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Chapter

Genetic Polymorphisms of Xenobiotics-Metabolizing Enzymes Contributing to Leukemia

Entesar Tebein and Abozer Y. Elderdery

Abstract

Polymorphisms in xenobiotic-metabolizing enzymes have been linked to an increased risk of developing leukemia (XMEs). XMEs are found in all higher organisms and are one of the first lines of defense against environmental chemicals. Toxins, including therapeutic agents, are completely metabolized and eliminated from the body by an enzyme system that is encoded by specific genes. The majority of these genes are polymorphic, and some of the polymorphic forms have altered enzyme activity. Phase I XMEs, such as cytochrome P450s (CYPs), and phase II biotransformation enzymes, such as glutathione S-transferases (GST), UDP-glucuronosyltransferases (UGT), and N-acetyltransferases (NAT), are the most important. The majority of genetic variation discovered during clinical testing is due to single-nucleotide polymorphisms (SNPs). The purpose of this chapter is to highlight information about of some genetic polymorphisms of XMEs, contributing to AML, ALL, CML, and ALL. Several keywords were used to search the databases PubMed, Google Scholar, and Web of Science. Currently, numerous manuscripts suggested that genetic polymorphisms of XMEs were associated with ALL, CLL AML, and CML susceptibility.

Keywords: polymorphism, xenobiotic, SNPs, ROS

1. Introduction

Leukemia is a blood cancer that affects the hematopoietic system. Due to a variety of complicated features [1], it has a depraved prognosis. Leukemias are classified primarily by the type of white blood cells affected as myeloid or lymphoid, and as acute or chronic, based on the percentage of blasts or leukemia cells in bone marrow or blood [2]. There are four main types: leukemia, namely acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML) [3]. Despite the fact that leukemogenesis research has been going on for a long time, the mechanisms underlying the development of this hematologic malignancy are still unknown [1]. Leukemia is known to be caused by a number of risk factors, including genetic variables such as constitutional genetic variation in components of DNA damage response pathways, which have become the focus of research [4, 5].

Variants that are more common than mutations in the genome, such as short tandem repeats (STR), variable number tandem repeats (VNTR), and (SNPs), began to be identified more rapidly with the completion of the human genome project and the development of new technologies [6]. This strongly shows that SNPs could be utilized as an useful biomarker for assessing an individual's genetic background for cancer prognosis, and it points to an exciting new area of cancer research [7].

The interaction between environmental contact and genetic factors has been hypothesized as expected cause of various types of cancers [8]. Functional polymorphisms in the genes encoding detoxification enzymes cause inter-individual differences, which contribute to leukemia predisposition [9].

XMEs are found in all eukaryotes, which act as first line against environmental chemicals, toxic materials, and biotransformation of drugs present in the cells. The most important XMEs are classified into phase I such as cytochrome P450s (CYPs), and phase II biotransformation enzymes, glutathione S-transferases (GST), UDP-glucuronosyltransferases (UGT), and *N*-acetyltransferases (NAT) [10].

In recent years, an increasing number of studies have indicated that cancer beginning is a complex process involving genetic predisposition as well as diverse environmental variables [11–13]. As a result, identifying genetic risk factors that contribute to the large burden of disease in the general population is necessary for the development of wide cancer preventive therapy techniques [7]. Therefore, variations in GSTM1, GSTT1, methylenetetrahydrofolate reductase (MTHFR) C677T, and XRCC1 Arg399Gln have been linked to an increased risk of leukemia [14] . The aim of this chapter is to highlight on information of some genetic polymorphisms of XMEs contributing to AML, ALL, CML, and ALL.

