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Influences of Genetic Abnormality on the Risk of Acute Lymphoblastic Leukemia

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Abstract

Recent studies have provided evidence that common genetic variations could account for a proportion of leukemia in adult or children. To evaluate the contribution of candidate gene association studies to the understanding of genetic susceptibility to acute lymphoblastic leukemia we conducted a systematic review from published studies. The polymorphisms of genes encoding carcinogen-metabolizing enzymes (CYP family, NQO1, GST), enzymes involved in folate metabolism (MTHFR, MTRR, SHMT, TS), and DNA repair enzymes (RAD51, XRCC1, ERCC2), chromosome translocation and epigenetic events discussed in this review, can be introduced as candidate alterations in acute lymphoblastic leukemia.

Keyword: Acute lymphoblastic leukemia, genetic predisposition to disease, DNA repair enzymes, translocation, review.

Introduction

A single nucleotide polymorphism (SNP) is a source variance in a genome. A SNP ("snip") is a single base mutation of DNA. SNPs are the most simple form and most common source of genetic polymorphism in the human genome [1].

SNP related functional proteomics involve the identification of functional SNPs that modify proteins and protein active sites structure and function. Functional proteomics is closely tied to modern (post-genomic) drug design, and functional SNP information helps to discover new therapeutic targets [2]. Most interestingly, by developing a database of the modifications generated by functional (coding) SNPs in disease related proteins, new compounds can be made for correcting or enhancing the effects of those mutations in the population [3].

Acute lymphoblastic leukemia (ALL) is a malignant disease resulting from the accumulation of genetic alterations of B or T lymphoid precursor cells [4] and characterized by the malignant clonal proliferation of lymphoid cells that are blocked at an early stage of differentiation. ALL is the most common leukemia in children and accounts for 20% of acute leukemias in adults. The 5-year event-free survival is over 80% for children but only approximately 40% for adults with ALL [5]. Some factors have been introduced for ALL detection. These factors include clinical characteristics [gender, initial white blood cell count (WBC) and age at diagnosis], immunological features (leukemic immunophenotype), and somatic features (non-random recurrent chromosomal aberrations such as the Philadelphia chromosome), as well as germline genetic characteristics, which are assessable at diagnosis [6-8].

The environmental toxicants to which an individual is exposed are biotransformed and eliminated from the body after metabolic conversion mediated by Phase I and Phase II xenobiotic-metabolizing enzymes [9]. Phase I enzymes catalyze hydroxylation, reduction and oxidation reactions of xenobiotics (carcinogens/ drugs), often converting them into more active or toxic compounds [10]. Phase II enzymes catalyze conjugation reactions (glucuronidation, acetylation, methylation), thereby converting the metabolites into non-reactive, water-soluble products that are eliminated from the organism [11]. The genetic polymorphism underlying the variation in enzyme activity can modify susceptibility to diverse cancers, probably by influencing the activation and removal

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of toxicants [12].

Here we present a review to present a good model for studies that want to investigate the genetic abnormality and find a probable pathway for increased risk to ALL.

Genetic

Gene mutations

Carcinogen metabolism genes

Metabolic gene variants that have been investigated as risk factors for ALL include polymorphisms in NQO1 (NADPH: quinone oxidoreductase) a cytosolic enzyme catalyzing reduction of quinones and prevention of their participation in redox cycling and thus in oxidative stress [13, 14]. Moreover, this protein was shown to interact with and stabilize the tumor suppressor protein p53 [15, 16]. NQO1 is expressed in most tissues including the bone marrow, where expression is thought to be highly inducible by xenobiotic with quinone moieties, and is up regulated during times of oxidative or electrophonic stress [17]. NQO1 can contribute to the formation of reactive oxidation species via oxidative cycling and therefore can act as a pro-oxidant [18].

Cytochrome P450 (CYP) 1A1 is a key enzyme in phase I bioactivation of xenobiotics and its polymorphism is associated with elevated enzymatic activity [19]. The P450 cytochrome system (CYP450) is a group of enzymes involved in steroid hormone biosynthesis as well as in metabolic activation of carcinogens [20]. genetic variants of enzymes which are involved in the oxidation activation and subsequent conjugation detoxification of carcinogens, such as PAHs and aromatic amines, may also play a role in susceptibility to leukemogenesis [21, 22].

