Review Article

Human Catalase, Its Polymorphisms, Regulation and Changes of Its Activity in Different Diseases

(catalase / oxidative stress / polymorphisms / gene expression)

J. KODYDKOVÁ, L. VÁVROVÁ, M. KOCÍK, A. ŽÁK

4th Department of Internal Medicine – Department of Gastroenterology and Hepatology of the First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic

Abstract. Catalase (CAT) is a well-studied enzyme that plays an important role in protecting cells against the toxic effects of hydrogen peroxide. In human, it has been implicated in different physiological and pathological conditions. This review summarizes the information available on the function and role of CAT polymorphisms in pathogenesis of various pathophysiological states as well as on the regulation of *CAT* gene expression. Numerous studies have described the CAT polymorphisms and their link with various diseases. Changes in the CAT levels were reported in many different diseases and polymorphisms in the *CAT* gene were shown to be associated with different pathophysiological states, e.g. hypertension, diabetes mellitus, insulin resistance, dyslipidaemia, asthma, bone metabolism or vitiligo. Regulation of the *CAT* gene expression plays an important role in the levels of CAT. The catalase gene expression is regulated by various mechanisms involving e.g. peroxisome proliferator-activated receptor γ (PPARγ), tumour necrosis factor α (TNF-α), p53 protein and hypermethylation of CpG islands in the catalase promoter. Transcription of the *CAT* gene is mainly influenced by the -262 C/T and -844 A/G polymorphisms. A common polymorphism -262 C/T in the promoter region has been found to be associated with altered CAT activities. Apart from genetic factors, the activities of CAT may be affected by age, seasonal variations, physical activity, or a number of chemical compounds. Future investigations are necessary to elucidate the role of CAT in pathogenesis of oxidative stress-related diseases.

Received January 21, 2014. Accepted March 26, 2014.

Preparation of this manuscript was supported by research project RVO-VFN64165/2012 of the Ministry of Health of the Czech Republic and research project PRVOUK-P25/LF1/2 of the First Faculty of Medicine, Charles University in Prague.

Corresponding author: Jana Kodydková, 4th Department of Internal Medicine – Department of Gastroenterology and Hepatology of the First Faculty of Medicine, Charles University in Prague and General University Hospital, U Nemocnice 2, 128 01 Prague 2, Czech Republic. Phone: (+420) 224962477; Fax: (+420) 224 92 35 24; e-mail: jana.kodydkova@seznam.cz

Abbreviations: Ang II – angiotensin II, CAT – catalase, CP – chronic pancreatitis, DM1, 2 – diabetes mellitus, GPX – glutathione peroxidases, HCC – hepatocellular carcinoma, MetS – metabolic syndrome, NF-κB – nuclear factor κB, NOX – NADPH oxidases, PAX-6 – paired box 6, *PIG3* – p53-inducible gene 3, PPRE – PPARγ response element γ, PPARγ – peroxisome proliferator-activated receptor γ, ROS – reactive oxygen species, SARS – severe acute respiratory syndrome, SBP – systemic blood pressure, siRNA – small-interfering RNA, SIRS – systemic inflammatory response syndrome, TGF-β – transforming growth factor β, TNF-α – tumour necrosis factor α.

Introduction

Catalases (CAT, $H_2O_2 : H_2O_2$ – oxidoreductase, EC: 1.11.1.6) are enzymes with a long history that goes back to the 19th century, when they became one of the first sources of valuable information about the nature and behaviour of enzymes (Zámocký and Koller, 1999). The name catalase was given to the enzyme in 1900 owing to its catalatic action on hydrogen peroxide (Loew, 1900). Human catalase belongs to the group of monofunctional haem-containing catalases; members of this large subgroup are found in almost all aerobically respiring organisms (Zámocký and Koller, 1999; Chelikani et al., 2004). Catalase is primarily an intracellular enzyme; its highest concentrations in mammals are found in erythrocytes and liver and occasionally in the kidney (Deisseroth and Dounce, 1970). In tissues such as liver, catalase is found predominantly in peroxisomes (Quan et al., 1986).

Catalase is a tetrameric protein of 244 kDa with molecular 222 symmetry, comprising four identical subunits of 59.7 kDa. Each subunit contains 527 amino acid residues, one haem group, namely iron (III) protoporphyrin IX, and a tightly bound molecule of NADPH (Kirkman and Gaetani, 1984, 2007; Ko et al., 2000; Safo et al., 2001). Under physiological conditions erythrocytes contain 1.31–2.71 μg CAT/mg Hb. These values correspond to an expected concentration of 6.6 to 13.7 μM for catalase-bound NADPH in human erythrocytes (Kirkman and Gaetani, 1984). The exact role and

function of NADPH in catalase was discussed in various reports (Kirkman et al., 1987; Hillar and Nichols, 1992; Almarsson et al., 1993; Olson and Bruice, 1995; Kirkman et al., 1999; Rovira 2005; Kirkman and Gaetani, 2007) and it was estimated that NADPH prevents formation of the inactive form of CAT (iron (IV) oxo-protoporphyrin IX) and also mildly increases the rate of removal of this inactive form; thus, NADPH protects CAT against inactivation by H_2O_2 (Kirkman et al., 1987, 1999).

The main function of catalase is decomposition of hydrogen peroxide to water and oxygen – catalatic activity. During long-term exposure of CAT to H_2O_2, the catalase-bound NADPH became oxidized to $NADP^+$ and the activity of CAT fell to about one-third of the initial activity (Kirkman et al., 1987). In addition to a very efficient catalatic reaction mode, catalase could also catalyse 2-electron peroxidations of short-chain aliphatic alcohols at reasonable rates (Zámocký and Koller, 1999). The catalatic reaction predominates when the H_2O_2 concentration is higher than 10^{-4} M, while below this concentration in the presence of an acceptable hydrogen donor the peroxidatic reaction dominates (Maté et al., 1999).

It is known that H_2O_2 may play a key role in human physiological and pathophysiological processes. It is an important "second messenger" and signalling molecule at the cellular level. One of the main sources of reactive oxygen species are NADPH oxidases (NOX) that primarily produce superoxide, which is rapidly dismutated to H_2O_2 by superoxide dismutase. It has been shown that conditions in which NOX4 primarily generates superoxide lead to activation of proinflammatory transcription factors, and of stress-signalling pathways through mitogen-activated protein kinases, accumulation of Ca^{2+}, and decreased NO availability, which is linked to vascular inflammation and endothelial dysfunction. On the other hand, direct generation of H_2O_2 by NOX4 leads to signalling pathways that promote vasodilatation and cell protection (Touyz and Montezano, 2012).

