

Review

The Glu504Lys Polymorphism of Aldehyde Dehydrogenase 2 Contributes to Development of Coronary Artery Disease

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Coronary artery disease (CAD) is a leading cause of death, and its genetic mechanism has been always a major research concern. Recently, increasing evidence has indicated that the aldehyde dehydrogenase 2 (ALDH2) polymorphism, known as Glu504Lys (rs671), may contribute to CAD development. ALDH2 has been well known as a key enzyme in alcohol metabolism, and subjects with *504Lys allele exist in 30-50% of the East Asian population (6% of the world's population). However, recent studies have indicated that the *504Lys allele of the ALDH2 gene may be associated with the pathogenesis of CAD in a given number of Chinese, Japanese, and Korean people. This discovery has been further confirmed by a genome-wide association study in 2012 that identified the link of ALDH2 Glu504Lys polymorphism to CAD susceptibility. ALDH2 may therefore serve as an important target for CAD intervention. Several studies have suggested that ALDH2 polymorphism plays an important role in the progress of CAD through multiple mechanisms, including the regulation of alcohol consumption, inflammation, endothelial progenitor cells, oxidative stress, asymmetric dimethylarginine, endothelial nitric oxide synthase, and other CAD-promoting factors. Furthermore, the ALDH2 Glu504Lys polymorphism has been shown to be associated with certain traditional cardiovascular risk factors, such as dyslipidemia, hypertension, and diabetes mellitus or hyperglycemia. In this review, we update the current research on the association of the Glu504Lys polymorphism with the susceptibility to CAD. We also highlight and discuss the underlying mechanisms, by which the ALDH2 Glu504Lys polymorphism may be targeted for the prevention and treatment of CAD.

Keywords: aldehyde dehydrogenase 2; coronary artery disease; Glu504Lys polymorphism; mechanisms; susceptibility gene

Tohoku J. Exp. Med., 2014 October, **234** (2), 143-150. © 2014 Tohoku University Medical Press

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality. Over the years, the treatment strategy for CAD has shifted from treating the adverse outcomes of the disease to early diagnosis and prevention. Research in this field is progressing with the development of various techniques in genomics, proteomics and metabolomics, and new susceptibility genes and causative factors are being discovered. Aldehyde dehydrogenase 2 (ALDH2) was originally identified as a key enzyme in the metabolism of alcohol (ethanol). This enzyme has an important functional mononucleotide polymorphism rs671 (Glu504Lys

polymorphism), which exists primarily in East Asians, with an incidence rate as high as 30-50% (approximately 6% of the world's population) (Li et al. 2006; Li et al. 2009). Initial studies only focused on the relationship between this polymorphism and alcohol-related diseases, such as hepatitis and digestive system tumors, but in recent years, an increasing number of studies have suggested an important association between ALDH2 Glu504Lys polymorphism and CAD (Takagi et al. 2002; Jo et al. 2007; Xu et al. 2007a, b, 2011; Guo et al. 2010). In 2012, a genome-wide association (GWA) study further confirmed that the ALDH2 Glu504Lys polymorphism is associated with the susceptibility to CAD (Takeuchi et al. 2012). Many groups, includ-

Received March 26, 2014; revised and accepted September 5, 2014. Published online September 27, 2014; doi: 10.1620/tjem.234.143.

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ing ours, recently explored underlying mechanisms for the effects of this polymorphism on CAD (Churchill et al. 2009; Guo et al. 2010; Xu et al. 2011; Xue et al. 2012; Li et al. 2013). Several studies, including GWA studies, found that this polymorphism is also related to well-known cardiovascular risk factors, such as dyslipidemia (Hao et al. 2010; Wei et al. 2013), hypertension (Kato et al. 2011), diabetes (Wang et al. 2011), or hyperglycemia (Xu et al. 2010). These findings suggest that ALDH2 may become an important target for CAD intervention, especially in the people with the *504Lys allele. We review here the progress recently made in the area of the ALDH2 Glu504Lys polymorphism and CAD occurrence and development.

