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REVIEW ARTICLE

Pharmacogenetics of isoniazid-induced hepatotoxicity

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Abstract

Tuberculosis is still a major problem in some developed and developing countries. The poor compliance to the treatment of tuberculosis patients due to the adverse events was supposed to be an important factor contributing to the high prevalence. This review aims to clarify the role and the pharmacological mechanism of the genes involved in the isoniazid-induced hepatotoxicity. We selected English articles of studies in human from PubMed up to May 2014 with the keywords pharmacogenetic, isoniazid and hepatotoxicity, N-acetyl transferase 2 (NAT2), CYP2E1 and glutathione S transferase (GST). Polymorphisms of NAT2, CYP2E1 and GST1 could increase patients' susceptibility to isoniazid-induced hepatotoxicity. The rapid acetylators of *NAT2* and rapid metabolizers of *CYP2E1* showed increased concentrations of hepatotoxic metabolites. However, the rapid metabolizers of GST1 could decrease the concentration of hepatotoxic metabolites. Some studies of human leukocyte antigen (*HLA*), Uridine 5′-dippho-spho (UDP) glucuronosyltransferase (*UGT*), nitric oxide synthase (*NOS*), Broad complex, Tramtrack, Bric-a-brac (BTB) and cap'n'collar type of basic region leucine zipper factor family (CNC) homolog (*BACH*) and Maf basic leucine zipper protein (*MAFK*) polymorphisms showed their roles in isoniazid-induced hepatotoxicity by modifying the expression of antioxidant enzymes. A better insight into the role of polymorphisms of *HLA, UGT, NOS, BACH* and *MAFK* in addition to *NAT2, CYP2E1* and *GST1* in the hepatotoxicity of isoniazid may support physicians in monitoring patients hepatotoxicity symptoms and laboratory data and optimizing pharmacotherapy. Future studies about the role of such polymorphisms in different ethnicities are suggested.

Keywords

Genetic, hepatotoxicity, oral antituberculosis, polymorphism, tuberculosis

History

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Introduction

Tuberculosis is still a major problem in many countries over the world, especially in developed and developing countries (Cai et al., 2012). The ''WHO'' reported that there were 9 million TB sufferers annually (Anonymous, 2014). Currently, the problem of tuberculosis has become complex with the prevalence of multi-drug resistant tuberculosis, which reaches 600 000 cases in central Asian countries. One of the causes of the high prevalence of multi-drug resistant tuberculosis is presumed to be the poor compliance of patients, which reflected the treatment failure (Singla et al., 2014; Sotgiu & Migliori, 2014). The poor patients' compliance to the first-line treatment for tuberculosis, which are rifampicin, isoniazid, pyrazinamide and ethambutol, could partly be caused by the occurrence of liver injury as adverse event (Babalik et al., 2012; Huang, 2007; Li et al., 2013; Wada, 2001).

Among the oral antituberculosis drugs, isoniazid caused in 15–20% of the patients an increase in alanine and aspartate transaminase, and in about 1% of the patients' hepatotoxicity was observed (Lee, 1995; Metushi et al., 2011). The hepatotoxicity prevalence due to the isoniazid might be predicted by age, acetylator status, alcohol use and rifampicin use in an additional fashion (Steele et al., 1991). Rifampicin was proposed to stimulate the activities of amidase and CYP2E1, thus increasing the isoniazid-induced hepatotoxicity (Huang, 2014; Hussain et al., 2003). Currently, by affecting the isoniazid metabolism, genetic factors are also supposed to play a role in the isoniazid-induced hepatotoxicity (Metushi et al., 2011). Some patient characteristics like age, alcohol use and nutrition status were also general risk factors of antituberculosis-induced hepatotoxicity (Babalik et al, 2012; Roy et al., 2008).