In vivo, there are three families of enzymes which could remove hydrogen peroxides: catalases, glutathione peroxidases (GPX) and peroxiredoxins. Catalase may be the key enzyme for H_2O_2 removal in peroxisomes, although peroxiredoxin 5 may also contribute. At low H_2O_2 concentrations, GPX1 and peroxiredoxins are responsible for its degradation. Although peroxiredoxins are slower at catalysing H_2O_2 degradation than GPX1, it has been suggested that at low H_2O_2 concentrations, peroxiredoxins dispose of most H_2O_2 generated inside cells. Catalase plays an important role in removing higher intracellular H_2O_2 concentrations (Halliwell and Gutteridge, 2007).

In 2003 Heck et al. discovered that in keratinocytes CAT could generate reactive oxygen species (ROS) in response to UVB light. The ability of the enzyme to generate ROS was dependent on the dose of UVB light utilized and the concentration of CAT (Heck et al., 2003). Therefore, Chelikani et al. (2004) speculated that the NADPH cofactor could have a role in ROS generation. These results implicate another role for NADPH in the catalase physiology.

In this review we try to elucidate the link between catalase polymorphisms and its activity in different diseases. The second important point of this review is to summarize findings about the catalase activity regulation.

1. Gene characteristics

The isolation and characterization of the human catalase gene were done in 1986 by Quan et al. (1986). The gene for human catalase has been mapped to chromosome 11, band p13, and is split into 13 exons by 12 introns and spans (Quan et al., 1986). Numerous polymorphisms have been described in the promoter, 5′ and 3′- untranslated regions, exons and introns (Fig. 1). More precisely, the *CAT* gene is located from base pair 34,460,471 to base pair 34,493,606 on chromosome 11 (http://ghr.nlm.nih.gov/gene/CAT#location). The gene was shown to have eight initiation points of transcription, three CCAAT boxes, and three GC-like boxes, but to lack a TATA box and an initiator consensus sequence in the promoter region, which leads to multiple start sites of transcription (Sato et al., 1992; Toda et al., 1997).

2. Polymorphisms

In 2012, 245 catalase single-nucleotide polymorphisms were detected and described according to the NCBI database in different regions of the *CAT* gene (Crawford et al., 2012a). Significant correlations of the studied polymorphisms and various diseases are presented in Table 1. It has been shown that genetic variations in the *CAT* gene and its promoter may play a role in glucose disorders and may be risk factors for meta-

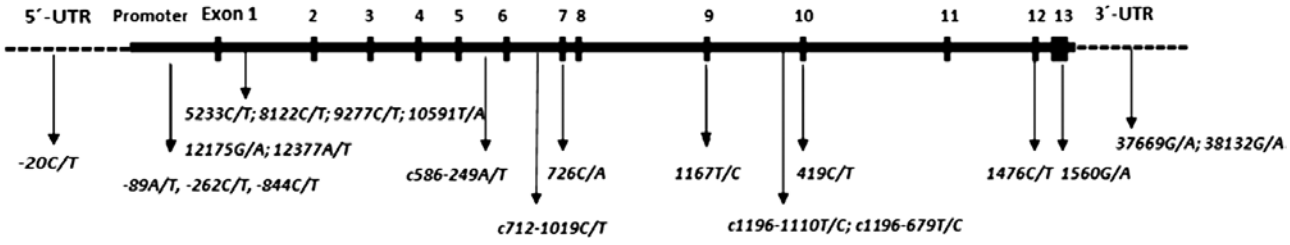

Fig 1. *CAT* gene and relevant single-nucleotide polymorphisms
UTR – untranslated region. Arrows correspond to catalase gene introns and exons. Source: Liu et al. (2010); Hebert-Schuster et al. (2012)

Table 1. Studied CAT gene single-nucleotide polymorphisms and their associated diseases

Polymorphism (NCBI ref. SNP ID)	Region of gene	Disease	Reference	Findings
-844C/T or -844G/A (rs769214)	Promoter	Hypertension	Jiang (2001)	TT genotype is associated with increased SBP
			Watanabe (2010)	Independently predicted risk of progression of hypertension
			Fabre (2008)	A allele is associated with lower renutrition efficiency
		Malnutrition	Hebert-Schuster (2011)	A allele is associated with lower renutrition efficiency
		Asthma	Podgoreanu (2006)	CT genotype is associated with postoperative myocardial infarction
-262C/T or 330C/T (rs1001179)	Promoter	Type 1 diabetes	Chistiakov (2004)	CC genotype represented higher DM1 risk
			Chistiakov (2006)	C allele is associated with higher DMI risk
		Breast cancer	Ahn (2005)	T allele is associated with increased breast cancer risk
			Quick (2008)	T allele is associated with increased breast cancer risk in non-Caucasians, no significant association in Caucasians
			Ahn (2006b)	CC genotype is associated with decreased breast cancer risk
		Hepatocelullar carcinoma (HCC)	Ezzikouri (2010)	TT genotype had increased risk to develop HCC
		Rheumatoid arthritis	Grabar (2009)	T allele is associated with lower activity of rheumatoid arthritis
		Asthma	Mak (2006)	T allele is associated with decreased risk of asthma in non-smokers
			Islam (2008)	T allele is associated with increased risk of asthma among Hispanic children, not in non-Hispanic white children
		Ulcerative colitis	Khodayari (2013)	CT genotype is associated with increased risk of ulcerative colitis
		Asbestosis	Franko (2008)	TT genotype is slightly associated with elevated risk of asbestosis
		Hyperkeratosis	Ahsan (2003)	CT/TT genotype is associated with increased risk of arsenic-induced hyperkeratosis
		Various	Christiansen (2004)	T allele is associated with improved physical functioning
-89A/T or -21A/T (rs7943316 rs17880664)	Promoter	Asthma	Polonikov (2009)	AA genotype is associated with increased risk of asthma
		Osteonecrosis	Kim (2008)	T allele is associated with protective effect on osteonecrosis
		Vitiligo	Liu (2010)	T allele is associated with increased risk of vitiligo
-20C/T (rs1049982 (rs17881315)	5'UTR	Hypertension	Mansego (2011)	T allele is associated with lower blood pressure
		Ostenecrosis	Kim (2008)	TT genotype is associated with increased risk of osteonecrosis
1167C/T; 389C/T, 22348 C/T; 111C/T; 389Asp/Asp (rs769217 or rs17880449)	Exon 9 Codon 389	Type 1 diabetes	Tarnai (2007)	T allele is associated with increased risk of diabetes mellitus 1
			Chistiakov (2004)	CC genotype is associated with increased risk of diabetes mellitus 1
		Type 2 diabetes	Chistiakov (2000)	
		Vitiligo	Gavalas (2006)	T allele is associated with increased risk of vitiligo
		Osteonecrosis	Kim (2008)	TT genotype is associated with increased risk of osteonecrosis
		Bone mineral density	Oh (2007)	T allele is associated with higher bone mineral density
5233C/T, c66+78C/T; +144C/T (rs10836235 or rs17886119)	Intron 1	Various	Rajic (2009)	CC genotype is associated with late cardiac toxicity in patients treated with anthracycline due to acute leukaemia in childhood
8122T/C, 3033C/T; c66+2967T/C (rs525938)	Intron 1	Osteonecrosis	Kim (2008)	CC genotype is associated with increased risk of osteonecrosis
19628A/T, 14539A/T; c586-249A/T (rs3758730)	Intron 5	Osteonecrosis	Kim (2008)	TT genotype is associated with increased risk of osteonecrosis
29502T/C, 24413T/C; c1196-679T/C (rs2284365)	Intron 9	Osteonecrosis	Kim (2008)	CC genotype is associated with increased risk of osteonecrosis

bolic diseases such as impaired glucose tolerance, insulin resistance, diabetes mellitus, hypertension, dyslipidaemia and osteoporosis and their comorbidities (Hebert-Schuster et al., 2012). Additionally discovered polymorphisms are mapped in the gene card (http://www.genecards.org/cgi-bin/carddisp.pl?id=847&id_type=entrezgene).