ALDH2 and its polymorphism

ALDH is an enzyme superfamily in human body that is responsible for the detoxification of biogenic and xenogenic aldehydes, including the alcohol-derived aldehyde, in various organs and cells (Jackson et al. 2011). Alcohol in the body is catalyzed by alcohol dehydrogenase into aldehyde, which is then converted to acetic acid by ALDH. To date, 19 ALDH isozymes have been discovered, of which ALDH1, ALDH2, ALDH3, and ALDH4 are predominant. Compared to the remaining three types of isozymes located in the cytoplasm (ALDH1, ALDH3 and ALDH4), ALDH2 primarily located in the mitochondria has a lower Michaelis constant (K_m) for aldehyde and plays a major role in converting aldehyde into acetic acid (Marchitti et al. 2008). ALDH2, consisting of 517 amino acids, has a molecular mass of 56 kDa, and functions as a homotetramer. ALDH2 possesses three domains: coenzyme- or NAD^+ -binding domain, catalytic domain and oligomerization domain. In addition to the dehydrogenase activity, ALDH2 has reductase activity and esterase activity (Chen et al. 2014) (Fig. 1). It is well known for its dehydrogenase activity in ethanol metabolism, as it can convert aldehyde to acetic acid. ALDH2 also metabolizes many other short-chain aliphatic aldehydes, some polycyclic aldehydes and aromatic aldehydes.

Mitochondrial ALDH2 is encoded by the ALDH2

gene, located on chromosome 12 (12q24). The protein is transported to the mitochondrial matrix, which is dependent on the amino-terminal 17 amino acids. ALDH2 gene consists of 13 exons. There is a single nucleotide polymorphism (rs671) in exon 12 (Crabb et al. 1989). Due to the presence of rs671, a base substitution from guanine (G) to adenine (A) occurs, resulting in a codon change from GAA to AAA. This subsequently changes the 504th amino acid of the enzyme from glutamic acid (Glu) to lysine (Lys). Therefore, ALDH2 gene has two alleles: wild-type allele (ALDH2*1, *504Glu) and mutant allele (ALDH2*2, *504Lys). There are three combinations of the enzyme genotype in the population: the wild-type homozygote (ALDH2*1/1), the heterozygote (ALDH2*1/2), and the mutant homozygote (ALDH2*2/2). Compared with the wild-type ALDH2, encoded by the ALDH2*1/1, the protein containing the 504Lys residue exhibits a 10-fold reduced catalytic constant (k_{cat}) and a 200-fold increase in the K_m for NAD^+ (Li et al. 2006). The wild-type ALDH2 shows normal enzymatic activity toward aldehyde, but the enzyme, encoded by the ALDH2*1/2, exhibits about 6% of normal activity and the enzyme, encoded by the ALDH2*2/2, displays negligible activity (Li et al. 2006).

Because the aldehyde-metabolising activity of the ALDH2 enzyme containing the 504Lys residue is significantly decreased, individuals that carry the *504Lys allele are prone to slow oxidation and a strong accumulation of aldehyde in the blood after alcohol consumption. This accumulation stimulates the release of vasoactive substances from mast cells and leads to vasodilation and other adverse reactions, such as flushing, sweating, palpitation, dizziness, headache, rash, dysphagia, and low blood pressure. In addition to the Glu504Lys polymorphism, ALDH2 has the His47Arg polymorphism which influences an individual's drinking habit independently of the Glu504Lys polymorphism (Matsuo et al. 2006).