Many reviews show the proposed isoniazid metabolism pathway (Huang, 2014; Metushi et al, 2011; Roy et al, 2008); however, there is no review about the pharmacological mechanisms of the genes involved in the hepatotoxicity of isoniazid, which could be related to the isoniazid metabolism. The genes mostly examined to understand the association between gene polymorphism and isoniazid-induced hepatotoxicity are N-acetyl transferase 2 (*NAT2*), *CYP2E1* and glutathione S transferase 1 (*GST1*) (Cai et al., 2012; Huang, 2007, 2014; Li et al., 2013; Metushi et al., 2011; Roy et al., 2008; Singla et al., 2014; Steele et al., 1991; Teixeira et al., 2007). Isoniazid is a derivative of hydrazine, which is

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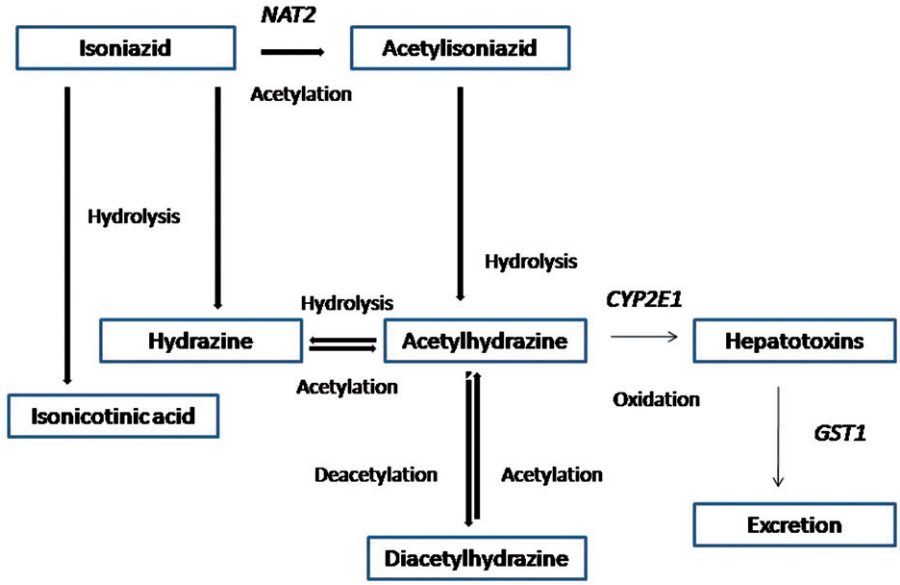

Figure 1. Pathways of metabolism of isoniazid (adapted from Huang, 2007; Roy, 2008).

hepatotoxic. There are two metabolites of isoniazid, hydrazine and acetylhydrazine, which are primarily involved in the mechanism of isoniazid-induced hepatotoxicity (Figure 1). The proposed metabolic pathways are the hydrolysis of isoniazid into hydrazine and isonicotinic acid and the acetylation of isoniazid into acetylisoniazid by NAT2. The next role of NAT2 is acetylation of hydrazine into acetylhydrazine (monoacetylhydrazine). Hydrazine and acetylhydrazine are known as toxic agents, thus they should be acetylated into non-toxic agents. Acetylhydrazine is metabolized into reactive acylating intermediates, which can bind covalently to tissue macromolecules and can cause Isoniazid-induced hepatotoxicity (Timbrell et al., 1980). A role of GST is to detoxify the toxic metabolites (Metushi et al., 2011; Roy et al., 2008). To date, the role of human leukocyte antigen (HLA) and superoxide dismutase (SOD) in the isoniazid metabolism is still being explored (Boelsterli & Lee, 2014; Du et al., 2013). Some genetic variants could interfere with the activity of the enzymes.

Metushi et al. (2014) found anti-Isoniazid antibodies and antibodies against CYP2E1, CYP3A4 and CYP2C9 in patients with isoniazid-induced liver injury. Isoniazid was found to form covalent adducts with CYP2E1, CYP3A4 and CYP2C9. This suggests that the immune system is involved in the Isoniazid-induced liver injury. Furthermore, it is suggested that mild cases of Isoniazid-induced liver injury resolve with immune tolerance and only when this immune tolerance fails more severe liver injury results.

This review is intended to shed more light on the role and the mechanism of the genes, which seem to be involved in the isoniazid-induced hepatotoxicity. The novelty of our study is that we add the pharmacological mechanism of some genes involved in the expression of reactive oxygen species (ROS) associated with the isoniazid-induced hepatotoxicity.

