Polymorphisms in the xenobiotic genes and susceptibility to bladder cancer

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Summary

It is thought that the interaction between genetic and environmental factors accounts for the different levels of susceptibilities to the development of bladder cancer. The well known etiological risk factors of bladder cancer are occupational exposure to certain carcinogens and cigarette smoking. Therefore, polymorphisms in the genes coding for the xenobiotic-metabolizing enzymes may cause individual variations in metabolizing the exposed carcinogens. Here we aimed to review the metabolising genes and respective polymorphisms and to demonstrate the association between xenobiotic-metabolising gene polymorphisms and bladder cancer. Among metabolizing enzymes, we will introduce N-acetyltransferases (NAT), glutathione-S-transferases (GST), sulphotransferases (SULT), NAD(P)H dehydrogenase quinone 1 (NQO1), methylenetetrahydrofolate reductase (MTFR), cytochrome P-450 (CYP) and aldo-Ketoreductases (AKR) with special emphasis on the last two enzyme group.

Keywords: Bladder cancer, xenobiotic metabolism, metabolising genes, genetic susceptibility, genetic polymorphism

Introduction

Cancer is regarded as a multifactorial disorder affected both by genetic and environmental factors, which culminate in dysregulated cell cycle. Although environmental risk factors are considered as the most important among others, epidemiological studies have shown that a certain part of the population is in fact more prone to develop cancers despite being exposed to the same type and amount of environmental risks. This
finding has led the molecular epidemiology studies to focus on predisposition to cancer via genetic factors. It has been speculated that either the polymorphisms in the DNA repair genes or those in carcinogen metabolizing genes should primarily be questioned as possible candidates of genetic modifiers. The polymorphisms in the DNA repair genes may alter the function of the related enzyme and thereby affect the repair capacity of the individual. This kind of alteration in the DNA repair mechanism may get the individual more sensitive to carcinogens and more susceptible to cancer formation (Franekova et al., 2008). Likewise, polymorphisms in the genes coding for the xenobiotic-metabolizing enzymes may cause individual variations in metabolizing the exposed carcinogens (Longuemaux et al., 1999). As a result, individuals with a certain genetic background may become more susceptible to develop cancer.

Xenobiotic metabolism

Xenobiotic metabolism (from the Greek xenos "stranger" and biotic "related to living beings") is composed of several metabolic pathways that modify the chemical structure of xenobiotics, e.g. drugs, carcinogens, poisons. Upon their intake by an organism, xenobiotics undergo several metabolic conversions to facilitate their solubility in order to expedite their removal from the organism. These so-called biotransformation processes consists of two consecutive steps; an initiation phase, where carcinogens are modified to accept reactive groups (Phase I) via the action of cytochrome P450 oxidases; and a second phase where they are converted into more easily extractable molecules by conjugation reactions (Phase II) via transferase enzymes. The xenobiotic metabolism can be regarded as a detoxification mechanism consisting of two phases, however, conversion reactions catalyzed by xenobiotic-metabolising enzymes can also activate potential carcinogens (Figure 1.). The reason for this is the vastly diverse chemical structures of carcinogens which can not be compensated by the limited number of conversion reactions catalyzed by xenobiotic enzymes. The capability of the xenobiotic metabolism to either activate or detoxify carcinogens constitute a fragile balance between activation and detoxification of carcinogens, which defines the amount of DNA damage accumulated in the cells. Alterations affecting enzyme activity shifts this balance towards either detoxification or activation of carcinogens.

Metabolising genes and susceptibility to bladder Cancer

Polymorphisms in the xenobiotic-metabolising genes are pivotal to the above-mentioned alterations and therefore have been intensively investigated in many cancer types. Foremost of these cancers is the bladder cancer, for which the well-known etiological risk factors are occupational exposure to certain carcinogens and cigarette smoking. In fact, smoking is proved to be the primary cause of approximately 70% of the bladder cancer cases (Parkin 2008). It is thought that the interaction between genetic and environmental
factors accounts for the different levels of susceptibilities to the development of bladder cancer. Bladder cancer incidence varies highly between distinct regions worldwide, with developed countries having the highest incidence (Silverman et al., 1999; Parkin et al., 2002). Higher bladder cancer incidence in developed countries despite increased awareness against risk factors indicates the existence of genetic factors affecting bladder cancer susceptibility. Thereby, polymorphisms with possible association to bladder cancer have been widely investigated. Many metabolizing genes and their polymorphisms have been identified as responsible for individual susceptibility to cause BC.