Distribution of ALDH2 polymorphism

Early studies have demonstrated that there is a significant difference in the incidences of ALDH2 alleles in dif-

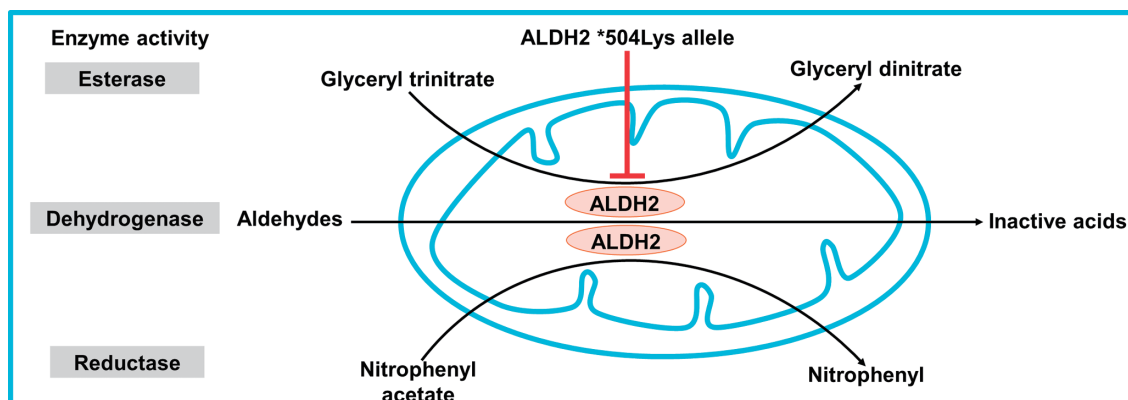


Fig. 1. ALDH2 enzyme activity.

Mitochondrial ALDH2 has dehydrogenase activity, esterase activity and reductase activity.

ferent races. ALDH2 *504Lys allele rarely exists in Caucasian and individuals of African descent. However, this polymorphism exists in 30-50% of East Asians (Li et al. 2009). Therefore, obvious flushing of the skin due to alcohol consumption is rare in Caucasians, but it is common in East Asian populations. Moreover, there are variations in the distribution of the ALDH2 *504Lys allele among the different countries in East Asia, such as China, South Korea, and Japan (Li et al. 2009).

It is not known why the Glu504Lys polymorphism is so common in Asian. It was postulated that between 2,000 and 3,000 years ago, this polymorphism became the most common genetic enzymopathy. A few hypotheses have been put forth recently, although none of them has been confirmed. For example, infection of hepatitis B virus might have contributed to the evolution of the Glu504Lys polymorphism among Chinese Han (Lin and Cheng 2002).

ALDH2 polymorphism and CAD

Previous studies on ALDH2 polymorphism and disease have usually focused on the relationship between ALDH2 and alcohol-related diseases, such as hepatitis, cirrhosis, alcoholic cardiomyopathy, and digestive system tumors (Yokoyama et al. 1996; Tanabe et al. 1999; Ding et al. 2008; Ma et al. 2009). In addition to these disease, the Glu504Lys polymorphism is also shown to be associated with stroke, neurodegenerative disorders like Parkinson's disease and Alzheimer's disease, fanconi anemia, radiodermatitis, osteoporosis, the process of aging, pain and so on (Chen et al. 2014). This may be due to the accumulation of harmful aldehyde, which is a carcinogen and cytotoxin. Aldehydes and their precursors are widely present in food and in our environment, and reactive aldehydes are generated easily during oxidative stress. Harmful aldehydes can spread through cell membranes easily and bind to proteins, DNA and lipids, leading to their dysfunction. However, the ability to clear these detrimental aldehydes of the Glu504Lys polymorphism is low or negligible, which leads to the accumulation of aldehydes, resulting in disease.