Methods

We selected English articles of studies in human from PubMed with the keywords Pharmacogenetic AND Isoniazid AND hepatotoxicity. We found eight articles with two articles reviewing pharmacogenomic and genetic variations in anti-tuberculosis-induced hepatotoxicity or liver injury (Huang, 2014; Roy et al., 2008). However, to obtain the articles on the pharmacological mechanism of some genes related to the isoniazid-induced hepatotoxicity, we searched in PubMed with the keywords isoniazid AND pharmacogenetic AND NAT2, isoniazid AND pharmacogenetic AND CYP2E1, isoniazid AND GST, isoniazid AND HLA, isoniazid AND HLA AND pharmacogenetic, isoniazid AND pharmacogenetic AND NAT2 AND CYP2E1 AND GST, isoniazid AND NAT2 AND CYP2E1 AND GST, as well as isoniazid AND polymorphism AND NAT2 AND CYP2E1 AND GST. Figure 2 shows the search strategy for retrieving articles related to the above-mentioned keywords. We limited the search strategy up to May 2014.

Results and discussion

Regarding the search strategy for pharmacogenetics of isoniazid-induced hepatotoxicity, we found eight articles, but we limited the articles to the human species, thus we only retrieved five articles. According to the search strategy of the pharmacological mechanism of some genes related to the isoniazid-induced hepatotoxicity, we found 30 articles related to NAT2 and 25 articles related to human species, 6 articles related to CYP2E1 with 5 articles among them were related to the human species. There were 20 articles related to GST with 7 articles among them related to the human species, 29 articles related to HLA and 3 articles related to the polymorphisms of HLA with 27 and 2 articles among them related to the human species, respectively. Furthermore, it was only 1 review article related to the three genes, 5 articles with 1 review article and 4 articles related to the isoniazid and polymorphisms of the three genes in the human species.

Pharmacological mechanisms of isoniazid-induced hepatotoxicity

In the proposed isoniazid metabolism pathway, NAT2 has a role in the acetylation of isoniazid to acetylisoniazid, which will be hydrolyzed to acetylhydrazine. CYP2E1 oxidizes

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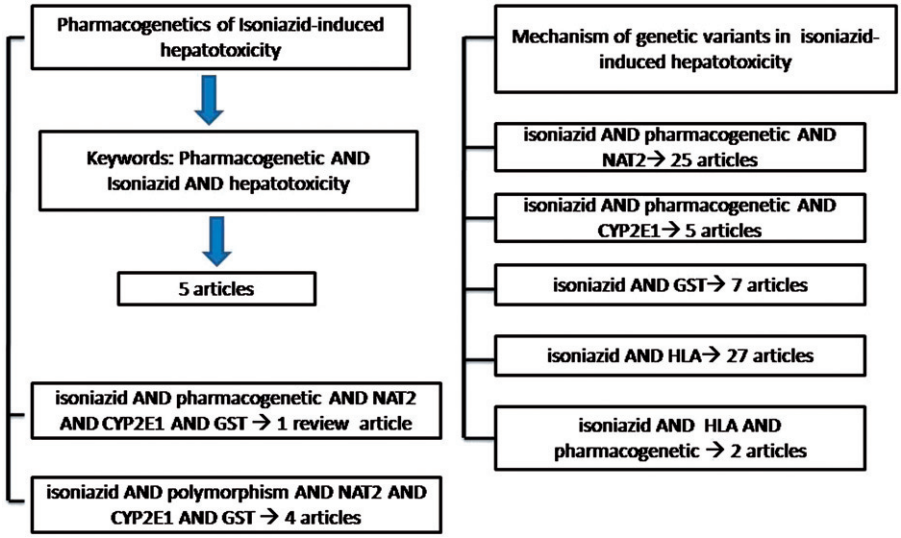
Figure 2. Secrch strategy for retrieving the articles.



acetylhydrazine into toxic agents. These toxic agents are detoxified by GST by conjugation (Huang, 2007). Isoniazid has a role in the imbalance between pro-oxidant and anti-oxidant activity. It can both stimulate the pro-oxidant level or decrease the level of anti-oxidant (Boelsterli & Lee, 2014). The ROS was proposed to be associated with isoniazid-induced hepatotoxicity by producing the oxidative stress (Bhadauria et al., 2007; Chowdhury et al., 2006). Mechanisms that were proposed were the damage of enzyme by superoxide resulting from molecular oxygen reduction, the inflammatory response of the immune system and the increase of mitochondrion dysfunction (Bhadauria et al., 2010; Boelsterli & Lee, 2014). With respect to ROS, hydrazine can produce oxygen radicals or superoxide, which can disrupt proteins and cause degradation of polypeptide chains (Timperio et al., 2005). Superoxide was found to be increased along with the isoniazid treatment.