This review is written as an attempt to demonstrate the association between xenobiotic-metabolising gene polymorphisms and bladder cancer. Among metabolizing enzymes, we will introduce N-acetyltransferases (NAT), Glutathione-S-transferases (GST), Sulphotransferases (SULT), NAD(P)H dehydrogenase Quinone 1 (NQO1), Methylene tetrahydrofolate reductase (MTHFR), Cytochrome P-450 (CYP) and Aldo-Ketoreductases (AKR) with special emphasis on the last two enzyme groups and related polymorphisms.

**N-acetyltransferases**

In humans, genetic locus for the two isoenzymes of NAT, NAT1 and NAT2, resides at chromosome 8p22. NAT1 and NAT2 are polymorphic and both catalyze N- and O-acetylation of aromatic and heterocyclic amines (Franekova et al., 2008). NAT2, one of the Phase II enzymes, play roles in the bio-conversion of heterocyclic amines to electrophilic nitrenium ions. NAT2 catalyzes the activation and deactivation of various aromatic amines, heterocyclic amines and hydrazin drugs. Polymorphisms in the NAT2 gene have been strongly associated with bladder cancer. Based on the 13 SNPs, 30 different NAT2 alleles have been defined (http://louisville.edu/medschool/pharmacology/NAT.html). Depending on the effects of the polymorphisms, NAT2 alleles have been categorised in two groups as slow and fast acetylators. Individuals who lack both of the two functional NAT2 alleles have been designated as slow acetylators. A meta-analysis with combined results from 31 different studies has shown that NAT2 slow acetylation alleles increase the risk of bladder cancer (OR=1,4; 95CI=1,2-1,7) (Garcia-Closas et al., 2005).

NAT1 enzyme transfers one acetyl group from acetyl-coA to arylamine and hydrazin substrates. Many NAT1 variants have been defined to date (http://louisville.edu/medschool/pharmacology/NAT.html), however studies have revealed conflicting results (Hung et al., 2004) and their functional significance could not be fully identified yet.

Since aromatic amines are present in cigarette smoke are the major risk factors for bladder cancer and are metabolized by NAT enzymes, it is for sure that the polymorphisms of the NAT genes have important roles in predisposing the individuals to bladder cancer (Franekova et al., 2008).

**Glutathione-S-transferases**

Cytosolic GSTs belong to a superfamily of Phase II enzymes, which contain sub-families and polymorphic isoenzymes. The genetic polymorphisms of these enzymes affect the individual susceptibility to cancer, cardiovascular and respiratory diseases. GSTs facilitate the detoxification of electrophilic compounds by glutathione conjugation. They interact with a wide variety of substrates including polycyclic aromatic hydrocarbon (PAH) epoxides and oxidative stress by-products. GSTM1 detoxifies carcinogenic PAH-like benzopyrene. A common deletion polymorphism in GSTM1 gene causes the loss of enzyme activity and has been shown to be strongly associated with increased risk for bladder cancer (Jiang et al., 2011, Salinas-Sánchez et al., 2010). According to a meta-analysis conducted to show the overall effect of this polymorphism, an odds ratio (OR) of 1.5 has been calculated (95CI=1.3-1.6) (Garcia-Closas et al., 2005). GSTT1 detoxifies smaller reactive hydrocarbons, like ethylene oxide. GSTT1 deletions, which have high frequency in Caucasians, have been associated with increased risk for bladder cancer (Abdel-Rahman et al., 1998; Srivastava et al., 2004). GSTP1 is involved in the conjugation and detoxification of many xenobiotics. The results of the studies investigating GSTT1 and GSTP1 gene polymorphisms are generally conflicting (Brockmoller et al., 1996; Lee et al., 2002).