Recently, researchers have focused on the correlation between the ALDH2 gene and CAD (Takagi et al. 2002; Jo et al. 2007; Xu et al. 2007a, b). Japanese investigators demonstrated that after adjusting for the traditional cardiovascular risk factors and alcohol consumption, ALDH2

*504Lys allele is an independent risk factor of myocardial infarction (MI) in Japanese populations (Takagi et al. 2002). Subsequently, our group also found that the ALDH2 *504Lys allele is a MI risk factor in Han Chinese independent of traditional risk factors and alcohol consumption (Xu et al. 2007a, b). A study in South Korea confirmed that the ALDH2 *504Lys allele is an independent MI risk factor in South Korean males (Jo et al. 2007). These results were corroborated by another study that showed that carriers of ALDH2 *504Lys allele are at increased risk of CAD in Japan (Hashimoto et al. 2002). These studies suggested that ALDH2 *504Lys allele is a risk factor for CAD. However, another study in Japan reached a seemingly contradictory conclusion (Narita et al. 2003). The authors found that after adjusting for the traditional cardiovascular risk factors and alcohol consumption, the ALDH2 *504Lys allele is significantly negatively correlated with the carotid artery plaque score. The results suggested that the ALDH2 *504Lys allele may be a protective factor against carotid atherosclerosis. Previous studies have confirmed that the severity of carotid atherosclerosis is positively correlated with CAD. Therefore, this study suggested that the ALDH2 *504Lys allele may be a protective factor for coronary atherosclerosis, which is contrary to clinical studies performed in China, Japan, and South Korea (Hashimoto et al. 2002; Takagi et al. 2002; Jo et al. 2007; Xu et al. 2007a).

Based on these seemingly contradictory results, we conducted a case-control study with a larger sample size (1,092 cases) to explore the relationship between ALDH2 polymorphism and acute coronary syndrome (ACS) in Han Chinese (Xu et al. 2011). The results revealed that the ALDH2 *504Lys allele is an independent genetic risk factor for ACS in Han Chinese. A similar conclusion was also made regarding a sub-group of patients with an initial onset of ST-segment elevation MI. Recently, another study on the Han Chinese population confirmed this conclusion (Guo et al. 2010). The conclusion was confirmed using two independent Han Chinese sample populations, which strongly enhances the reliability of the findings. In 2012, the association between the ALDH2 *504Lys allele and CAD occurrence and development was further confirmed by a GWA study in a Japanese population, which demonstrated that ALDH2 Glu504Lys polymorphism is associated with the susceptibility to CAD (Takeuchi et al. 2012). Our experi-

Table 1. Characteristics of studies about ALDH2 Glu504Lys polymorphism as a susceptibility gene of CAD.

Author	Publication year	Study type	Population	Nationality	Numbers
Takagi et al.	2002	Case-control	male MI	Japanese	342 patients, 1,820 controls
Xu et al.	2007	Case-control	CAD	Chinese	89 patients, 142 controls
Jo et al.	2007	Case-control	Elderly male MI	Korean	122 patients, 439 controls
Guo et al.	2010	Case-control	CAD	Chinese	417 patients, 448 controls
Xu et al.	2011	Case-control	ACS	Chinese	546 patients, 546 controls
Takeuchi et al.	2012	GWAS	CAD	Japanese	3,052 patients, 6,335 controls

MI, myocardial infarction; CAD, coronary artery disease; ACS, acute coronary syndrome; GWAS, genome-wide association study.

ment in 2013 with human aortic endothelial cells also suggested that ox-LDL stimulates progression of cardiovascular diseases partly due to its inhibition of ALDH2 dehydrogenase activity via inducing ALDH2 deacetylation by PARP mediated SIRT3 upregulation (Wei et al. 2013). All these findings suggest confirmation of the association between ALDH2 Glu504Lys polymorphism and CAD (Table 1).

Underlying mechanisms of *504Lys allele influencing CAD

Alcohol consumption

ALDH2 is one of the key enzymes in alcohol metabolism. A number of studies indicated that, independent of gender, moderate drinking vs. a small amount of alcohol consumption or heavy drinking reduce the incidence of cardiovascular events (Mukamal et al. 2005a, b; Hvidtfeldt et al. 2010). The post-drinking response of individuals with different ALDH2 genotypes varies greatly. Populations with the ALDH2 *504Lys allele often consume significantly less alcohol or even completely abstain from alcohol due to adverse reactions to drinking. Therefore, the ALDH2 gene may affect the occurrence and development of CAD by influencing a population's drinking habits.