With respect to the mitochondrion activity, isoniazid can translocate cytochrome c from the mitochondrion to the cytosol. This translocation can alter the mitochondrion permeability and start the hepatotoxic pathway in isoniazid treatment (Bhadauria et al., 2010). ROS was also produced in HepG2 cells in which NAT2 and CYP2E1 were expressed. The low expression of HepG2 cells explained the slow alteration of isoniazid into metabolites. This condition resulted in a high concentration of isoniazid, which means that the risk of occurrence of isoniazid-induced hepatotoxicity is increased (Bhadauria et al., 2010; Brandon et al., 2003). Some of the mitochondrial defects which was discussed could be due to a limited number of carbon-centered reactive intermediates that contribute to the aberrant redox chemistry additional to ROS.

Isoniazid was hydrolyzed into hydrazine and isonicotinic acid. Hydrazine and its derivatives were oxidized by the enzyme systems of cytochrome P-450 (NADPH-dependent hydrazine oxidase) and NADPH-independent hydrazine oxidase (Coomes & Prough, 1983). Cytochrome P-450 and monoamine oxidase oxidize the nitrogen of hydrazine and its derivatives. In addition, cytochrome P-450 also removes nitrogen of monoalkylhydrazines (Erikson & Prough, 1986). In this way, monoalkylhydrazines are converted into hydrocarbon forms with involvement of oxygen and a NADPH-regenerating systems. Monoalkylhydrazines rapidly form monoalkyldiazene intermediates leading to the formation of alkane and nitrogen using free radicals (Prough et al., 1969).

With respect to the role of alkane production cytochrome P450 metabolism, it should be mentioned that for iproniazid is shown that reactive metabolites involved in the hepatotoxicity are propane and propylene (Moloney et al., 1985). These metabolites could be react as GST's substrates, which would increase the toxicity of iproniazid by decreasing the GSH levels and also by the inhibiting GST's function (Spearman et al., 1984).

Furthermore, hydrazine and some derivatives also decreased the function of cytochrome P-450, which was demonstrated by the loss of enzyme activity in the hepatocyte during the preincubation with hydrazine derivatives (Wiebkin et al., 1982).

Related to the oxidative stress, isoniazid not only can produce ROS but also can interfere with glucose-6-phosphate dehydrogenase (G6PD). G6PD can protect the eukaryotic cells from ROS activity. The mechanism of protection is proposed by the regeneration of glutathione from glutathione disulfide. Glutathione can protect the cells from oxidative stress (Bhadauria et al., 2007, 2010). However, hydrazine can decrease the glutathione formation directly and can also reduce the expression of G6PD. This mechanism can alter the antioxidant activity of glutathione (Bhadauria et al., 2007).

Besides the mechanism of G6PD as antioxidant, SOD, also has antioxidant activity by catalyzing the conversion of superoxide radical anions to hydrogen peroxide (H_2O_2) (Du et al., 2013).

H_2O_2 is a strong oxidizing agent that can cause oxidative damage and generate ROS. Isoniazid can diminish the catalase activity of SOD, resulting in the accumulation of H_2O_2 (Bhadauria et al., 2007).