Another member of carcinogen metabolism genes are glutathione S-transferases, a family of phase-II enzymes responsible for the detoxification of mutagenic electrophiles including polyaromatic hydrocarbons (PAHs) [23]. Glutathione S-transferase (GST) gene is one of the potential candidate genes to increase the risk of leukemia because it plays a significant role in Cadmium (a carcinogen) biotransformation and detoxification [24]. The principal function of GST enzymes is conjugation of hydrophobic and electrophilic compounds with reduced glutathione. The intracellular binding reaction with GSH is catalyzed by the GSTs and leads to stable GSH-metal conjugates being transported out of the cell and excreted via feces and urine [25]. Seven GSTs gene families (Alpha, Mu, Pi, Theta, Sigma, Omega, and Zeta) have been described and genetic polymorphisms have been reported for GSTM1, GSTP1, and GSTT1, resulting in altered enzyme activity [26, 27]. GSTT1 and GSTM1 are particularly important, because they have a deletion polymorphism resulting in impaired catalytic activity, which is associated with greater sensitivity to toxic compounds. The homozygous deleted (null genotype) of GSTT1 and GSTM1 genotypes have been associated with the loss of the enzyme activity and enhanced genotoxicity, and are believed to be key factors in determining susceptibility to diseases associated with exposure to xenobiotics such as leukemia [28] .

The human multidrug resistance 1 (MDR1) gene encodes P-glycoprotein, a membrane transport protein that extrudes a wide variety of lipophilic compounds, including xenobiotic and cellular metabolites [29]. P-glycoprotein uses an ATP-dependent efflux transport mechanism to minimize the exposure of potentially toxic compounds to the intracellular environment [30]. Interestingly, MDR1 is also highly expressed in several subclasses of bone marrow and peripheral leukocytes [31]. There is evidence demonstrating the involvement of P-glycoprotein in the release of interleukin-2, interleukin-4, and IFN-γ from lymphocytes [32].. Accordingly, P-glycoprotein could serve a role in leukemia etiology based on its transport of xenobiotics or modulation of immune function.

Folate metabolism genes

Dysfunctional folate metabolism is an attractive candidate in the etiology of ALL [33]. Folate levels along with genetic regulation of folate metabolism have been the focus of many investigations [34-37], predicated on the notion that they may influence the creation and/or expansion of the preleukemic clone via DNA hypomethylation of key regulator γ genes as well as uracil misincorporation into DNA, leading to double-strand breaks and chromosomal aberrations [38, 39]. Central to folate metabolism are the enzymes 5,10-methylenetetrahydrofolate reductase (MTHFR;), methionine synthase (MTR) and methionine synthase reductase (MTRR;). variants in These genes may impact on ALL risk through affecting folate metabolism [40-43]. Serine

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hydroxyl methyltransferase (SHMT), thymidylate synthase (TS) and reduced folate carrier 1 (RFC1, a Folate transport), has also been proposed as risk factors for ALL [37, 44, 45].

A critical component of the folate metabolic pathway is methylenetetrahydrofolate reductase (MTHFR), which controls the balance between DNA methylation and synthesis via the irreversible conversion of 5,10-methylenetetrahydrofolate (5,10-MeTHF), required for DNA synthesis, to 5-methyltetrahydrofolate (5-MeTHF), a methyl donor for conversion of homocysteine to S-adenosylmethionine (SAM). Two common polymorphisms in MTHFR (677 C>T and 1298 A>C) result in decreased catalytic activity [46, 47]. Methionine synthase is a vitamin B12-dependent enzyme, which catalyzes the remethylation of homocysteine to methionine and the concurrent demethylation of 5-methyltetrahydrofolate to tetrahydrofolate. Methionine synthase has a key role in maintaining adequate intracellular folate, methionine and normal homocysteine concentrations. Methionine is an essential amino acid and precursor of S-adenosylmethionine, which is a universal methyl-group donor involved in methylation reactions including DNA methylation[48]. Polymorphism in methionine synthase (MTR) gene was initially thought to be associated with lower enzyme activity causing homocysteine elevation, DNA hypomethylation, CpG island and hypermethylation in tumor suppressor genes[49]. SHMT1 SNPs reduce the circulating folate levels, thus shunting 5,10-MeTHF toward DNA synthesis[50]. Another important enzyme in folate metabolism is thymidylate s ynthetase, a crucial factor in the synthesis of dTMP (2 ′-deoxythymidine-5 ′-monophosphate) in dividing cells that inhibition of either leads to "thymineless death". Thus TS represents an attractive target for developing antitumor agents, since genetic variant in this gene causes decreased enzyme activity, which is related to cancer [51].

DNA repair genes

Leukemia commonly arises as a result of DNA translocation, inversion or deletion in genes regulating lymphocyte development. Formation of translocations in leukemia are thought to involve DNA double-strand break formation by means other than aberrant V(D)J recombinase activity[53]. ALL is characterized by specific chromosomal abnormalities, such as translocations and changes in ploidy, that may result from unrepaired DNA damage such as double-strand breaks (DSBs) [33].