Our group found that carriers of the ALDH2 *504Lys allele drink significantly less than carriers of the wild-type ALDH2 (Xu et al. 2011), which was consistent with other studies in Chinese populations (Muramatsu et al. 1995; Ding et al. 2008). Additionally, when alcohol consumption was incorporated into the regression analysis model as an independent variable, the correlation between ALDH2 *504Lys allele and ACS decreased but was still significant (Xu et al. 2011). Studies conducted by Japanese and South Korean scholars reached similar conclusions (Takagi et al. 2002; Jo et al. 2007). These results suggested that, the ALDH2 *504Lys allele can increase ACS risk because it causes the patient to drink significantly less; however, *504Lys allele also exerts other effects on ACS independent of alcohol consumption.

Traditional cardiovascular risk factors

Previous studies have shown that alcohol influences CAD through its effects on high density lipoprotein cholesterol (HDL-C), fibrinogen, and glycosylated haemoglobin (Mukamal et al. 2005a). Another study found that alcohol consumption can raise HDL-C levels by increasing the transport of its apolipoproteins (De Oliveira et al. 2000). Does the ALDH2 *504Lys allele also affect lipid levels in the body? Our group demonstrated that HDL-C levels in patients with the ALDH2 *504Lys allele are significantly lower than in those with the wild-type ALDH2 (Xu et al. 2011), which is consistent with the results of a previous study in Japan (Takagi et al. 2002). Moreover, our recent meta-analysis suggested that the HDL-C level in carriers of the ALDH2 *504Lys allele is still significantly lower than in carriers of the wild-type (Hao et al. 2010). However,

another study in Japan found no correlation between ALDH2 *504Lys allele and HDL-C levels (Hashimoto et al. 2002). Our study of 1,092 samples, which incorporated HDL-C into a logistic regression analysis model, demonstrated that the ALDH2 gene polymorphism is still significantly correlated with ACS (Xu et al. 2011). Therefore, the role of HDL-C in this polymorphism affecting ACS occurrence needs further investigation with larger study samples.

Recently, several studies have explored the relationship between ALDH2 Glu504Lys polymorphism and hypertension. All suggested that the ALDH2 *504Lys allele is a protective factor for hypertension. Some studies found that the mechanism is closely related to decreased alcohol consumption. After adjusting for alcohol consumption, the *504Lys allele and hypertension were no longer correlated (Takagi et al. 2001; Amamoto et al. 2002; Wang et al. 2013). However, other studies have demonstrated that the mechanism is not related to alcohol consumption (Hui et al. 2007; Hasi et al. 2011). Recently, GWA studies further confirmed that this polymorphism is associated with the susceptibility to hypertension (Hiura et al. 2010; Kato et al. 2011). Why is the *504Lys allele a protective factor for hypertension, but a risk factor for CAD? The GWA study on hypertension in 2011 suggested that the reason may be the impact of *504Lys allele on lipid levels (decreases HDL and increases LDL) is more significant than its protective effect on hypertension (Kato et al. 2011).

A study in Japan (Dakeishi et al. 2008), along with our study (Xu et al. 2010), indicated that carriers of the ALDH2 *504Lys allele (and with no chronic diseases) exhibit blood sugar levels that are significantly higher than those of carriers of the wild-type. Moreover, we demonstrated in another study that an increased blood sugar level may inhibit ALDH2 activity through the activation of oxidative stress signalling pathways (Wang et al. 2011). Therefore, these two mechanisms may form a vicious cycle, leading to higher blood sugar levels and making carriers of the ALDH2 *504Lys allele diabetes-prone. Our study suggested that the rate of concurrent diabetes was higher in CAD patients with the ALDH2 *504Lys allele and that the mechanism is related to the impact of this allele on inflammatory cytokines (Xu et al. 2010), indicating that the ALDH2 gene polymorphism may affect ACS occurrence and development by influencing the blood sugar level in the body and the onset of diabetes.