Besides the role of ROS, the distraction of endogenous metabolism by isoniazid metabolites was proposed to be involved in the isoniazid hepatotoxicity. Hydrazine as a reactive metabolite of isoniazid could react to some endogenous factors. One of this mechanisms was known as the

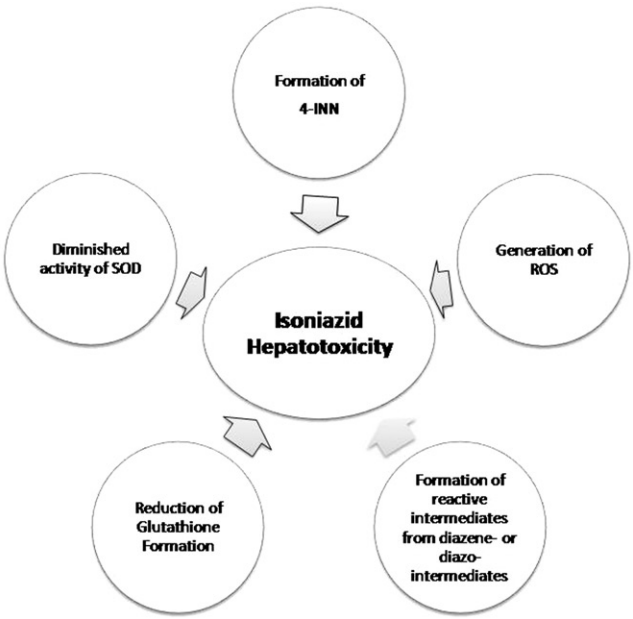


Figure 3. Pharmacological mechanisms of isoniazid induced hepatotoxicity (adapted from Boelsterli & Lee, 2014).

reaction to diminish the *Mycobacterium tuberculosis* by the formation of Isoniazid-Nicotinamide Adenine Dinucleotide (INH-NAD^+). The INH-NAD^+ is hydrolyzed into 4-isonicotinoylnicotinamid (4-INN), which can be found in the urine after two months treatment with isoniazid. The formation of 4-INN was supposed to be related with the loss of nicotinic acid, which can cause isoniazid hepatotoxicity (Boelsterli & Lee, 2014; Mahapatra et al., 2012).

HLA is a gene that has a role in the human immune system and is suspected as a gene, which has association with isoniazid hepatotoxicity. However, the mechanism of association is still unclear (Boelsterli & Lee, 2014; Huang, 2014). A summary of the pharmacological mechanisms of isoniazid induced hepatotoxicity is presented in Figure 3.

Genetic variations associated with isoniazid-induced hepatotoxicity

The most published genetic variations involved in isoniazid-induced hepatotoxicity were in *NAT2, CYP2E1* and *GST1* (Cai et al., 2012; Huang, 2014). Genetic variations involved in isoniazid-induced hepatotoxicity are listed in Table 1.

NAT2 metabolized isoniazid into acetylisoniazid and it was hydrolyzed into acetylhydrazine, which will be oxidized by CYP2E1 into some hepatotoxic metabolites (Huang, 2014). The previous study in Japanese showed that patients who were rapid acetylators had elevated serum transaminotransferases. The rapid acetylators will quickly metabolize isoniazid into hepatotoxic agents, which was shown by the increase of serum transaminotransferases (Yamamoto et al., 1986). In slow acetylators, it was demonstrated that acetylation of acetylisoniazid into diacetylisoniazid leads to non toxic agents (Lauterburg et al., 1985). Thus, both the rapid and slow acetylators had significant contributions to the mechanism of isoniazid-induced hepatotoxicity (Lauterburg et al., 1985; Peretti et al., 1987). Currently, the studies showed that the slow acetylators had a higher risk of isoniazid-induced hepatotoxicity than rapid acetylators (Huang, 2007; Lee et al., 2010; Singla et al., 2014). The *NAT*2* is wild-type and is known as the highest activity variant (Cai et al., 2012; Gupta et al., 2013). The other variants of NAT2, such as NAT2*5, NAT2*6 and NAT2*7, are known as decreased activity alleles. The availability of variant alleles, such as two variants of decreased activity alleles, one variant of decreased activity allele and two wild-type could be phenotyped into slow acetylators, intermediate acetylators and rapid acetylators, respectively (Huang, 2007; Roy et al., 2008; Xiang et al., 2014). A study in China showed that most of the patients recruited in the study were intermediate acetylators (37%), followed by slow acetylators (24%) and rapid acetylators (15%) (Xiang et al., 2014). This study is also in accordance with other reviews and studies, which showed that Chinese and Japanese as a part of the Asian ethnicity have a high frequency of intermediate acetylators. However, populations from India showed in most of the patients the slow acetylator genotype (Roy et al., 2008). The high frequency of slow acetylators and intermediate acetylators in the Asian population showed that these populations are more susceptible for isoniazid-induced hepatotoxicity (An et al., 2012; Huang, 2014). There are 36 variants of the *NAT2* gene identified in human populations with seven most common SNPs forming the variations (Teixeira et al., 2007; Zang et al., 2007). Considering the high polymorphism of the *NAT2* gene, the occurrence of isoniazid-induced toxicity will be more.