2.1. Polymorphisms in the promoter region

2.1.1. Polymorphism -262C/T

In the promoter region of the *CAT* gene there is a common polymorphism of C to T substitution at position -262 (db SNP ID: rs1001179). This polymorphism may influence *CAT* transcription by modulation of the transcriptional factor binding position and increased basal CAT expression in various cell types as well as the CAT level in erythrocytes (Forsberg et al., 2001; Galecki et al., 2009a, Hebert-Schuster et al., 2012). The relationship between the -262C/T polymorphism and catalase concentration in whole blood was demonstrated by Forsberg et al. (2001). Carriers of the less common -262T allele display higher CAT levels compared to CC homozygotes (wild type) (Forsberg et al., 2001). Other authors described the association between the -262C/T *CAT* polymorphism and CAT activity. It was shown that CC homozygotes had higher activity of CAT compared to those with CT or TT genotype (Ahn et al., 2005, 2006b; Nadif et al., 2005; Perianayagam et al., 2007). Conversely, in the study of Mak et al. (2007) no association between the *CAT* -262C/T polymorphism and CAT

activity was observed. The presence of the -262 T allele prevents neurodegeneration and impaired physical fitness, and was associated with cognitive function improvement (Christiansen et al., 2004; Galecki et al., 2009a). Carriers of the CC genotype were observed to be the most frequent (Christiansen et al., 2004).

This polymorphism has been studied in different populations as well as in different pathophysiological states. No statistically significant differences were found in -262C/T genotype frequencies between controls and patients with systemic lupus erythematosus (Eny et al., 2005; D'Souza, 2008; Warchol et al., 2008; Ghaly et al., 2012), vitiligo (Gavalas et al., 2006; Kósa et al., 2012), pseudoxanthoma elasticum (Zarbock et al., 2007), Alzheimer's disease (Goulas et al., 2002; Capurso et al., 2008), schizophrenia (Boškovič et al., 2013), pancreatic cancer (Tang et al., 2010), prostate cancer (Choi et al., 2007), lung cancer (Ho et al., 2006), colorectal cancer (Funke et al., 2009b), cleft lip/palate-affected pregnancies (Mostowska et al., 2007), non-Hodgkin's lymphoma (Lightfoot et al., 2006; Farawela et al., 2012), hypertension (Hsueh et al., 2005; Zhou et al., 2005), chronic obstructive pulmonary disease (Mak et al., 2007), instent restenosis (Shuvalova et al., 2012) or bronchial asthma (Polonikov et al., 2009).

No association was found between the -262C/T *CAT* polymorphism and hepatocellular carcinoma in cirrhosis (Nahon et al., 2009), adult brain tumours (Rajaraman et al., 2008; Bhatti et al., 2009), chronic kidney disease and its progression (Crawford et al., 2012b), appearance of precancerous changes in the gastric mucosa (Steenport et al., 2007), depressive disorder (Galecki et al., 2009a, b) or adverse outcomes in acute renal failure (Perianayagam et al., 2007).

The study of Rajić et al. (2009) estimates no correlation between this polymorphism and late cardiotoxicity in patients treated for acute leukaemia in childhood. In the study by Funke et al. (2009a), no association of the *CAT* -262C/T polymorphism with survival in rectal cancer patients who received radiotherapy was observed. Similarly, in the study by Koistinen et al. (2006), no associations between the *CAT* -262C/T polymorphism and the overall survival of patients with acute myeloid leukaemia were found.

On the contrary, Ezzikouri et al. (2010) found that patients with the *CAT* TT genotype had 3.41-fold increased risk of hepatocellular carcinoma and reduced CAT activity.

In a Russian population, Chistiakov et al. (2004, 2006) have found significant association of polymorphism *CAT* -262C/T with diabetes mellitus type 1 (DM1); whereas the C allele and the CC genotype represented higher risk of the disease. Other studies did not confirm the association between this polymorphism and DM1 (Pask et al., 2006) or DM2 (Szelestei et al., 2005; Dos Santos et al., 2006; Chen et al., 2012a).

An association was found between this polymorphism and breast cancer risk (Ahn et al., 2005); however, the studies of Quick et al. (2008) and Li et al. (2009) did not found any association between the *CAT* -262C/T polymorphism and breast cancer. According to the studies of Ambrosone et al. (2005) and Ahn et al. (2006a), there were no associations between the -262C/T *CAT* polymorphism and the outcome after treatment for breast cancer.

In Hong-Kong Chinese population, Mak et al. (2006) have found that the C allele is significantly different between patients with asthma and controls. They also found a significant difference in the prevalence of catalase CC and combined CT and TT genotypes between the patients and controls. Islam et al. (2008) have reported an association of the *CAT* -262C/T variant with asthma in Hispanic-white children. Among Hispanic-white children, carriers of the T allele were at increased risk of new-onset asthma compared with children who were homozygous for common allele CC. Among non-Hispanic-white children this polymorphism was not associated with asthma risk. Wenten et al. (2009) did not find any association between the *CAT* -262C/T polymorphism and asthma status in white Hispanic and non-Hispanic subjects.

A correlation between the *CAT* -262C/T polymorphism and the disease activity was found in patients with rheumatoid arthritis (Grabar et al., 2009); however, in a previous study by El-Sohemy et al. (2006) no association was observed. An association was also observed between this polymorphism and delayed graft function of kidney allografts (Dutkiewicz et al., 2010).

2.1.2. Polymorphism -89A/T (-21A/T)

The next polymorphism examined in the promoter region of *CAT* was the -89A/T polymorphism (db SNP ID: rs7943316), also known as -21A/T. This polymorphism was studied in patients with DM (Ukkola et al., 2001; Nemoto et al., 2007; Flekac et al., 2008), asthma (Mak et al., 2006; Polonikov et al., 2009), chronic obstructive pulmonary disease (Young et al., 2006), hypertension (Jiang et al., 2001), osteonecrosis (Kim et al., 2008) and vitiligo (Park et al. 2006; Liu et al., 2010) and in patients after cardiac surgery (Podgoreanu et al., 2006).