In summary, polymorphisms of GSTM1, GSTT1 and GSTP1 constitute risk factors for many cancer types. Especially the null alleles of GSTM1
and GSTT1 are risk factors for bladder cancer in chain smokers.

**Sulphotransferases**

SULTs are encoded by a supergene family and catalyze the sulphonation of many xenobiotic compounds, including drugs and carcinogens. SULT enzymes play role as one of the main detoxification systems in adults and in developing human fetuses. This gene family is not very polymorphic, except SULT1A1. SULT1A1 Arg213His polymorphism, which causes a decrease in enzyme activity and thermal stability, has been suggested as a protective factor for bladder cancer (Zheng et al., 2003).

**NAD(P)H dehydrogenase, Quinone 1**

NQO1 enzyme protects the cell against electrophilic and oxidizing metabolites of xenobiotic and endogenous quinone compounds. The gene coding for the NQO1 enzyme harbors several polymorphisms affecting enzyme activity. A187C transition results in the replacement of proline with serine and decreases enzyme activity. Accordingly, Ser187 allele has been shown to increase bladder cancer risk (Franekova et al., 2008).

**Methylenetetrahydrofolate reductases**

MTHFR converts 5,10-methylenetetrahydrofolate (a methyl donor in deoxythymidine monophosphate synthesis) to 5-methyltetrahydrofolate. Folate deficiency is related to breakage of DNA strands and binding of urasil to DNA. If an MTHFR variant causes a decrease in the folate levels by decreasing the enzyme activity; one can expect a tendency to DNA strand breakage and cancer formation. On the other hand, variant MTHFR activity alters the amount of methyl donors and thereby involves in bladder cancer formation by changing the status of promotor methylation. MTHFR 677C>T and 1298A>C polymorphisms are proved to decrease enzyme activity. However, the relationship between the mentioned polymorphisms, enzyme activity and susceptibility to bladder cancer should be more extensively studied to seek for confirming results (Karagas et al., 2005).

**Cytochrome P-450 genes**

CYP enzymes catalyze Phase I reactions and belong to the microsomal enzyme super family. The CYP enzyme system consists of over 20 highly polymorphic CYP enzymes (http://www.cypalleles.ki.se/). Human CYP1A1 enzyme is expressed in epithelium and plays a key role in the activation of many procarcinogens including PAHs and aromatic amines arising from tobacco-related products. Ile-Val (m2) mutation located in heme-binding domain and MspI (m1) mutation has been shown to increase enzyme activity. White blood cells of smokers harboring a Ile-Val mutation have been shown to contain more PAH-DNA adducts in comparison to non-smokers. Expression of CYP1A1 has been shown to elevate in bladder cancer patients in correlation with increased tumour stage (Bartsch et al., 2000). m1 and m2 mutations, on the other hand, are directly associated with increased risk for lung cancer (Aynacioglu et al., 1998). CYP1A1 mutations exhibit variations among different ethnic groups. In contrast to Caucasians, prevalences of m1 and m2 are high among Asian populations. M3 mutation was identified only in Africans. In molecular and epidemiologic studies, CYP1A1*2B allele, harboring m1 and m2 mutations, was found to be correlated with increased risk for lung cancer. Figure 2 shows the localisation of these four important mutations (m1, m2, m3, m4) on CYP1A1 gene. Human CYP1B1 gene is located at chromosome 2p21 and contains three exons in a 10kb region. It codes for the 543 amino acid long enzyme (Figure 3). It was found to be overexpressed in many cancer types including, colon, lung, skin, brain cancers in contrast to its lower expression in normal somatic tissues (Thier et al., 2002). CYP1B1 activates PAHs, aromatic and heterocyclic amines. It also catalyzes the conversion of benzo[a]pyrene to carcinogenic metabolite diol epoxide-2, which indicates its significant role in the activation of tobacco carcinogens. Studies conducted so far indicate that CYP1B1 polymorphisms, especially codon 432 polymorphism, change enzyme activity and contribute to carcinogenesis. CYP1B1 codon 432 polymorphism increases risk for smokers for head and neck cancers (Thier et al., 2002).

