH has revealed ≥ 5 or ≥ 3 extra copies of genes on a single anomalous chromosome 21. In such cases there is shorter EFS and OS when treatment is based on the standard-risk protocols [125]. More intensified chemotherapy may lead to improvement in its poor prognosis [126].

TCF3 (E2A) translocation: They are associated with Pre-B-ALL type phenotype. t(1;19) TCF3/PBX-1 gene fusion on chromosome 19 [127, 128]. TCF3 locus encodes protein which

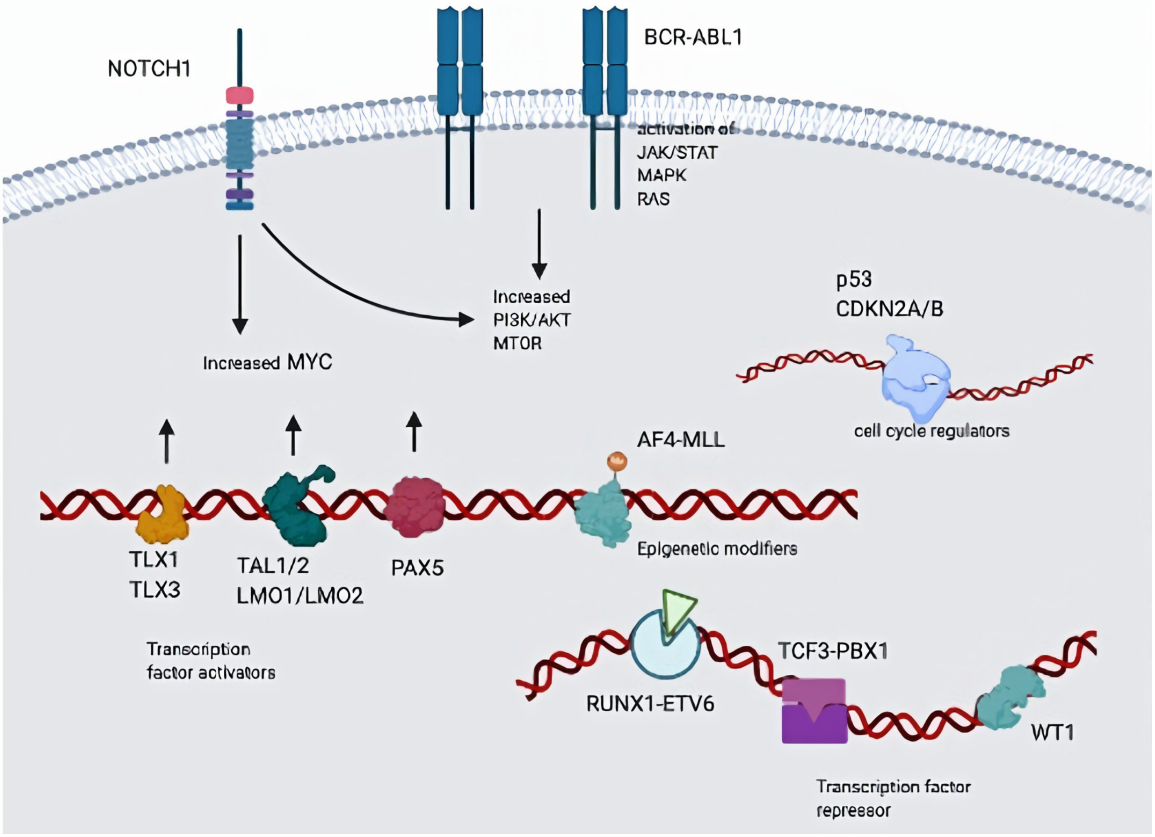

Figure 2. Genetic mutation landscape of ALL; Mutations involved at the level of transcription factor activators are mutations involving TLX1/3, TAL1/2, LMO1/2 and PAX5. Mutations at the level of transcription suppressors are t(12;21) [RUNX1-ETV6] t(1;19) [TCF3-PBX1] and WT1 mutation. Mutations at the level of epigenetic modifiers is t(4;11) [AF4-MLL]. Mutations at the level of kinases are t(8;21) [BCR-ABL1]. Mutations at the level cell cycle regulators are p53 mutation and CDKN2A/B mutations.

belongs to class I of βHelix-loop helix family (β-HLH) of transcription factor [129]. TCF3 (E2A) on heterodimerization interacts through the HLH domain with the member of class II β-HLH protein which is tissue specific. These transcriptional regulators are crucial for control of tissue specific genes during development. E2A protein is preferentially present in B lymphocytes [130]. In absence of E2A protein, there is complete block at the pro B cell stage prior to Ig gene rearrangement. Also, there is defective thymocyte differentiation with increased chances of development of B-ALL [131, 132].