CYP2E1 oxidizes the acetylhydrazine into hepatotoxic agents. Isoniazid and hydrazine could inhibit CYP2E1 activity, and isoniazid could also inhibit the variant of CYP2E1 with a lower activity than the wild type (Roy et al., 2008). The polymorphisms of *CYP2E1* were detected by *PstI, RsaI* and *DraI* restriction enzymes (Huang et al., 2003). The variant alleles $RSAI^-$ and $PstI^+$ are translated into c1 and c2. Furthermore, the wild-type of c1, the variants of c2 and the *DraI* are known as *CYP2E1*1A, CYP2E1*5* and *CYP2E1*6.* These variants showed increased activity (Roy et al., 2008). According to the previous studies, the presence of homozygous **1A/*1A* was high in India and less frequent in China. However, variants could increase the individual susceptibility to the isoniazid-induced hepatotoxicity (An et al., 2012; Roy et al., 2008).

GST is encoded by GSTM1, GSTT1 and GSTP1 (Strange et al., 2001). The presence of null homozygous of GSTM1 and GSTT1 may cause decreased enzyme activity thereby decreasing the detoxification of hepatotoxic metabolites. The frequencies of null homozygous of GSTM1 and GSTT1 among the Asian population were heterogeneous. The frequencies of null homozygous GSTM1 in Chinese, Malaysian and Indians were 35–63%, 62–100% and 20–79%, respectively. However, the frequencies of null homozygous in GSTT1 were 58%, 38% and 3–39% in those particular races (Huang, 2007, 2014; Roy et al., 2008).

The high concentration of ROS due to hydrazine's activity should be reduced by manganese SOD (MnSOD). It was found that patients heterozygous and homozygous for the mutant allele in the 47 position of the *MnSOD* gene experienced higher risk of antituberculosis induced hepatotoxicity (Huang, 2014; Huang et al., 2007).

Table 1. Genetic variations in the metabolism of hepatotoxic metabolites of isoniazid.

References	Patients (number and characteristics)	Gene	Gene variations	Phenotype	Possible mechanism	Results
Nanashima et al., 2012	100 unrelated new diagnosed Japanese tuberculosis patients	*NAT2*	*2, *5, *6, *7	Rapid acetylator	Rapid acetylators can induce the production of hepatotoxic agents, which increased ROS concentration	Increase of the concentration of hepatotoxic agents by acetylation
Nanashima et al., 2012	100 unrelated new diagnosed Japanese tuberculosis patients	*CYP2E1*	CYP2E1*1A,*5,*6	Rapid metabolizers	Rapid metabolizers can induce the production of hepatotoxic agents which induced ROS concentration	Increase of the concentration of hepatotoxic agents by metabolism
Nanashima et al., 2012	100 unrelated new diagnosed Japanese tuberculosis patients	*GST*	GSTM1 and GSTT1 null homozygous	Rapid eliminators	Rapid eliminators can quickly eliminate the toxic metabolites	Decrease of the concentration of hepatotoxic agents by elimination
Chang et al., 2012	98 tuberculosis patients	*UGT*	UGT1A1	Insertion of TA in UGT1A	The insertion could inhibit bilirubin glucuronidation	Increase of bilirubin glucuronidation
Sharma et al., 2002	346 tuberculosis patients who were compared to 275 healthy subjects	*HLA*	HLA-DQ	Susceptibility in drug-induced hepatotoxicity	Affect the peptide-binding preference and presentation of T cells (Balamurugan et al., 2004)	Increase of the susceptibility of drug-induced hepatotoxicity
Nanashima et al., 2012	100 unrelated new diagnosed Japanese tuberculosis patients	*NOS*	NOS2A	Upregulation of NOS2A	Gain function of iNOS activity	Increase of the production of reactive nitrogen species
Nanashima et al., 2012	100 unrelated new diagnosed Japanese tuberculosis patients	*BACH*	CC genotype at rs11080344	Expression of genes related to the antioxidant-responsive elements	Heterodimer complex of BACH and small Maf protein down regulates the antioxidant enzyme expression	Increase of the reactive oxygen species
Nanashima et al., 2012	100 unrelated new diagnosed Japanese tuberculosis patients	*MAFK*	homozygous mutant genotype at rs4720833	Expression of genes related to the antioxidant-responsive elements	Heterodimer complex of small Maf protein and BACH/Nrf 2 will down/upregulate the antioxidant enzyme expression	Increase/decrease of the reactive oxygen species