CYP2D6 gene codes for debrisoquine hydroxylase. Its substrates include aromatic amines and tobacco nitrosamines. The existence of homozygous recessive mutations in this gene results in the inability of metabolising certain compounds. Individuals with these mutations...
compromise nearly 5-10% of the Caucasian population which are categorised as poor metabolizers (PM) because of their inability to metabolise certain compounds. The PM phenotype is associated with increased susceptibility to cancer, indicating a possible role for this enzyme in the conversion of procarcinogens to active carcinogens.

Most common mutations responsible for the PM phenotype have been identified. G/A transition located on exon3-intron4 conjunction creates an early stop codon resulting in defective mRNA. This CYP2E1 metabolizes many procarcinogens, e.g. N’-nitrosonornicotine, 4-methylnitrosamino-1,3-pyridyl-1-butanone and other volatile nitrosamines, which are inhaled via cigarette smoking.

Inter-individual expression variants of human CYP2E1 gene have been identified. The most frequently studied RFLPs on the CYP2E1 gene are those residing at the 5’ end of the gene which are proved to alter enzyme activity. Among them, PstI/RsaI (mutant allele: CYP2E1*5B) and DraI (mutant allele: CYP2E1*6) polymorphisms. These two polymorphisms together constitute the CYP2E1*5A allele. In addition to this, Rsal (G.1259C) and PstI (C.1091T) alleles are in complete linkage disequilibrium with each other. CYP2E1*6 allele variant is present in nearly 10% of the European population. Recently, Haufroid et al. (2002) have shown that people with at least one CYP2E1*6 allele have lower chlorzoxazone than homozygous wild type individuals. There are ethnic variations in CYP2E1*5A allele frequencies among Asians and Europeans. Europeans are 5% heterozygous; Asians are 37% heterozygous and 6% homozygous for this allele. Because of the certain inter-ethnic variations of the CYP2E1*5A allele, genetic polymorphisms, enzyme expression and alterations in the chemical metabolism are still not clear and the studies are conflicting each other (Bolt et al., 2003).

Aldo-Ketoreductases

AKRs catalyze the conversion of carbonyl groups to alcohol derivatives. Their most common endogenic substrates are lipid aldehydes, steroids and prostoglandines. They also activate prodrugs and polycyclic aromatic hydrocarbons (PAHs). In addition, they have been shown to induce resistance against chemotherapeutic agents like cisplatine and doxorubicin. The essential function of AKRs is to convert aldehydes to primary and secondary alcohols by reduction (Flynn and Green 1993; Penning et al., 2004). This conversion enables the
conjugation reactions and therefore aldo-ketoreductases are considered as Phase I enzymes. Human AKRs interact with various substrates including drugs, carcinogens and reactive aldehydes. Their important role in the metabolism of these substrates signifies them as key enzymes in designating the carcinogenicity of these substrates.

There are 15 AKR families discovered so far. Human AKRs are categorised into 3 families as AKR1, AKR6 and AKR7. 8 of the 13 discovered human AKRs belong to the AKR1 family (AKR1A1, AKR1B1, AKR1B10, AKR1C1, AKR1C2, AKR1C3, AKR1C4 and AKR1D1). Most of the AKR enzymes are 34-37 kDa monomeric proteins with a catalytic tetrade region, conserved among family members. Their substrate binding domains, on the other hand, show great variety, representing the diversity of their substrates (Jin and Penning, 2007).

**AKRs and activation of PAHs**

There are three different pathways of PAH activation. These are P-450 peroxidase induced formation of radical cations, P-450 induced formation of diol-epoxides and AKR induced formation of reactive o-quinones. The latter are highly reactive molecules which can bind to most macromolecules including DNA, RNA and proteins preeminently (Jin and Penning, 2007). The formation of o-quinones generates reactive oxygen species as by-products, which activate RAS targets by inducing the expression of antioxidant response element (ARE) containing genes. Since RAS pathway is responsible for transmitting the extracellular growth signals to nucleus, o-quinones produced by AKRs are considered to effect both the induction and progress of carcinogenesis (Jin and Penning, 2007).