PBX-1 (Pre-B cell leukemia homeobox-1): It forms hetero-dimer with other homeobox proteins via homeodomain and C-terminal HOX cooperative motif (HCM) [133]. PBX-1 is not normally present in lymphocytes. PBX-1 knock-out mice develop multi-organ abnormalities [134]. PBX-1 is not a strong transactivator [135]. TCF3/PBX-1 fusion protein, developed by translocation between chromosomes 1 and 19 {t(1;19)(q23;p13)} has N-terminal 2/3 of TCF-3 protein that contain Activation Domain I & II and DNA binding domain of PBX-1. This leads to strong transactivation of target genes recognized by PBX-1 homeodomain [136]. In Pre-B cells, this transactivation of BMI-1 (its expression normally decreases during hematopoietic development) [137, 138]. BMI-1 inhibits cell cycle inhibitors; CDKN2A [137]. CDKN2A via P14ARF & P16INK4A prevent phosphorylation (inactivation) of Rb gene [139]. It decreases DNA synthesis in S phase [140, 141]. When there is repression of CDKN2A, there is increased DNA proliferation leading to leukemia. Another partner of TCF is HLF leading to t(17;19). TCF3/HLF fusion leads to acute leuke-

mia which is seen in adolescent patients; presenting with coagulopathy & hypercalcemia and usually associated with poor prognosis [142, 143]. Hepatic leukemia Factor (HLF) encodes DNA binding basic Zipper region can homo or heterodimerize with other b-ZIP protein. TCF3/HLF (transactivator of LMO2 & BCL2) is homologous to TCF3/PBX-1 protein. Unlike PBX1, HLF is strong transactivation [144, 145]. The remaining intracellular portion is translocated to the nucleus as a transcription regulator with DNA binding portion of CSL.

IKAROS: IKZF-1 gene encode for IKAROS transcription factor mutated in 76.2% cases of paediatric Ph+ B-ALL [146]. IKAROS is expressed in multi-potent HSCs and promotes lymphoid differentiation & also for repression of genes responsible for self-renewal & multipotency in the differentiating progeny of HSCs [147]. IKZF-1 mutation is associated with down regulation & up regulation of genes involved in cell cycle regulation, apoptosis regulation & DNA damage & JAK-STAT signalling pathway [148]. In B-ALL, there is downregulation of genes involved in B cell differentiation (RAG & EBF-1) which may cause arrest of B cell maturation [148]. Gene expression pattern is the same as BCR-ABL1 positive ALL therefore also known as BCR-ABL-1 like ALL or Ph like ALL [149] associated with mutation of CK receptor & signalling molecules. Therefore, kinase inhibitors can be used for treatment [150].

Kinases

BCR-ABL-1: It results from translocation between chromosome 9 and 22; t(9;22). This is most common ALL in adults [151]. 5' domain of BCR on chromosome 22 fuses with 3' domain of ABL1 gene on chromosome 9 [152, 153]. Mainly two most common types of break point region are there [151], major BCR which are also seen CML and gives rise to 210 KD protein [154], minor BCR which gives rise to 190 KD protein [155] and accounts for 80% of paediatric ALL and 50% of adults ALL [151]. These cases are associated with an aggressive outcome [156]. Up-regulation of BCR-ABL1 fusion gene leads to activation of multiple signalling pathways such as MAPK, Ras, NF-kB, c-Myc, PI-3 kinase, and JAK-STAT [157].

Treatment of Ph+ ALL remains manage-intensive. Initial response to chemotherapy is similar in both Ph+ ALL as well as Ph- ALL, but remissions tend to be short lived in Ph+ cases. However, trials using imatinib in conjunction with standard chemotherapy followed by bone marrow transplant during CR phase have been proven more successful [158, 159].

Novel mutations in B-ALL

RAS signalling: Mutations in various RAS Signalling genes (NRAS, KRAS, FLT3, PTPN11, NF1) are present in 48% of cases [160]. These mutations cause deregulation of the RAS-RAF-mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) kinase (MEK)-ERK signalling cascade [161]. Up regulation of RAS signalling, caused by mutations in RAS genes or in genes coding for proteins controlling RAS functions, represent major pathway for aberrant growth of malignant B-cell precursors [162].

NRAS & KRAS: Out of 3 RAS genes, mutations in HRAS are rare in hematologic tumors [163]. Various studies have identified presence of NRAS & KRAS mutations as recurrent genetic mutations in around 15 to 30% of childhood ALLs [162-164]. Presence of RAS mutations is not a significant risk factor [161, 165] and associated neither with adverse clinical outcome [166] nor with relapse-free survival [164].

PTPN11: PTPN11 encodes for SHP2 protein which is an activator of RAS pathway. Mutations of PTPN11 causes enhanced signalling of RAS through MAP kinase pathway [167]. About 6 to 7.3% children with B-cell precursor ALL have PTPN11 mutations [162, 167]. PTPN11 mutations occur with higher frequency in children and adolescents with hyper diploid DNA content [162].