Other possible genetic variations mechanisms involve HLA, UDP glucuronosyltransferase (UGT), nitric oxide synthase (NOS), BNB and CNC homolog (BACH) and Maf basic leucine zipper protein (MAFK). The last three enzymes are supposed to be involved in the antioxidant activity, and HLA is involved in the immunological reaction (Huang, 2014; Nanashima et al., 2012).

The principal product of heme catabolism, bilirubin, is eliminated by a conjugation reaction with glucuronic acid. The glucuronidation reaction is mediated by UGT. Currently, there are 15 isoforms of UGT in human, and 8 of these are encoded by *UGT1A*. An increase of bilirubin was supposed to be related with the insertion of TA in the *UGT1A*, which encodes UGT1A1. This insertion inhibits the bilirubin glucuronidation (Zucker et al., 2001). In the Taiwan population, it was shown that the variants of *UGT1A* were associated with antituberculosis-induced hepatotoxicity (Chang et al., 2012).

The high concentration of ROS should be eliminated by enzymes like GST, NQO1 (NAD(P)H dehydrogenase quinone) and heme oxygenase. The activation of these enzymes must be supported by the mechanisms of activation and repression of antioxidant pathways. These mechanisms will support the transcriptional regulation of antioxidant enzymes (Nanashima et al., 2012). During high concentrations of ROS, MAFK can associate with antioxidant-responsive elements (ARE), which allows the antioxidant enzymes expression. On the contrary, the association of BACH with ARE prevents the association between MAFK and ARE and results in the repression of antioxidant enzymes (Nanashima et al., 2012; Oyake et al., 1996). NO is one of the reactive nitrogen species, which is produced by NOS. If NOS is available in the cells, the inducible isoform of NOS (iNOS) will be upregulated. iNOS is encoded by NOS2A, therefore by this mechanism the increased activity of the *NOS2A* variant could result in the overproduction of NO (Jaeschke et al., 2003; Nanashima et al., 2012).

In the Japanese population, it was shown that the CC genotype of rs11080344 in *NOS2A*, the CC genotype at rs11080344 in *BACH1*, and the heterozygous and homozygous mutant genotype at rs4720833 in *MAFK* were associated with the occurrence of antituberculosis drugs-induced hepatotoxicity (Nanashima et al., 2012).

HLA is possibly involved in the resistance or susceptibility to tuberculosis. It is responsible for the presentation by T cells which initiate the protective immune response. It was shown that the high frequency of HLA class I could influence the TB treatment outcome. Its mechanism could be related with recognizing the common epitope in the peptide-binding and regulating NK cells activity (Balamurugan et al., 2004). One study showed that the presence of HLA-DQB1*0201 and the absence of HLA-DQA1*0102 are risk factors for drug-induced hepatotoxicity (Sharma et al., 2002).

Conclusion

Many studies showed that the polymorphisms of *NAT2, CYP2E1* and *GST1* could influence the concentration of hepatotoxic isoniazid metabolites in the blood. Some of the gene polymorphisms of *HLA*, *UGT*, *NOS*, *BACH* and *MAFK* are supposed to contribute to isoniazid-induced hepatotoxicity by modifying the antioxidant enzyme expression. However, the studies which explored this mechanism are still limited. A better insight into the role of polymorphisms in the hepatotoxicity of isoniazid may support physicians in monitoring patients hepatotoxicity symptoms and laboratory data and optimizing pharmacotherapy. Future studies about the role of such polymorphisms in different ethnicities are suggested.

Declaration of interest

All authors have no conflict of interest.

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