**Function and tissue specific expression of Aldo-Ketoreductases**

Human AKR1C family members; AKR1C1, AKR1C2, AKR1C3 and AKR1C4; show great homology to each other. They all contain 9 exons and are located on chromosome 10. The expression of AKR1C genes are regulated by AREs located in their promoters.

AKR1C1 and AKR1C2 have been shown to be expressed 50-fold more in lung tumors (Hsu et al. 2001). To confirm these results Palackal and colleagues have measured the expression levels of AKR1C1, AKR1C2 and AKR1C3 isoforms in lung adenocarcinoma cells and obtained similar results (Palackal et al., 2002). Furthermore a study conducted by Dozmorov et al. have shown that increased AKR1C3 expression induce angiogenesis and increase cell survival (Dozmorov et al., 2010).

**AKR polymorphisms**

Even though the structural difference between AKR1C1 and AKR1C2 arises only from 7 different aminoacids, they have vastly different functions. Nonhomologous aminoacids are T38V, R47H, L54V, C87S, V151M, R170H and Q1721 which are highly polymorphic. Common polymorphisms in the AKR1C1 gene are T38A, T38I and R47H, whilst H47R, S87C, L172Q and V38A are common polymorphisms in AKR1C2. There have been 17 polymorphisms identified in the coding regions of AKR1C3. Nine of these polymorphisms results in amino acid changes while the other eight are synonymous (Table 1.).

One of the nonsynonymous polymorphisms, the G106T polymorphism, has been shown to produce truncated protein; and another nonsynonymous polymorphism, A230G, has been associated with decreased cholesterol levels in the blood (Jakobsson et al., 2007). AKR1C4*5 (L311V) polymorphism is located on the C-terminal and has been shown to affect substrate binding specificity (Kume et al., 1999).

There are a few studies conducted to investigate the association between the AKR polymorphisms and cancer. AKR polymorphisms have been investigated in Non-Hodgkin lymphoma and AKR1A1 rs2088102 polymorphism has been shown to be associated with increased risk (Lan et al., 2004). Another study, where the association between prostate cancer and AKR1C3 polymorphism have been investigated has shown an increased risk for rs7741 polymorphism (Cunningham et al., 2007).

Studies concerning rs12529 polymorphism gave conflicting results. rs12529 has been shown to be associated with increased lung cancer (OR=1.84, 95%CI= 0.98-3.45), while it has been shown to confer protection for bladder cancer (Lan et al., 2007; Figuerova et al., 2008; Tiryakioğlu, 2011). Figuerova et al.(2008) investigated 8 polymorphisms located in two regions of AKR1C3 gene, which are likely to affect bladder cancer risk (Table2).
Table 1. Exonic polymorphisms of AKR1C3 gene (http://www.med.upenn.edu/akr/polymorphisms.shtml)

<table>
<thead>
<tr>
<th>Exon</th>
<th>Polymorphism</th>
<th>Function</th>
<th>Nucleotide change</th>
<th>Aminoacid change</th>
<th>Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>rs7741</td>
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<td>G90A</td>
<td>P30</td>
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<td>K39</td>
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<td>Q5H</td>
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<td>1</td>
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<td>C15G</td>
<td>E36term</td>
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<td>9</td>
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<td>C772T</td>
<td>R258C</td>
<td>AKR1C3*10</td>
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</table>

In this study, rs3763676, rs12775701 and rs1937843 polymorphisms were found to be associated with increased bladder cancer risk; rs1937845, rs12529, rs4881400 and rs4641368 polymorphisms were found to confer protection against bladder cancer. Recently, rs12529 polymorphism has been shown to be associated with decreased bladder cancer risk (Tiryakioğlu, 2011). According to this retrospective study, homozygous GG variant genotype protects against bladder cancer (OR=0,255; %95CI=0,101-0,644), which supports the findings of Figuerova et al. (2008), where OR=0,78; %95CI= 0,52-1,18. Upon adjustment of these figures according to important risk factors in bladder cancer, namely, sex and cigarette smoking status, Tiryakioğlu (2001) have shown that rs12529 GG genotype still conserves its protective effect (OR=0,243).