2. Xenobiotic

The word xenobiotic is derived from Greek word Xeno meaning strange and biotic meaning life; thus, xenobiotic defined as foreign compound initiating from medicine, food, pesticides, or environment is actively transported and metabolized by the renal proximal tubular cells [15]. *Toxicity in biological systems caused by xenobiotic is variable*, so that the xenobiotics that arrive in living cells are eliminated through the XMEs [16, 17]. Xenobiotic metabolism and biotransformation occur in phases, namely phase 1, 11, and 111 reactions [18]. Hydrophobic molecules are converted into more polar, hydrophilic metabolites during phase I reactions (cytochrome P450), which are more easily excreted by the excretory system via oxidation, reduction, or hydrolysis. Various transferases are involved in phase II biotransformation reactions (also known as the conjugation phase); the most common form of exogenous compound conjugation is the reaction of glucuronide formation catalyzed by UDP-glucuronyl transferases. Conjugates are also more polar and soluble in water than parent substances, so they are excreted from the body more easily. In phase III, these transformations allow for the transport and excretion of xenobiotic metabolites. It is divided into superfamilies: SLC transporters and ATP-binding cassette (ABC) transporters (**Figure 1**) [17, 19, 20].

2.1 Metabolism of xenobiotic

The body eliminates xenobiotics through xenobiotic metabolism. This consists of xenobiotic deactivation and excretion, which occur primarily in the liver. Urine, feces, breath, and sweat are the four excretory routes. Hepatic enzymes are responsible for
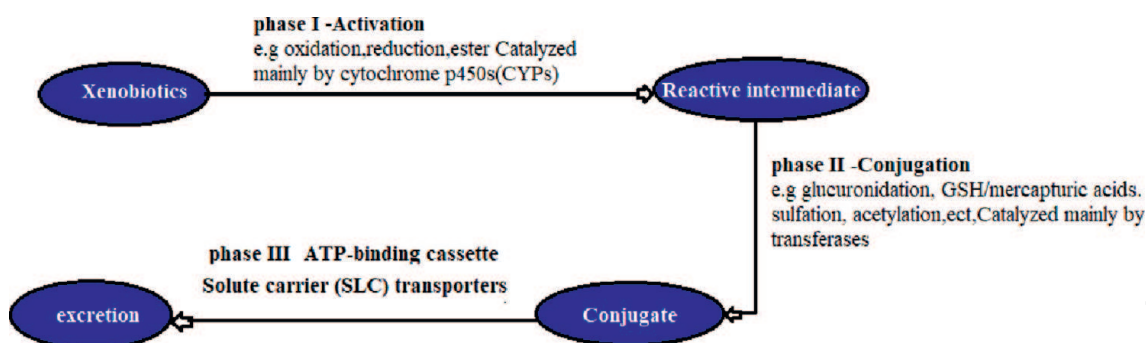
Figure 1.
A schematic representation of the pathways of biotransformation enzymes (phases 1, 11, and 111).

xenobiotic metabolism, which involves first activating, then oxidizing (via cytochrome P450 monoxygenases, flavin-containing monoxygenases, or alcohol/aldehyde dehydrogenases), reduction (*via* cytochrome P450 reductases), hydrolysis and/or hydration (*via* esterases and epoxide hydrolases), and finally conjugating the active secondary metabolite with glucuronic acid, sulfuric acid, or glutathione, and finally by excretion in bile or urine [21].

Biotransformation comes with the generation of reactive oxygen species (ROS) through a multitude of reactions both directly by releasing ROS as part of the respective reaction and indirectly as a consequence of the products generated by transformation of the xenobiotic [17].

The transition from the biotransformation of drugs, xenobiotics, and environmental pollutants causes an increase in free radical production in the body, resulting in lipid peroxidation, oxidative stress, and oxidative damage. Free radicals interact with various macromolecules such as nucleic acids, proteins, and lipids, altering critical intracellular signaling pathways that are responsible for cellular homeostasis maintenance [22].

Free radicals disrupt cellular equilibrium and cause mitogenesis, mutagenesis, genotoxicity, and cytotoxicity, either directly or indirectly through the mediation of oxidative and inflammatory signals. The role of free-radical-mediated damage in the pathophysiology of various diseases such as diabetes, hypertension, atherosclerosis, infertility, and cancer [23].

2.2 Genetic variation in xenobiotic metabolism and leukemia risk

Toxins, including therapeutic agents, are completely metabolized and eliminated from the body by a system of enzymes encoded by specific genes. The majority of these genes are polymorphic, with some polymorphic forms exhibiting altered enzyme activity. Enzymes involved in phase I (bio-activation) and phase II (detoxification) metabolism maintain a critical balance of activation and inactivation of a wide range of chemical exposures that cause ALL, AML, CML, and CLL [12, 24–29].