BRAF: BRAF gene is part of RAF family and acts downstream in the RAS/RAF/MAP kinase pathway. BRAF mutations have been reported in 20% of B-cell ALLs cases [168, 169]. BRAF acts by inhibiting need of cytokine for proliferation of hematopoietic cells leading to their uncontrolled proliferation [168]. According to J.W. Lee et al. BRAF inhibitors can be utilised for treatment of acute leukemias with mutant BRAF [168].

JAK/STAT signalling: JAK mutations in pseudokinase and kinase domains have been observ-

ed in 10% of BCR-ABL negative high risk paediatric ALL cases [164, 170, 171] and these mutations are associated with poor outcome [164]. According to one study, mutations in JAK alleles lead to activation of JAK stat pathway in mouse hematopoietic cells expressing erythropoietic receptor [172]. And also, JAK1/2 inhibitor can be used for treating patients harbouring these mutations [171, 172].

JAK mutations are present simultaneously with mutations in IKZF1 and CDKN2A/B indicating activation of multiple pathways leading to induction of aggressive lymphoid leukemia in high risk BCR-ABL1-ALL [171]. Gain function mutation of JAK2 is seen in about 18% of ALL Down's syndrome (DS-ALL) cases [173] and inhibition of JAK2 may be therapeutically useful in treating such cases [174].

TP53/RB1 pathway: P53 plays a crucial role in cell cycle regulation and apoptosis after DNA damage. TP53 alterations result in either a loss of protein expression or the generation of protein variants with (partly) impaired function. Expression of the p53 protein is strictly controlled by MDM2 and its homolog MDMX, which together form an E3 ubiquitin ligase complex that inhibits p53, resulting in nuclear export and subsequent degradation. Mutations in TP53 suppressor gene are rare events in BCP-ALL, occurring in only 3% of primary cases especially with low hypo-diploid type [175, 176]. In relapsed ALL, the frequency of TP53 mutations increases and represents a strong and independent predictor of treatment failure [177]. There is strong correlation between platelet count and MRD positivity following induction chemotherapy. Therefore, it can be used as prognostic factor for risk stratification trials [178]. "p53 reactivation and induction of massive apoptosis" (PRIMA-1) and its methylated derivative PRIMA-1, also known as APR-246 leads to reactivation of mutant p53 [179].

T cell-acute lymphoblastic leukaemia

They originate from T-lymphocytes. As seen in AMLs and B-ALLs not much is known about the genetics of T-ALLs. However, some of the genes that have some prognostic significance are described in brief here.

NOTCH1

NOTCH1 is a regulatory protein that is important in many cell fate decisions, including commitment to T-cell lineage and choice of αβ lineage [180-182]. It was first cloned from a t(7;9)(q34;q34) translocation occurring in a T-ALL patient [183]. The t(7;9) translocation turned out to be rare in T-ALL but targeted sequencing revealed that over 60% of T-ALL patients have activating mutations in NOTCH1 [184]. NOTCH1 is synthesized as a single polypeptide protein that is cleaved in the golgi body at site S1 into two sub-units, the ligand-binding NEC (extracellular) and NTM (transmembrane), both bind non-covalently at the hetero-dimerization domain. Upon binding of ligand to NEC, the NTM is cleaved at site S2 by a metalloproteases, and cleaved at S3 by gamma secretase [185]. The remaining intracellular portion, ICN1, goes to the nucleus, where it acts as a transcriptional regulator with DNA-binding protein CSL [186]. The majority of the activating mutations in NOTCH1 found in T-ALL occurs in the heterodimerization domain or in PEST domain. The PEST domain regulates the turnover of NOTCH1. Therefore, the hetero-dimerization domain mutants leads to activation of NOTCH1 even in absence of ligand and the PEST domain mutants increases NOTCH1 protein stability [184]. The NOTCH1 has many targets affecting various pathways required for cell maturation. Among these, MYC and HES1 appear to be important for T-cell leukemogenesis [187-189]. The unique proteolytic pathway leading to activated NOTCH1 can be targeted by small molecule inhibitors of the gamma secretase enzyme that is required for S3 cleavage [190, 191].