Coronary stenosis

A previous study from Japan suggested that the ALDH2 *504Lys allele has a protective effect on carotid atherosclerosis (Narita et al. 2003). Does *504Lys allele affect CAD occurrence and development through its effects on coronary atherosclerosis? A preliminary study with a small sample size conducted by our group observed no significant difference in the coronary Gensini score and the number of coronary lesions among CAD patients with different ALDH2 genotypes (Xu et al. 2007a). We made simi-

lar findings in another study that examined a larger sample size (Xu et al. 2011). Furthermore, multivariate regression analysis showed no correlation between ALDH2 polymorphism and the severity of coronary lesions as measured by the number of coronary lesions and the Gensini score in this study (Xu et al. 2011). These results demonstrate that the ALDH2 gene may not have a significant impact on the severity of coronary lesions.

Why is this polymorphism a susceptibility gene of CAD while not significantly correlated with coronary lesion severity? One hypothesis is that the two measurements of coronary lesion severity in our study—the number of coronary lesions and the Gensini score—were both based on arteriography. Arteriography can only reflect changes of the vascular lumen and cannot sufficiently reflect the degree of vascular atherosclerotic plaque burden. Therefore, the two measurements mainly reflect the severity of arterial luminal stenosis and have certain limitations in the evaluation of the severity of coronary atherosclerosis. Consequently, the impact of ALDH2 on the occurrence and development of atherosclerosis cannot fully be determined based on current evidence. Clinical studies with luminal evaluation using intravascular ultrasound and animal experiments using an atherosclerotic model could answer this question. We have recently conducted animal experiments toward this end.

Endothelial function and endothelial nitric oxide synthase (eNOS)

Recent studies on a nitroglycerine tolerance mechanism may also help to explain the mechanism of ALDH2 Glu504Lys polymorphism on CAD development and ACS occurrence. Sublingual nitroglycerine is an effective means of relieving angina. Nitroglycerine is metabolised into nitric oxide, and nitric oxide promotes the relaxation of vascular smooth muscle through the cyclic guanosine monophosphate signal transduction pathway, thereby relieving myocardial ischemia. However, in some patients, sublingual nitroglycerine is not effective in relieving angina. Recent studies have found that mitochondrial ALDH2 is also a critical enzyme for converting nitroglycerine into nitric oxide (Li et al. 2006). ALDH2 inhibition can significantly reduce the vasodilatory effects of nitroglycerine (Mackenzie et al. 2005; Daiber et al. 2009). Another canine study also confirmed that the inhibition of ALDH2 activity can significantly reduce the dilation of canine coronary vessels (Zhang et al. 2004). Therefore, regardless of the impact of ALDH2 *504Lys allele on coronary atherosclerosis, the significant activity reduction may decrease the production of vasodilators such as nitric oxide and then induces coronary spasm which triggering ACS occurrence. Of course, there are many vasodilators in the body, not just nitric oxide, and the amount of nitric oxide in the human body is affected not only by ALDH2 activity but also by endothelial and inducible nitric oxide synthase. It is necessary then to verify the role of coronary spasm in the effect of the ALDH2 gene polymorphism on ACS through addi-

tional studies.

A study in a Chinese population found that the serum level of asymmetric dimethylarginine (ADMA) in carriers of the ALDH2 *504Lys allele was significantly higher than in carriers of the wild-type (Guo et al. 2010). Further *in vitro* experiments also demonstrated that umbilical vein endothelial cells carrying the ALDH2 *504Lys allele have significantly higher levels of ADMA synthesis and secretion than those carrying the wild-type (Guo et al. 2010). ADMA is an endogenous inhibitor of nitric oxide synthase, can cause endothelial dysfunction through a variety of mechanisms, and has been proven to be a risk factor for CAD. Therefore, Guo and co-workers (2010) suggested that endothelial dysfunction may be involved in the effect of the ALDH2 gene polymorphism on CAD.