3. Phase 1 genetic polymorphisms most frequently associated with AML, ALL, CLL, and CML

Cytochrome P450 (CYP450), a phase I biotransformation enzyme, is responsible for the metabolism of both endogenous and exogenous compounds and has the

ability to convert xenobiotics or procarcinogens into DNA reactive metabolites [30]. The human genome contains 57 putatively functional, protein-coding cytochrome P450 (CYP) genes, which have been classified into 18 families and 44 subfamilies based on sequence homology. Over a dozen CYP isozymes from families 1, 2, 3, and 4 are primarily responsible for drug and xenobiotic metabolism [31]. The majority of these polymorphisms, such as T6235C of CYP1A1 (CYP1A1*2A), C-1019T of CYP2E1 (CYP2E1*5B), and A290G of CYP3A4 (CYP3A4*1B), are thought to increase enzymatic activity. They have been linked to the bioactivation of several chemical carcinogens as well as the conversion of polyaromatic hydrocarbons in tobacco smoke into intermediate reactive metabolites, some of which can cause DNA damage [32]. The CYP1 family's expression increases in lymphoblastic and myeloblastic cell lines and plays a role in environmental factor detoxification. As a result, CYP1A1 enzymes may be involved in the development of cancer in hematopoietic cells. Indeed, there is evidence that an increased frequency of the CYP1A1 Val/Val genotype in ALL patients is a risk factor for developing ALL [33].

AML is a group of diseases characterized by clonal expansion of immature myeloid blasts, resulting in hematopoietic failure [34]. Through the inactivation of enzymatic activity, certain SNPs at the CYP genetic loci (CYP2D6, CYP1A1, CYP3A5, and CYP2E1) may be considered risk factors for many types of cancer and hematological malignancies, such as AML, ALL, and myelodysplastic syndromes (MDS) [35].

A number of studies have been undertaken to determine the role of CYP450 polymorphisms in the development of AML leukemia; however, these yielded conflicting findings. Increased susceptibility to AML has been described by Botros *et al.*, who state that A CYP2B6 gene mutation increases the risk of developing AML by threefold (odds ratio [OR], 3.0; 95% confidence interval [CI], 1.3–6.9), whereas a CYP3A4 gene mutation increases the risk by approximately fourfold (OR, 3.8; 95% CI, 1.4–10.1) [35]. According to the dominant model, the T3801C polymorphism in CYP1A1 is associated with an increased risk of AML in Asians [14, 36]. According to Gassoum et al., genetic polymorphisms in CYP1A1 heterozygous AG show no significant association with AML, whereas homozygous GG shows a protective effect. CYP2D6 shows no association with AML risk in both heterozygous intermediate metabolizer (IM) and mutant homozygous poor metabolizer (PM) [37].

ALL accounts for about 10% of leukemias in the United States. About 6000 new cases of ALL are diagnosed each year, and ALL accounts for approximately 74% of the leukemia cases among children [38]. Polymorphisms in xenobiotics are thought to influence susceptibility to childhood ALL [39].

Swinney et al. investigated the link between CYP1A1 and ALL susceptibility in three ethnic groups, namely Caucasian, Hispanic, and African-American children. Overall, CYP1A1*2C and *2B homozygous variant alleles have been linked to an increased risk of ALL [40]. Vijayakrishna and Houlston conclude in a meta-analysis that there is a significant association between CYP1A1*2A and childhood ALL [41]. Pakakasma et al., on the other hand, found no significant difference in the distribution of CYP3A4(A290G) polymorphism between case and control [42]. This disparity may be explained by differences in acute leukemia risk factors between children and adults [35].

CML is one of several diseases known collectively as a myeloproliferative disorder of pluripotent hemopoietic stem cells (HSCs). In this case, chromosomal translocation results in an oncogenic BCR-ABL gene fusion that increases tyrosine kinase (TK) activity. Kinases that are abnormally activated disrupt downstream signaling pathways, resulting in abnormal cell proliferation, differentiation, and resistance to cell

death [43]. Joshi *et al*. reported the CYP2C19 gene polymorphisms in susceptibility to CML. Taspiner *et al*. suggested that polymorphic CYP1A1 and GSTT1 genes appear to affect susceptibility to CML [33].