Alterations in innate DNA repair, cell cycle, or genomic maintenance processes may play a role in leukemia development [54] ,therefore DNA repair gene variants have been introduced as risk factors for ALL [55, 56]. SNPs in RAD51 gene, a protein

essential for homologous recombination and DNA repair, have been reported as risk factor in increased risk to ALL [57]. XRCC1 (X-Ray repair-cross complementing group 1) play a role in DNA single strand repair by forming protein complexes with DNA repair associated proteins [58]. There have been a number of studies on the association between XRCC1 polymorphisms and the risk of ALL [59-64]. Polymorphic variants in other DNA repair genes, including ERCC2 (excision repair-complementing group 2) have also been evaluated as risk factors for ALL for similar reasons [65]. BRCA2 plays a key role in the maintenance of genomic integrity, particularly through regulation of DNA repair by homologous recombination repair (HR)[66], a process that is also controlled by another tumor suppressor protein, BRCA1. HR is a largely an error-free process that restores the original sequence at the site of a DNA double-strand breaks (DSBs)[67].

Chromosome translocation

The development of ALL involves chromosomal changes including translocations causing fusion genes, as well as hyperdiploidy containing more than 50 chromosomes [4]. MLL rearrangements including t(4;11), t(11;19) and t(9;11) translocations are found in 8–13% of both adult and pediatric B-ALLs [68]. The most common alterations above 1 Mb have been reported as deletion 6q , 12p and 9p and duplication 4q and Xq [69]. The t(1;19) translocation in pediatric pre-B-cell acute lymphoblastic leukemia (ALL) fuses the genes, which encode the transcriptional activator E2A and homeobox pre-B-cell leukemia transcription factor 1 (PBX1), resulting in expression of the chimeric transcription factor E2A-PBX1. E2A-PBX1 can promote cell transformation both in vitro and in vivo [70]. The rare translocation t(8;14)(q11.2;q32) has been described in patients with B-cell acute lymphoblastic leukemia (ALL) [71]. The most significant structural chromosomal changes include: the poor-

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risk abnormalities; t(9;22) (q34;q11), giving rise to the BCR/ABL fusion and rearrangements of the MLL gene; abnormalities previously designated as poor-risk; t(1;19) (q23;p13), producing the E2A/PBX1 and rearrangements of MYC with the immunoglobulin genes; and the probable good risk translocation t(12;21) (p13;q22), which results in the ETV6/AML1 fusion (72). These abnormalities occur most frequently in B-lineage leukemias, while rearrangements of the T cell receptor genes are associated with T-lineage ALL. Abnormalities of the short arm of chromosome 9, in particular homozygous deletions involving the tumor suppressor gene (TSG) p16(INK4A), are associated with a poor outcome [73]. Numerical chromosomal abnormalities are of particular importance in relation to prognosis. High hyperdiploidy (51-65 chromosomes) is associated with a good risk, whereas the outlook for patients with near haploidy (23-29 chromosomes) is extremely poor [74].

Epigenetic

Abnormalities in the epigenetic regulation of chromatin structure and function can lead to aberrant gene expression [75]. Chromatin remodeling is an important mechanism of epigenetic gene dysregulation in human cancers [76]. The epigenetic mechanisms currently believed to play a role in cancer include:

1) DNA methylation of cytosine bases in CG rich sequences, called CpG Islands; 2) post-translational modifications of histones, which are proteins that form the nucleosomes, which regulate the packaging structure of the DNA (called chromatin); 3) micro RNAs and non coding RNAs; and 4) nucleosome positioning [77].

Aberrant methylation of tumor suppressor genes is observed frequently in human malignancies, including acute leukemias [78]. Aberrant epigenetic lesions, in particular DNA methylation of promoter associated CpG islands, are common in acute lymphocytic leukemia (ALL) [79]. Hypermethylation of EPHA2 , -A4, -A5, -A6, -A7, -A10, EPHB1, -B2, -B3, -B4, EFNA1, -A3, -A5, and EFNB1 a nd -B2 genes have been detected in leukemia cell lines and primary ALL bone marrow samples [80]. The role of aberrant epigenetic modifications in cancer development and particularly in hematological malignancies such as acute leukemias has clearly been recognized [81]. It has been found that 154 genes are methylated in ALL patients. Interestingly, the expression of 13 genes implicated in the TP53 pathway is downregulated by hypermethylation[82]. Expression of ASPP1 is significantly reduced in ALL and is dependent on hypermethylation of the ASPP1 gene promoter. Abnormal ASPP1 expression is associated with abnormal function of the tumor-suppressor gene TP53 in ALL [83]. DNA methylation of promoter-associated CpG islands in estrogen receptor (ER), multidrug resistance gene 1 (MDR1), p73, p15, and p16 genes is the epigenetic DNA modification observed in acute leukemias [84]. It has been reported PPP2R3A (protein phosphatase 2, regulatory subunit B", alpha) is frequently methylated in T and B-ALL. While FBLN2 (fibulin 2) and THRB (thyroid hormone receptor, beta)