No association was found between the -89A/T polymorphism and DM1 (Flekac et al., 2008), DM2 (Ukkola et al. 2001; Flekac et al. 2008), or diabetic nephropathy (Panduru et al., 2010) or coronary atherosclerosis in diabetic patients (Nemoto et al., 2007). No associations between hypertension (Jiang et al., 2001), chronic obstructive pulmonary disease (Young et al., 2006) and this polymorphism were observed.

In Russian population, Polonikov et al. (2009) found a significant difference in the distribution of genotypes of polymorphism -89A/T between patients with asthma and controls – the homozygous genotype -89AA was more frequent among asthmatics than among the controls. Mak et al. (2006) demonstrated no differences in genotype distribution between the patients with asthma and controls.

The results of the studies of vitiligo patients are also inconsistent. In Korean population no association be-

tween the *CAT* -89A/T polymorphism and vitiligo was demonstrated (Park et al., 2006), whereas Liu et al. (2010) observed association of AT and TT genotypes in Chinese population with increased vitiligo risk. According to the study of Kim et al. (2008), the T allele of -89A/T had a protective effect on osteonecrosis of the femoral head. In the study by Fabre et al. (2008), the -89A/T polymorphism was defined as a possible marker for predicting efficiency of renutrition. According to the study of Podgoreanu et al. (2006), the -89A/T polymorphism was not found to be a predictor of postoperative myocardial infarction in patients after cardiac surgery.

2.1.3. Polymorphism -844C/T

The third demonstrated polymorphism in the promoter region is -844C/T (db SNP ID: rs769214). This polymorphism may influence *CAT* transcription by modulation of the transcriptional factor binding position polymorphism (Hebert-Schuster et al., 2011, 2012). It has been shown that the T allele of the -844C/T polymorphism is associated with higher CAT activity in basal conditions, depending however on the binding site of transcriptional factor PAX6 (paired box 6). It has been shown that CAT is associated with transcription factor PAX6 that is involved in glucose homeostasis (Hebert-Schuster et al., 2011). In the presence of PAX6, this T allele is associated with decreased CAT activity in comparison with the C allele (Hebert-Schuster et al., 2012). Similarly, Nadif et al. (2005) found association of this polymorphism with CAT activity, when subjects with TT genotype had lower activity than those with CC genotype (Hebert-Schuster et al., 2012). According to the study of Yanping et al. (2004), carriers of the -844T variant had higher CAT transcriptional activity than carriers with the C variant.

Jiang et al. (2001) observed strong association of the -844C/T polymorphism with essential hypertension; these results are in accordance with Watanabe et al. (2010), whereas in the study of Zhou et al. (2005) this association was not confirmed. Islam et al. (2008) reported that there is a lack of association between -844C/T and risk of asthma. Similarly, Rajaraman et al. (2008) did not observe any association between this genotype and risk of some central nervous system tumours (such as glioma, glioblastoma, meningioma, and acoustic neuroma).

In the study of Fabre et al. (2008) the -844C/T polymorphism was specified as a promising marker for predicting efficiency of renutrition. *In silico* analysis has shown that the A allele of the polymorphism -844 A/G (commonly called -844C/T) carries a PAX6-binding site. PAX6 is required for differentiation of cells producing glucagon and thus important in glucagon biosynthesis. Fabre et al. (2008) found inefficient renutrition caused by the A allele of the *CAT* gene. Binding of PAX6 could modify transcription of *CAT* and thus influence glucagon secretion. It was shown that this polymorphism is an independent predictor of postoperative myocardial infarction in patients who underwent cardiac surgery (Podgoreanu et al., 2006).

2.2. Polymorphism -20C/T

In the 5'UTR region of the *CAT* gene, there is the well-described -20C/T polymorphism (db SNP ID: rs1049982). According to the study of Kim et al. (2008), this polymorphism is associated with osteonecrosis of the femoral head in the Korean population. In the study by Fabre et al. (2008) this polymorphism was defined as a possible marker for predicting efficiency of renutrition. In a larger genetic study the polymorphism -20C/T was associated with a risk of hypertension, when carriers of the T allele had decreased values of blood pressure (Mansego et al., 2011).

Other studies of this polymorphism did not show its association with essential hypertension (Jiang et al., 2001), bone mineral density and bone turnover markers (Oh et al., 2007), asthma status (Wenten et al., 2009) or with vitiligo (Casp et al., 2002).

2.3. Polymorphism 389C/T

Some polymorphisms were also detected in the exon regions of the *CAT* gene. Common polymorphisms are the 389C/T polymorphism of exon 9 (db SNP ID: rs769217), also marked as 1167C/T, 111C/T or 22348C/T, and the 419C/T polymorphism of exon 10 (db SNP ID: rs11032709). The study of Oh et al. (2007) indicates that the 389C/T polymorphism may be a useful genetic marker for bone metabolism. Carriers of the T allele had significantly higher bone mineral density and decreased osteocalcin levels. An association was also demonstrated between this polymorphism and the risk of osteonecrosis of the femoral head (Kim et al., 2008).

The 389C/T polymorphism was explored mainly in two diseases – vitiligo and diabetes mellitus. No difference in genotypes or allele frequencies between patients with vitiligo and controls was found in the studies by Casp et al. (2002), Liu et al. (2010), Shajil et al. (2007) and Park et al. (2006); the only studies that observed a difference in alleles and genotype frequencies was the study of Gavalas et al. (2006) and Lv et al. (2011). In vitiligo patients, an increased prevalence of the T allele was found in comparison with controls (Gavalas et al., 2006). Meta-analysis concerning the association between the 389 C/T polymorphism and the risk of vitiligo suggested that the CT genotype of the *CAT* gene is associated with an increased vitiligo risk and carriers with the T allele had higher risk of progressing vitiligo (Lv et al., 2011). Low CAT activity in vitiligo patients could be a result of the inhibitory effect of H_2O_2, or allelic variations in the *CAT* gene that may influence the expression of the enzyme or their function. Casp et al. (2002) reported that *CAT* mutations could lead to a risk of vitiligo by changes in the gene expression or structure in melanocytes and/ or keratinocytes.

The results of the studies focused on polymorphism 389C/T in patients with DM are not homogenous. The 389C/T polymorphism of *CAT* was associated with DM1 (Chistiakov et al., 2004; Tarnai et al., 2007) and also DM2 (Chistiakov et al., 2000), whereas Pask et al.

(2006) found no association between this polymorphism and diabetes mellitus type 1. Chistiakov et al. (2006) investigated the association between this polymorphism and diabetic neuropathy in patients with diabetes mellitus type 1 and found no significant association. No significant differences were found between complicated and uncomplicated hypertensive patients with diabetes mellitus type 2 with respect to the allelic or phenotypic distribution of the 389C/T polymorphism (Sergeeva et al., 2001).