One of the most common types of leukemia is CLL. It most commonly affects elderly patients and has a highly variable clinical course. Specific genomic changes that disrupt the regulation of proliferation and apoptosis in clonal B-cells initiate leukemic transformation [44]. Only one study found that Cytochrome P450 Allele CYP3A7*1C rs45446698 was associated with CLL mortality [45].

4. Phase 11 genetic polymorphisms most frequently associated with AML, ALL, CLL, and CML

Among the XMEs, the NAT and GST enzymes, both of which are phase II enzymes, are of particular interest to hematologists because they metabolize a variety of products, including chemotherapeutic and carcinogenic agents, and they serve as targets for antitumor drug therapies [46].

Phase II enzymes catalyze the conjugation of glutathione or glucuronide with reactive electrophiles and thus detoxify procarcinogens and carcinogens. GST group is widely expressed in mammalian tissues and has broad substrate specificity. GSTs are polymorphic genes and involved in the metabolism of a wide range of xenobiotics, including environmental carcinogens, chemotherapeutic agents, and reactive species. The frequencies of GSTs polymorphic alleles especially GSTT1 and GSTM1 have been reported in various cancers [33]. Previous study by Mortazavi *et al.* identified that GSTT1 null genotype can increase the risk of AML, particularly when combined with CYP1A1*2A allele. GSTM1 null genotype can also play a protective role and reduce the risk of AML [25]. A study conducted by Lemas et al. stated that the *GSTM1* analysis failed to reveal any association with the CLL [47].

Regarding the theoretical correlation between NAT2 SNPs and cancer, a variety of reports have been published to date [12, 48–50]. Among these, the data described by Zou *et al*. reported that *NAT2* gene polymorphism rs1799931 was associated with decreased risk of AML and was likely to be a protective factor against AML development [12]. Contradictory to this findings, a study by Abdel Ghafar *et al*. showed that NAT2 gene rs1799931 (G857A) is associated with increased susceptibility to AML in the Egyptian population [51]. A meta-analysis by Jiang *et al*. investigated the relationship between NAT2 polymorphisms and onset risk of acute leukemia and reported there is no significant difference found between the fast-acetylator incidence of NAT2 haplotype and the onset risk of acute lymphoblastic leukemia (ALL, OR = 0.70, 95% CI = 0.45–1.08) or AML, OR = 0.79, 95% CI = 0.46–1.47) [52]. No significant difference was found in NAT2 fast and slow acetylator frequencies between CML patients and controls [47], while Tebien et al. revealed the protective effect of NAT2A 803G and G857A against CML [43].

5. Detection of genetic polymorphisms in leukemia

Clinical genetic testing is being used more frequently in the treatment of cancer patients. By providing information on future illness risk, diagnosis confirmation, and more recently, therapy choice, and prognosis, these tests aid in a range of clinical decisions. SNPs account for the majority of genetic variation found during clinical

testing [53]. DNA extraction is the first step in any SNP detection test [54]. Methods of genotyping commonly used were gel-electrophoresis-based genotyping methods include polymerase chain reaction (PCR) coupled with restriction fragment length polymorphism analysis [55], multiplex PCR [56], as well as allele-specific amplification fluorescent dye-based high-throughput genotyping procedures such as oligonucleotide ligation assay [57], next-generation sequencing (NGS) [58], and TaqMan allelic discrimination [59].

6. Conclusion

XMEs are found in all eukaryotes and serve as a first line of defense against environmental chemicals, toxic materials, and drug biotransformation in cells. The most important XMEs are classified as phase1, phase11, and phase111 biotransformation enzymes. The interaction of environmental and genetic factors has been proposed as a possible cause of various types of cancer. Functional polymorphisms in genes encoding detoxification enzymes cause inter-individual differences that contribute to leukemia susceptibility. Enzymes involved in phase I (CYP enzymes) and phase II (N-acetyltransferases (NAT) and glutathione S-transferases) metabolism regulate the activation and inactivation of a wide range of chemical exposures that cause ALL, AML, CML, and CLL. Several studies have been conducted to determine the role of xenobiotics genetic polymorphisms in the development of AML, ALL, CLL, and CML, with the majority of them yielding significant results.

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