Recently, an *in vitro* experiment conducted by our group found that stimulation with an appropriate amount of ethanol can enhance mitochondrial ALDH2 activity in arterial endothelial cells and improve the activity of eNOS. However, if ALDH2 activity is inhibited during ethanol stimulation, eNOS activity does not increase, which suggested that ALDH2 is involved in the activation of eNOS by ethanol (Xue et al. 2012). We also found that without ethanol stimulation, direct inhibition of ALDH2 activity did not significantly reduce eNOS activity (Xue et al. 2012). In another clinical study conducted by our group, high-resolution ultrasound was used to detect the brachial artery of ACS patients (Xu et al. 2011). The results revealed no significant differences in endothelium-dependent vasodilation between patients with different ALDH2 genotypes. However, after taking sublingual nitroglycerine, the degree of brachial artery dilatation in patients with the ALDH2 *504Lys allele was significantly lower than in those with the wild-type (Xu et al. 2011). These results demonstrate that the ALDH2 *504Lys allele exerts a significant effect on non-endothelium-dependent vasodilation and an insignificant effect on endothelium-dependent vasodilation, which is consistent with previous studies (Zhang et al. 2004; Mackenzie et al. 2005). Previous studies have confirmed that coronary spasm is significantly correlated with damaged endothelium-but not with non-endothelium-dependent vasodilation. Therefore, there is insufficient evidence to support the hypothesis that the ALDH2 gene polymorphism affects ACS occurrence by causing endothelial dysfunction and coronary spasm.

Inflammation and oxidative stress

Recent studies on myocardial ischemic preconditioning mechanisms indicated that increased ALDH2 activity plays an important role in myocardial ischemic preconditioning. Increased ALDH2 activity may ultimately reduce the myocardial necrosis area that results from ischemia by 60% (Chen et al. 2008). There are significant differences in the degree of myocardial injury caused by cardiac ischemia in carriers of the different ALDH2 genotypes (Chen et al. 2008). A further study also demonstrated that high ALDH2

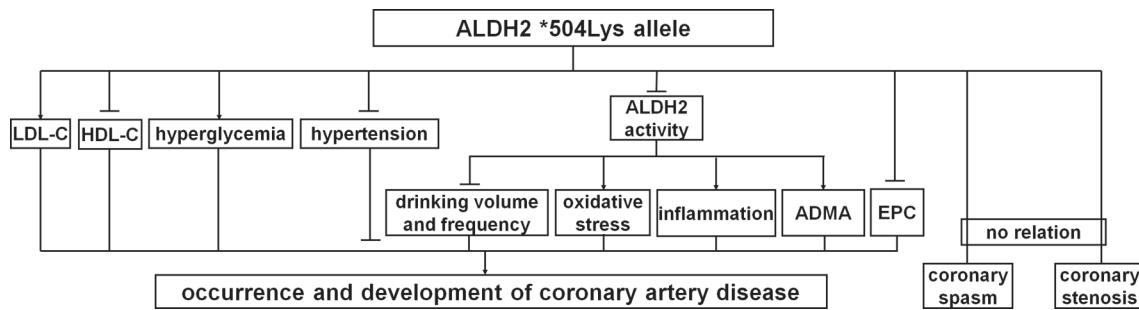


Fig. 2. ALDH2 Glu504Lys polymorphism and occurrence and development of coronary artery disease.

ALDH2 *504Lys allele induces the occurrence and development of CAD probably through a variety of mechanisms, such as alcohol consumption, dyslipidemia, hyperglycemia, oxidative stress, inflammatory cytokines, and EPCs, although it shows a protective effect on hypertension and no significant relation with coronary spasm and stenosis evaluated with coronary angiography.