The 419C/T polymorphism was examined in patients with vitiligo in comparison with controls and there was no difference in the frequency of alleles or genotypes between these two groups (Casp et al., 2002; Gavalas et al., 2006; Liu et al., 2010).

2.4. Inherited catalase deficiency – acatalasemia

The deficiency of catalase was for the first time described by Takahara and Miyamoto in Japanese population in 1948 (Góth, 2001a). Three main types of CAT deficiency have been distinguished – Japanese, Hungarian and Swiss. Catalase deficiency is an inherited disease; its inheritance pattern is autosomal recessive. The homozygous condition is called acatalasemia, the heterozygous condition is designated as hypocatalasemia (Ogata et al., 2008). The deficiencies in mammalian catalase were described in detail in reviews by Ogata et al. (2008) and Góth and Nagy (2013). Acatalasemia is characterized by clinical features such as oral infections, mouth ulcers and gangrene, as well as altered lipid and carbohydrate metabolism (Góth et al., 2004; Góth and Nagy, 2012).

Japanese acatalasemia has been classified into two subtypes, by splicing mutation (G to A substitution) in position 5 of intron 4 and frame-shift mutation (T deletion) in position 358 in exon 4 (Ogata et al., 2008). In the individuals with homozygous condition the CAT activity is less than 10 % of normal erythrocyte activity, the heterozygous individuals have approximately half of normal erythrocyte catalase activity (Góth, 2001a). Takahara described oral progressive gangrene in Japanese acatalasemic patients; this gangrene due to acatalasemia was called Takahara's disease (Ogata et al., 2008). This disease was not observed in other types of acatalasemia (Góth, 2001a) and the incidence of the disease in Japanese acatalasemic patients decreased significantly (Ogata et al., 2008).

There are four subtypes of Hungarian acatalasemia – type A is characterized by the frame-shift mutation (GA insertion) in position 138 of exon 2, type B is described as frame-shift mutation (G insertion) in position 79 of exon 2, type C is defined as splicing mutation (G to T substitution) in position 5 of intron 7, and type D is defined as coding region mutation (G to A substitution) in position 5 of exon 9 (Ogata et al., 2008). All these subtypes of Hungarian acatalasemia were described by Góth (2001a,b) and Góth et al. (2000, 2001, 2005).

3. Regulation of catalase gene expression

The regulation of *CAT* gene expression plays an important role in the levels of catalase. The expression is regulated at the transcription, post-transcription and post-translation levels (Nishikawa et al., 2009). It was shown that the *CAT* gene expression is regulated by peroxisome proliferator activated receptor γ (PPARγ). PPARγ is a ligand-activated transcription factor that controls expression of the *CAT* gene by binding to a distal PPARγ response element (PPRE) in its promoter region (Okuno et al., 2010; Yang et al., 2011). Girnun et al. (2002) showed that PPARγ ligands, in general thiazolidinediones (ciglitazone, rosiglitazone, pioglitazone), increase the catalase mRNA and activity, and this is mediated *via* a functional PPRE in the rat catalase promoter. It has been shown that PPARγ binds the promoter of *CAT* to regulate its expression in endothelial cells. Current data demonstrate that *CAT* is a PPARγ target gene. Way et al. (2001) recently demonstrated *in vivo* that a non-thiazolidinedione PPARγ ligand can increase catalase expression in tissues that contain PPARγ.

Chen et al. (2012b) investigated the cardioprotective role of PPARγ activation with rosiglitazone and pioglitazone in rabbit newborn and adult hearts. Activation of PPARγ with rosiglitazone regulates *CAT* expression in newborn heart, with over-expression of PPARγ in newborn rabbit heart. Yang et al. (2011) found that angiotensin II (Ang II) inhibited CAT and PPARγ protein and mRNA expression. Transfection with PPARγ small-interfering RNA (siRNA) led to a reduction in *CAT* expression. PPARγ ligands enhanced *CAT* expression and inhibited extracellular signal-regulated kinase 1/2 (ERK 1/2) activation. The authors have found that Ang II decreased *CAT* expression in a time-dependent manner after a transient increase. Specific activation of PPARγ by ligands (15d-PGJ2 and pioglitazone) remarkably increased CAT protein and mRNA levels in fibroblasts and attenuated the decrease of CAT in response to Ang II.

In their study Min et al. (2010) observed that down-regulation of catalase is caused by hypermethylation of a CpG island in the catalase promoter during prolonged exposure to reactive oxygen species (ROS). In hepatocellular carcinoma cells, transcription factor Oct-1 binds to the catalase promoter and acts as an activator. Similarly, Quan et al. (2011) found that prolonged exposure to ROS down-regulates catalase expression by hypermethylation of CpG sites in the promoter. Transcription factor Oct-1 binds to the catalase promoter and acts as a transcriptional activator of the catalase gene. Reactive oxygen species regulates catalase not only by a direct mechanism, but also through the transcriptional activator Oct-1 (Quan et al., 2011). Catalase down-regulation and methylation of its promoter *via* ROS effect is reversible in HCC cells (Min et al., 2010). Min et al. (2010) also showed down-regulation of catalase expression both in hepatocellular carcinoma (HCC) cells and

in HCC tissues, thus confirming that exposure to ROS is associated with catalase down-regulation and methylation of *CAT* promoter during the HCC development.

Another mechanism by which catalase can be regulated is p53 protein and p53-inducible gene 3 (*PIG3*). In their study Kang et al. (2013) observed that p53 protein and *PIG3* repressed the catalase activity. They have also found that catalase activity is decreased when p53 protein is over-expressed. Similarly, ectopic expression of *PIG3* decreased the CAT activity and caused increased ROS production (Kang et al., 2013). Catalase-binding regions of p53 and *PIG3* are important for interaction with CAT and for the regulation of CAT activity and ROS levels. High levels of p53 protein and *PIG3* down-regulates the CAT activity especially in cells under severe genotoxic conditions. On the contrary, in the study of Hussain et al. (2004), no effects of p53 on the expression of catalase protein were found. Strong CAT down-regulation at the protein level was shown in a liver cancer cell line by Ngoka (2008). This down-regulation is probably caused by genetic reprogramming in favour of increased proliferation of the cancer cells (Ngoka, 2008). Down-regulation of antioxidant enzymes is determinant in the process of neoplastic transformation of cells (St Clair et al., 1992). Some hypotheses for CAT deficiency in tumours and cancer cells have been proposed, such as hypermethylation of the *CAT* promoter or implication of transcription factors (Glorieux et al., 2011). Cancer cells are rapidly proliferating cells that produce increased H_2O_2 levels and had strongly decreased CAT activities in comparison with normal cells. Hydrogen peroxide functions as a second messenger of mitogenic signalling processes and stimulates cell proliferation, whereas CAT suppresses growth factor-dependent activation of MAPK and proliferation of cells. Signalling molecules PKA and PKC are involved in mitogenic signalling and could up-regulate the activity of catalase.