Transcription factor

TAL1 gene mutations: There are 3 TAL1 related genes; TAL1, TAL2 and LYL1. These genes are not normally present in normal T lymphocytes but various mutations involving these genes leads to aberrant expression of these genes in T-ALLs [192]. TAL1 gene mutation related translocations accounts for 1-3% of all childhood ALLs. They include t(1;14)(p32;q11), t(1;14)(p34;q11) and t(1;7)(p32;q34) with other partner genes such as TR-A and TR-D [193]. Also, there are some point mutations seen in TAL1 gene. All these mutations lead to overexpression of these gene [146]. All these mutations causes silencing of target genes encoding for E47 and E12 variants of E2A transcription factors [194, 195]. TAL-1 overexpression is associated with poor prognosis except TAL-1/TCRα/β gene t(1;14) is having good prognosis

[196]. TAL-1 is expressed in erythroid, megakaryocytes & mast cell lineage but not in T cells. In non-erythroid cells, TAL-1 is expressed in stem cells but not in differentiated cells [197]. Complete absence of TAL-1 is embryonically lethal [198, 199]. Reactivation of silenced genes by administering histone deacetylase (HDAC) inhibitors may prove efficacious in T-ALL patients expressing *TAL1* [193].

TAL2 [t(7;9)(q34;q32)]: TAL2 related translocation juxtaposes with TRB gene, t(7;9)(q34;q32), leading to its activation. Both TAL1 and TAL2 gene promotes proliferation of T-ALL blast by a common pathway [200].

LYL1 [t(7;19)(q34;p13)]: In t(7;19)(q34;p13) LYL1 gene juxtaposes with TRB leading to its activation. In normal T lymphocytes this gene is not expressed but seen in T-ALLs. LYL1-transgenic mice developed CD4+, CD8+ precursor T-cell ALL (pre-T-LBL), by its effect on E2A transcription factor, leading to down-regulation of E2A; as result of block in normal development [200].

LMO gene abnormalities: LMO gene encodes for two types of proteins LMO1 and LMO2. This gene is very frequently rearranged with TCR, resulting in over-expression of LMO1 or LMO2 protein in T-ALLs [201]. De Keersmaecker et al. study on transgenic mice showed that TAL1 expression alone is not sufficient for development of T-ALL and develops only when it is coexpressed with either LMO1 or LMO2 [191].

Homeodomain protein: HOX is major gene family being dysregulated in T-ALL & mutually exclusive to b-HLH gene & LMO gene [202]. This family of transcription factors is divided into two classes. Class I HOX gene includes 4 gene clusters; HOXA, HOXB, HOXC and HOXD present at chromosomes 7p15, 17q21, 12q13 and 2q31 respectively. Class II HOX genes are present throughout the genome. In class I HOX genes HOXA is involved in the development of T-ALL and in class II HOX genes TLX1 (HOX11) and TLX3 (HOX11L2) are the most common genes involved [192].

TLX1 (HOX11) gene translocation: TLX-1 is overexpressed in 7% TALL and associated with good prognosis [203, 204]. Two types of translocations are seen involving TLX1 gene t(10;14) leading to fusion between TLX1 gene and TRA1 and t(7;10) leading to fusion of genes between TLX1 gene and TRB. TLX-1 (associated with t(10;14) TLX-1/TRD) mutation leads block at cortical stage [205, 206]. Loss of TCR rearrangement leads to aberrant expression of TLX1 gene in T lymphocytes [191].

TLX3 (HOX11L2) gene translocation: TLX3 shows fusion of t(5;14)(q35;q32) genes and BCL11B resulting into ectopic expression of TLX3 gene in T lymphocytes [208]. TLX-3 is deregulated by t(5;14) in 20% of adult T-ALL [208, 209]. This ectopic expression of TLX3 gene in children with T-ALL is associated with poor prognosis [191]. Other variants of this translocation is t(5;7)(q35;q21) in which CDK6 gene is fused with TLX3 gene.

Novel gene mutations

Inv(7)(p15q34): The inversion leads to juxtaposition of part of TRB locus 7(q34-35) with the HOX-A cluster 7(p15). This leads to over expression of HOXA10 and HOXA1. HOXA is dysregulated by inv7 in 5% of T-ALL [210-212]. These genes are normally expressed in maturing thymocytes, but, there down regulation is required for normal maturation of both CD4 and CD8 positive T lymphocytes [191]. MLL & its partners PICALM & MLLT10 deregulate expressions of HOX-A. MYB duplication is seen in 8.4% of T-ALL [213, 214]. Deletion or missense mutation of BCL11b gene leads to defect in T cell maturation [215, 216]. PHF6 mutation is 10-fold more prevalent in males and it is uncommon in TLX-negative cases [217].

Conclusion

Molecular studies for genetic mutations that are involved in acute leukaemia's have improved our knowledge about synchrony of various pathobiological events in the form of mutations, expression and changed downstream signalling pathways. This knowledge can be utilized to sub-classify these with the target of prognostic risk stratification and clinical management. The compiled reviews were aimed to give a brief insight of the already discovered and upcoming newer mutation and their contributory role in leukemogenesis. The article also emphasizes the impact of such research being translated in to the treatment protocols with overall arching goal of personalized therapy.

Disclosure of conflict of interest

None.

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