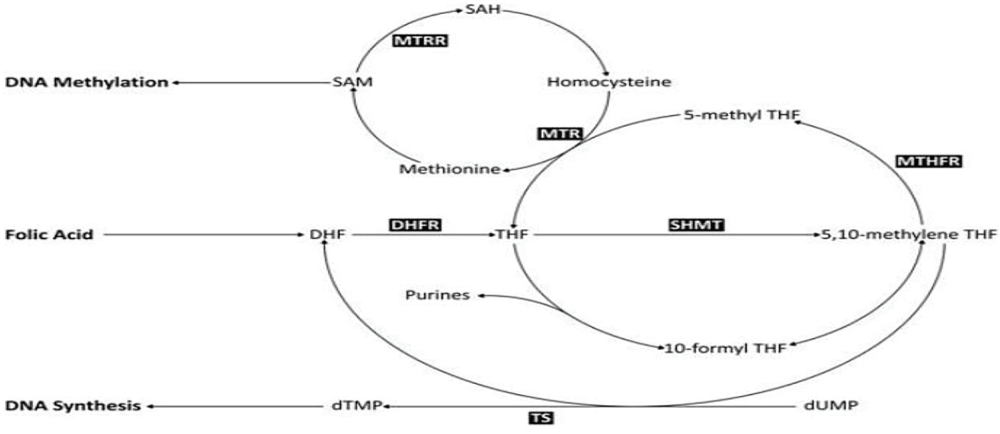


Figure 1: Metabolic folate pathway.

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show frequent methylation in B-ALL, but are less frequently methylated in T-ALL[85]. A recent large-scale genome-wide study to identify genes methylated in adult ALL employing different high throughput approaches validated 15 genes as showing frequent methylation in ALL (GIPC2, RSPO1, MAGI1, CAST1, ADCY5, HSPA4L, OCLN, EFNA5, MSX2, GFPT2, GNA14, SALL1, MYO5B, ZNF382, MN1) (79). The post-translational modification of the core histones is critical to the regulation of chromatin structure that influence gene transcription [86]. Also, histone modifications contribute to the dysregulation of miRNAs in acute lymphoblastic leukemia (ALL) [87].

Conclusion

Genetic alteration in ALL has been extensively

Table1: Polymorphism of genes as risk factor for acute lymphoblastic leukemia.

Class/Gene	Polymorphism	Effect
Carcinogen metabolism		
CYP1A1	CYP1A1*2A,T6235C (rs4646903) CYP1A1*2B/*2C, A4889G (rs1048943)	Increased enzymatic activity
CYP2D6	CYP2D6*4, G1934A (rs3892097) CYP2D6*3, del2637 (rs35742686)	Abnormal splicing Premature termination
CYP2E1	CYP2E1*5B, G-1293C/C-1053T, (rs3813867/ rs2031920)	Altered expression in vitro
GSTT1	Deletion	Absent activity
GSTM1	Deletion	Absent activity
GSTP1	A1578G (rs1695)	Altered activity
NQO1	C609T (rs1800566), C465T (rs1131341)	Abolishes activity Alters mRNA splice site
MDR1	C3435T (rs1045642) G2677T/A (rs2032582)	Lower expression Altered activity
Folic acid pathway		
MTHFR	A1298C (rs1801131) C667T (rs1801133)	Altered activity Decreased activity
MTRR	A66G (rs1801394)	Altered activity
MTR	A2756G (rs1805087)	Reduced activity
SHMT	C1420T (rs1979277)	Reduced red blood cell folate levels.
RFC1	G80A (rs1051266)	Unknown
TS	Tandem repeat polymorphism in the 5-prime un-translated region	Triple-repeat allele results in higher TYMS expression
DNA repair pathway		
ERCC2	A35931C (rs13181) G23591A (rs1799793)	
XRCC1	C26304T (rs1799782) G27466A (rs25489) G28152A (rs25487)	Defective polymerase β Defective polymerase β Defective polymerase β
BRCA2	rs139052578	Reduced activity
RAD51	(G135C) rs 201838885	Altered activity

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studied, and it continues to evolve. Advances in understanding of chromatin structure, histone modification, transcriptional activity, DNA methylation gene mutation, have lead to an integrated approach to the role of genetic and epigenetics in carcinogenesis. The deeper understanding of the mechanisms of lymphoblastic genetic alterations and epigenetic phenomenon, opens ways to define the prognosis of this common cancer.

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