Catalase derivatives such as Gal-catalase (galactosylated) and Suc-catalase (succinylated) inhibited activation of nuclear factor κB (NF-κB) in liver and tumour cells and thus reduced metastases on the surface of the liver (Nishikawa et al., 2009). It has been shown that polyethylene glycol conjugate derivatives of CAT (PEG-catalase) inhibited early steps of tumour metastasis growth in the lung (Nishikawa et al., 2009). Catalase down-regulation was also shown to be caused by tumour necrosis factor (TNF-α) (Hebert-Schuster et al., 2011). Moreover, it has been shown that catalase expression is inhibited by transforming growth factor (TGF-β) in the airway smooth muscle cells of asthmatic and chronic obstructive pulmonary disease patients (Michaeloudes et al., 2011a,b).

Several studies have demonstrated that *CAT* gene expression could be stimulated by hydrogen peroxide (Tate et al., 1995; Lai et al., 1996) or by oxidized lipids (Meilhac et al., 2000).

4. Catalase activity in various diseases

The activities of CAT have been investigated in various pathophysiological states associated with increased oxidative stress. Decreased CAT activity was found in patients with diabetes mellitus type 1 (Twardowska-Saucha et al., 1994; Atalay et al., 1997; Merzouk et al., 2003; Abou-Seif and Youssef, 2004) and in patients with DM2 (Kedziora-Kornatowska et al., 1998; Bhatia et al., 2003; Abou-Seif and Youssef, 2004; Komosińska-Vassev et al., 2005; Ramakrishna and Jailkhani, 2008) in comparison to controls. In contrast, there are some studies showing increased activity of CAT in patients with DM1 (Gil-del Valle et al., 2005) and DM2 (Sözmen et al., 1999; Kesavulu et al., 2000, 2001; Sailaja et al, 2003). Activities of CAT were observed in patients with metabolic syndrome (MetS) with inconsistent results. Reduced CAT activity was observed in patients with MetS in comparison with healthy controls in the study of Koziróg et al. (2011) and Vávrová et al. (2013), whereas no difference in the CAT activity was observed in the studies of Broncel et al. (2010) and Pizent et al. (2010). Increased CAT activity was described by Cardona et al. (2008a,b). In patients with only one component of MetS – obesity (Viroonudomphol et al., 2000), hypertension (Rodrigo et al., 2007), or insulin resistance (Shin and Park, 2006) – a decrease in CAT activity was observed.

Increased CAT activities were found in patients with depressive disorders (Szuster-Ciesielska et al., 2008; Galecki et al., 2009a,b), multiple sclerosis (Miller et al., 2011) and bipolar disorder (de Sousa et al., 2014), whereas no differences in CAT activities were observed in depressive women (Kodydková et al., 2009) and patients with major depression (Bilici et al., 2001) compared to controls. Ozcan et al. (2004) described decreased CAT activities in erythrocytes of patients with affective disorders.

Observations of CAT activity in patients with various types of cancer are inconsistent. Casado et al. (1995) found decreased CAT levels in patients with lymphoma, breast cancer, head and neck cancer, gynaecological, and urological cancer. Increased CAT levels were found in patients with non-small cell lung cancer compared to controls (Tsao et al., 2007; Esme et al., 2008). Decreased CAT activity was reported in patients with prostate cancer (Arsova-Sarafinovska et al, 2009; Akinloye et al., 2009) and pancreatic carcinoma (Kodydkova et al., 2013).

The activity of catalase has also been investigated in patients with systemic inflammatory response syndrome (SIRS), sepsis, septic shock, or those suffering from severe acute respiratory syndrome (SARS). Increased CAT activity in patients with sepsis was reported by Warner et al. (1995), Leff et al. (1992, 1993) and Kapoor et al. (2006). In their study Leff et al. (1993) showed that patients with sepsis and ARDS had higher CAT activity than those without ARDS. Differences were observed in CAT activity between patients with ARDS and healthy

subjects (Metnitz et al., 1999). Some authors described decreased CAT activities in chronic pancreatitis (CP) (Quillot et al., 2005), whereas Szuster-Ciesielska et al. (2001a) found increased CAT activities in patients with CP compared to controls. No differences were observed in the studies of Fukui et al. (2004) and Kodydkova et al. (2013). Furthermore, it was shown that serum CAT was higher in patients with acute pancreatitis than in healthy controls (Góth et al., 1982, 1989; Szuster-Ciesielska et al., 2001; Fukui et al., 2004), whereas no significant differences were observed in erythrocyte CAT activity between patients with acute pancreatitis and control subjects in the study of Chmiel et al. (2002) and Vávrová et al. (2012).

5. Catalase activity and environmental factors

Apart from genetic factors, CAT activities are influenced by a number of environmental factors.

5.1. Catalase and age

Inconsistent results were reported in the studies investigating age-related changes of catalase. Liles et al. (1991) found an age-related decrease in catalase activity in human retinal pigment cells. This decrease could have resulted from a decrease in expression of catalase gene products, formation of inactive catalase complexes, or deficiencies in essential metal cations (e.g. iron, zinc and copper). Furthermore, Guemouri et al. (1991) showed only slightly diminished catalase activity in the elderly. Whereas Andersen et al. (1997) observed no age-related changes for CAT activity in erythrocytes, Jozwiak and Jasnowska (1985) described positive correlation of CAT activities with increased age.

5.2. Catalase and seasonal variations

In their study Balog et al. (2006) determined the effect of seasonal variation on the activity of catalase in a population of 12 trained subjects and age- and sex-matched sedentary controls. The authors observed seasonal variations in catalase in sedentary women; the lowest activity was observed in spring compared to the autumn and winter, and no seasonal variations were investigated in sedentary men. Some variations persisted in the trained women and men, but the season with lowest CAT activity in women was summer compared to autumn, whereas in trained men the CAT activity was decreased in autumn compared to spring. The seasonal variation in CAT activity could be explained by different levels of hormones such as melatonin, testosterone and oestradiol, and melatonin could up-regulate the antioxidant enzyme activity. Testosterone has pro-oxidant while oestradiol has antioxidant properties.

5.3. Catalase and physical activity

In the same study, Balog et al. (2006) determined the effect of sports on the activity of catalase. A difference in CAT activity was noticed between trained men and trained women; women had usually higher CAT activity than men. In women sports had no effect, while in men sports decreased CAT activity in the autumn.

5.4. Catalase and chemical and physical influence

Catalase is sensitive to a number of substances that interact with the active site of the enzyme and inhibit the enzyme activity. Studies were focused on the effects of cyanide, azide, hydroxylamine, aminotriazole, S-ethylisothiosemicarbazide and mercaptoethanol on CAT activities (Margoliash et al., 1960; Switala and Loewen, 2002). Banerjee et al. (2010) found increased CAT activities in the serum of individuals with chronic arsenic exposure. They also found moderate positive correlation between arsenic concentration in urine and CAT activity in the serum.