ALDH2, aldehyde dehydrogenase 2; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; ADMA, asymmetric dimethylarginine; EPC, endothelial progenitor cell.

activity may play a myocardial protection role by reducing the level of oxidative stress induced by 4-hydroxynonenal (Churchill et al. 2009). Related studies suggested that changes in ALDH2 activity may affect oxidative stress levels in the body (Daiber et al. 2009; Choi et al. 2011). The findings not only explain the mechanism of the impact of ALDH2 on ‘the degree of myocardial injury after infarction’ but also highlight the mechanisms underlying the impact of ALDH2 on ‘the occurrence of ACS or MI’. Scholars now believe that the main cause of ACS is the inflammation-induced rupture of vulnerable plaque and thrombogenesis rather than the degree of coronary stenosis (Libby 2002; Naghavi et al. 2003a, b). Previous studies have confirmed that oxidative stress is an important secondary outcome of inflammation. There are many interactions between these factors, which form a complex, interactive network (Nathan 2002). This led to our hypothesis that the different levels of ALDH2 activity expressed by the different genotypes may affect ACS occurrence through the effects of ALDH2 on oxidative stress and inflammation levels in the body.

Further studies by our group revealed that the level of inflammatory cytokines was significantly higher in carriers of the ALDH2 *504Lys allele than in carriers of the wild-type allele, in both the ACS patient group and the “healthy” control group with no chronic diseases (Xu et al. 2011). Moreover, after the level of inflammatory cytokines was incorporated into the regression analysis model as an independent variable, the correlation between ALDH2 polymorphism and ACS was significantly reduced (Xu et al. 2011). These results suggest that the ALDH2 *504Lys allele may affect plaque vulnerability by inducing inflammation, thereby resulting in the occurrence of acute coronary events. This speculation was further supported by another study conducted by our group, which demonstrated that alpha-lipoic acid, a natural dithiol compound with antioxidant properties, could decrease the serum levels of 8-isoprostaglandin F_{2α}, a marker of oxidative stress, via increasing ALDH2 activity in patients with ACS (Li et al. 2013).

Other factors

Our study also discovered that the endothelial progenitor cell (EPC) count in the peripheral circulation in carriers of the ALDH2 *504Lys allele was significantly lower than in carriers of the wild-type (Xu et al. 2011). We also found that after the circulating EPCs and inflammatory cytokines were incorporated into the regression analysis model as independent variables, the correlation between ALDH2 polymorphism and ACS no longer existed (Xu et al. 2011). Previous studies confirmed that EPCs play an important role in CAD occurrence and development and can repair damaged endothelium and stabilise plaques (Hill et al. 2003). The results suggest that the ALDH2 gene polymorphism may affect plaque vulnerability not only by inducing inflammation but also by decreasing circulating EPCs, which can result in acute coronary events.

Conclusion

An increasing number of studies have confirmed the existence of an important correlation between ALDH2 Glu504Lys polymorphism and CAD occurrence and development. The ALDH2 gene may affect the occurrence and development of atherosclerosis and ACS through a variety of mechanisms, such as alcohol consumption, blood lipid levels, blood glucose level, blood pressure, oxidative stress, inflammatory cytokines, and EPCs (Fig. 2). Several of these mechanisms still need to be verified with further cell and animal experiments. Based on the high incidence of the ALDH2 polymorphism in East Asian populations and prevalence of alcohol consumption throughout the world, these studies will help promote early screening, personalized prevention, and development of new molecular target drugs for CAD-susceptible populations.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (81170136, 81100147, 81300103, 81300219), the National 973 Basic Research Program of China (2010CB732605), Grant from Department of Science and Technology of Shandong

Province (2011GGE27037, 2011GSF11806, ZR2013HQ012), Shandong Provincial Outstanding Medical Academic Professional Program, 1020 Program from the Health Department of Shandong Province, Taishan Scholar Program of Shandong Province, Major Orientation Foundation of Shandong University (2011DX003), and Grant from Jinan Science and Technology Bureau (201102073).

Conflict of Interest

The authors declare no conflict of interest.

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