Table 2. AKR1C3 polymorphisms associated with bladder cancer

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Genotype</th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td>rs12529</td>
<td>GG</td>
<td>OR=0,255; %95CI=0,101-0,644</td>
</tr>
<tr>
<td>rs1937845</td>
<td>GG</td>
<td>OR=0,78; %95CI=0,52-1,18</td>
</tr>
<tr>
<td>rs3763676</td>
<td>AG</td>
<td>OR=1,28; %95CI=1,05-1,55</td>
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<tr>
<td>rs4881400</td>
<td>GG</td>
<td>OR=0,53; %95CI=0,33-0,85</td>
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<tr>
<td>rs461368</td>
<td>TT</td>
<td>OR=0,42; %95CI=0,20-0,91</td>
</tr>
<tr>
<td>rs12775701</td>
<td>GG</td>
<td>OR=1,41; %95CI=1,05-1,90</td>
</tr>
</tbody>
</table>

Conclusion

The genetic variations in the human genome is truly a powerful source for the investigation of the complex diseases where genetic and environmental factors interact to characterize the final outcome. Over the past ten years, researchers agreed on that rare genetic defects imputed to certain populations are not usually responsible for ever increasing cancer cases; rather polymorphic
variations in the DNA sequences confer individual susceptibilities. This notion has been accepted for many cancer promoting mechanisms, including bladder cancer (Kim and Quan, 2005). Bladder cancer still conserves its importance regarding genetic and epidemiologic studies, since environmental factors, mainly cigarette smoking and occupational exposure to certain carcinogens play major roles in the formation of this cancer type. There are reasons for the high importance of this cancer type in terms of molecular research. In the first place, genetic polymorphisms in the metabolizing genes may alter the functions of the related enzymes, which will result in abnormalities in the xenobiotic functions of the cell. As an outcome, the environmental carcinogens may not be detoxified properly and hence cause bladder cancer. Identification of the polymorphisms in the xenobiotic genes and their functional relevance to bladder cancer formation will certainly highlight the importance of inter-individual genetic variations and the phenomenon of genetic susceptibility, which can be adapted easily to other genetic conditions. Looking at the same view from another direction we can still come up with the importance of genetic polymorphisms in defining disease risks. Since bladder cancer is caused mainly by environmental factors, people living at the same standards in terms of cigarette smoking, diet and other environmental exposures can be investigated for the frequency of occurrence of bladder cancer. Keeping the environmental factors constant, the only remaining factor will be the genetic variations. Comparing the frequencies of the genetic polymorphisms among bladder cancer cases and healthy controls exposed to the same environments, genetic polymorphisms responsible for the bladder cancer formation can be identified. There are for sure hundreds of genetic loci to investigate, however, it will be wise to begin with the genes coding for the xenobiotic-metabolizing enzymes.

On the other hand, the above-mentioned studies should be performed for each ethnic and geographic population in order to delineate genotypic distributions and to define genetic susceptibility loci. Using the accumulated data, researchers can establish diagnostic and even pre-symptomatic criteria on the basis of genetic polymorphisms. Until now, the prognostic and diagnostic value of the current accumulated data prove to be problematic to utilize. The main reason for this is the conflicting results in addition to overlooked environmental and demographic factors. Another reason is the small scope of the most studies, focusing on a few genes instead of taking the whole metabolic systems into account. Also, sample sizes of the studies are one of the major problems; wider retrospective research studies including hundreds of samples should be constructed. With the ever reducing time and money costs of whole genome association studies, it becomes rapidly easier to perform wide-range studies, paving the way for more rewarding research.

References