A study of Lubkowska et al. (2009) has shown that single whole-body cryostimulation (-130 °C) in the course of 3 minutes resulted in a decrease of catalase activity in human erythrocytes measured 30 minutes after the low temperature challenge.

6. Conclusion

Catalase as one of the major antioxidant enzymes has been studied in a number of diseases associated with oxidative stress (e.g., atherosclerosis, hyperlipidaemia, diabetes mellitus, hypertension, and neurodegenerative diseases). Oxidative stress is implicated in the pathogenesis of these diseases. Catalase decomposes hydrogen peroxide generated by dismutation of superoxide catalysed by superoxide dismutase. Although it appears that increased CAT activities could be beneficial in the pathogenesis of atherosclerosis and metabolic diseases, the CAT role in pathogenesis of these diseases along with other enzymes degrading hydrogen peroxide (such as glutathione peroxidase and peroxiredoxins) and superoxide dismutase should be determined.

Further studies are required to elucidate the role of the *CAT* gene as a possible risk factor in the aetiology of oxidant-related diseases. Future investigations of the regulation of *CAT* gene expression could lead to new therapeutic approaches.

References

Abou-Seif, M. A., Youssef, A. A. (2004) Evaluation of some biochemical changes in diabetic patients. *Clin. Chim. Acta* **346**, 161-70.

Ahn, J., Gammon, M. D., Santella, R. M., Gaudet, M. M., Britton, J. A., Teitelbaum, S. T., Terry, M. B., Nowell, S., Davis, W., Garza, C., Neugut, I., Ambrosone, Ch. B. (2005) Associations between breast cancer risk and the catalase genotype, fruit and vegetable consumption, and supplement use. *Am. J. Epidemiol*. **162**, 943-952.

Ahn, J., Ambrosone, C. B., Kanetsky, P. A., Tian, Ch., Lehman, T. A., Kropp, S., Helmbold, I., von Fournier, D., Haase, W., Sautter-Bihl, M. L., Wenz, F., Chang-Claude, J. (2006a) Polymorphisms in genes related to oxidative stress (CAT, MnSOD, MPO and eNOS) and acute toxicities from radia-

tion therapy following lumpectomy for breast cancer. *Clin. Cancer Res.* **12**, 7063-7070.

Ahn, J., Nowell, S., McCann, S. E., Yu, J., Carter, L., Lang, N. P., Kadlubar, F. F., Ratnasinghe, L. D., Ambrosone, C. B. (2006b) Associations between catalase phenotype and genotype: modification by epidemiologic factors. *Cancer Epidemiol. Biomarkers Prev.* **15**, 1217-1222.

Ahsan, H., Chen, Y., Kibriya, M. G., Islam, M. N., Slavkovich, V. N., Graziano, J. H., Santella, R. M. (2003) Susceptibility to arsenic-induced hyperkeratosis and oxidative stress gene myeloperoxidase and catalase. *Cancer Lett.* **201**, 57-65.

Akinloye, O., Adaramoye, O., Kareem, O. (2009) Changes in antioxidant status and lipid peroxidation in Nigerian patients with prostate carcinoma. *Pol. Arch. Med. Wewn*. 119, 526-532. (in Polish)

Almarsson, Ö., Sinha, A., Gopinath, E., Bruice, T. C. (1993) Mechanism of one-electron oxidation of NADPH and function of NADPH bound catalase. *J. Am. Chem. Soc.* **115**, 7093-7102.

Ambrosone, C. B., Ahn, J., Singh, K. K., Rezaishiraz, H., Furberg, H., Sweeney, C., Coles, B., Trovato, A. (2005) Polymorphisms in genes related to oxidative stress (MPO, MnSOD, CAT) and survival after treatment for breast cancer. *Cancer Res.* **65**, 1105-1111.

Andersen, H. R., Nielsen, J. B., Nielsen. F., Grandjean, P. (1997) Antioxidative enzyme activities in human erythrocytes. *Clin. Chem*. **43**, 562-568.

Arsova-Sarafinovska, Z., Eken, A., Matevska, N., Erdem, O., Sayal, A., Savaser, A., Banev, S., Petrovski, D., Dzikova, S., Georgiev, V., Sikole, A., Ozgök, Y., Suturkova, L., Dimovski, A. J., Aydin, A. (2009) Increased oxidative/nitrosative stress and decreased antioxidant enzyme activities in prostate cancer. *Clin. Biochem*. **42**, 1228-35.

Atalay, M., Laaksonen, D. E., Niskanen, L., Uusitupa, M., Hänninen, O., Sen, C. K. (1997) Altered antioxidant enzyme defences in insulin-dependent diabetic men with increased resting and exercise-induced oxidative stress. *Acta Physiol. Scand*. **161**, 195-201.

Balog, T., Sobočanec, S., Švecko, V., Krolo, I., Ročić, B., Marotti, M., Marotti, T. (2006) The influence of season on oxidant-antioxidant status in trained and sedentary subjects. *Life Sciences* **78**, 1441-1447.

Banerjee, M., Banerjee, N., Ghosh, P., Das, J. K., Basu, S., Sarkar, A. K., Statesm J. C., Giri, A. K. (2010) Evaluation of the serum catalase and myeloperoxidase activities in chronic arsenic-exposed individuals and concomitant cytogenetic damage. *Toxicol. Appl. Pharmacol.* **249**, 47-54.

Bhatia, S., Shukla, R., Venkata Madhu, S., Kaur Gambhir, J., Madhava Prabhu, K. (2003) Antioxidant status, lipid peroxidation and nitric oxide end products in patients of type 2 diabetes mellitus with nephropathy. *Clin. Biochem*. **36**, 557-562.

Bhatti, P., Stewart, P. A., Hutchinson, A., Rothman, N., Linet, MS., Inskip, P. D., Rajaraman, P. (2009) Lead exposure, polymorphisms in gene related to oxidative stress and risk of brain tumors. *Cancer Epidemiol. Biomarkers Prev.* **18**, 1841-1848.

Bilici, M., Efe, H., Koroglu, M. A., Uydu, H. A., Bekaroglu, M., Deger, O. (2001) Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments. *J. Affect. Disord*. **64**, 43-51.

Bošković, M., Vovk, T., Saje, M., Goričarm, K., Dolžan, V., Kores Plesničar, B., Grabnar, I. (2013) Association of SOD2, GPX1, CAT, and TNF genetic polymorphisms with oxidative stress, neurochemistry, psychopathology, and extrapyramidal symptoms in schizophrenia. *Neurochem. Res.* **38**, 433-442.

Broncel, M., Kozirog, M., Duchnowicz, P., Koter-Michalak, M., Sikora, J., Chojnowska-Jezierska, J. (2010) Aronia melanocarpa extract reduces blood pressure, serum endothelin, lipid, and oxidative stress marker levels in patients with metabolic syndrome. *Med. Sci. Monit*. **16**, CR28-34.

Capurso, C., Solfrizzi, V., D'Introno, A., Colacicco, A. M., Capurso, S. A., Bifaro, L., Menga, R., Santamato, A., Seripa, D., Pilotto, A., Capurso, A., Panza, F. (2008) Short arm of chromosome 11 and sporadic Alzheimer's disease: catalase and cathepsin D gene polymorphisms. *Neurosci. Lett*. **432**, 237-242.

Cardona, F., Tunez, I., Tasset, I., Murri, M., Tinahones, F. J. (2008a) Similar increase in oxidative stress after fat overload in persons with baseline hypertriglyceridemia with or without the metabolic syndrome. *Clin. Biochem*. **41**, 701-705.

Cardona, F., Túnez, I., Tasset, I., Montilla, P., Collantes, E., Tinahones, F. J. (2008b) Fat overload aggravates oxidative stress in patients with the metabolic syndrome. *Eur. J. Clin. Invest.* **38**, 510-515.

Casado, A., de la Torre, R., López-Fernández, M. E., Carrascosa, D., Casado, M. C., Ramírez, M. V. (1995) Superoxide dismutase and catalase blood levels in patients with malignant diseases. *Cancer Lett.* **93**, 187-192.

Casp, C. B., She, J. X., McCormack, W. T. (2002) Genetic association of the catalase gene (CAT) with vitiligo susceptibility. *Pigment Cell Res.* **15**, 62-66.

Chelikani, P., Fita, I., Loewen, P. C. (2004) Diversity of structures and properties among catalases. *Cell. Mol. Life Sci.* **61**, 192-208.

Chen, H., Yu, M., Li, M., Zhao, R., Zhu, Q., Zhou, W., Lu, M., Lu, Y., Zheng, T., Jiang, J., Zhao, W., Xiang, K., Jia, W., Liu, L. (2012a) Polymorphic variations in manganese superoxide dismutase (MnSOD), glutathione peroxidase-1 (GPX1), and catalase (CAT) contribute to elevated plasma triglyceride levels in Chinese patients with type 2 diabetes or diabetic cardiovascular disease. *Mol. Cell. Biochem*. **363**, 85-91.

Chen, T., Jin, X., Crawford, B. H., Cheng, H., Saafir, T. B., Wagner, M. B., Yuan, Z., Ding, G. (2012b) Cardioprotection from oxidative stress in the newborn heart by activation of PPARγ is mediated by catalase. *Free Radic. Biol. Med*. 53, 208-215.

Chistiakov, D. A., Savost'ianov, K. V., Turakulov, R. I., Scherbacheva, L. N., Mamaeva, G. G., Balabolkin, M. I., Nosikov, V. V. (2000) Nucleotide substitution C1167T in the catalase gene and position of nearby polymorphic markers D11S907 and D1S are connected with development of diabetes mellitus type 2. *Mol. Biol. (Mosk.)* **34**, 733-736. (in Russian)

Chistiakov, D. A., Savosťanov, K. V., Turakulov, R. I., Titovich, E. V., Zilberman, L. I., Kuraeva, T. L., Dedov, I. I., Nosikov, V. V. (2004) A new type 1 diabetes susceptibility locus containing the catalase gene (chromosome 11p13) in a Russian population. *Diabetes Metab. Res. Rev.* **20**, 219-224.

Chistiakov, D. A., Zotova, E. V., Savosťanov, K. V., Bursa, T. R., Galeev, I. V., Strokov, I. A., Nosikov, V. V. (2006) The 262T>C promoter polymorphism of the catalase gene is associated with diabetic neuropathy in type 1 diabetic Russian patients. *Diabetes Metab*. **32**, 63-68.

Chmiel, B., Grabowska Bochenek, R., Piskorska, D., Skorupa, A., Cierpka, L., Kuśmierski, S. (2002) Red blood cells deformability and oxidative stress in acute pancreatitis. *Clin. Hemorheol. Microcirc.* **27**, 155-162.

Choi, J. Y., Neuhouser, M. L., Barnett, M., Hudson, M., Kristal, A. R., Thornquist, M., King, I. B., Goodman, G. E., Ambrosone, C. B. (2007) Polymorphisms in oxidative stress-related genes are not associated with prostate cancer risk in heavy smokers. *Cancer Epidemiol. Biomarkers Prev.* 16, 1115-1120.

Christiansen, L., Petersen, H. Ch., Bathum, L., Frederiksen, H., McGue, M., Christensen, K. (2004) The catalase -262C/T promoter polymorphism and aging phenotype. *J. Gerontol. A Biol. Sci. Med. Sci.* **59**, 886-889.

Crawford, A., Fassett, R. G., Geraghty, D. P., Kunde, D. A., Ball, M. J., Robertson, I. K., Coombes, J. S. (2012a) Relationships between single nucleotide polymorphisms of antioxidant enzymes and disease. *Gene* **501**, 89-103.

Crawford, A., Fassett, R. G., Coombes, J. S., Kunde, D. A., Ahuja, K. D., Robertson, I. K., Ball, M. J., Geraghty, D. P. (2012b) Relationship between antioxidant enzyme genotype and activity and kidney function: a case-control study. *Clin. Nephrol.* **78**, 135-144.

D'Souza, A., Kurien, B. T., Rodgers, R., Shenoi, J., Kurono, S., Matsumoto, H., Hensley, K., Nath, S. K., Scofield, R. H. (2008) Detection of catalase as a major protein target of the lipid peroxidation product 4-HNE and the lack of its genetic association as a risk factor in SLE. *BMC Med. Genet.* **9**, 62-70.

de Sousa, R. T., Zarate, C. A. Jr, Zanetti, M. V., Costa, A. C., Talib, L. L., Gattaz, W. F., Machado-Vieira, R. (2014) Oxidative stress in early stage bipolar disorder and the association with response to lithium. *J. Psychiatr. Res.* **50**, 36-41.

Deisseroth, A., Dounce, A. L. (1970) Catalase: physical and chemical properties, mechanism of catalysis, and physiological role. *Physiol. Rev.* **50**, 319-375.

Dos Santos, K .G., Canani, L. H., Gross, J. L., Tschiedel, B., Pieres Souto, K. E., Roisenberg, I. (2006) The catalase -262C/T promoter polymorphism and diabetic complications in Caucasians with type 2 diabetes. *Dis. Markers* **22**, 355-359.

Dutkiewicz, G., Domanski, L., Binczak-Kuleta, A., Pawlik, A., Safranow, K., Ciechanowicz, A., Dziedziejko, V., Ciechanowski, K. (2010) The association of -262 C/T polymorphism in the catalase gene and delayed graft function of kidney allografts. *Nephrology* **15**, 587-591.

El-Sohemy, A., Cornelis, M., Park, Y., Bae, S. C. (2006) Catalase and PPARγ2 genotype and risk of rheumatoid arthritis in Koreans. *Rheumatol. Int*. **26**, 388-392.

Eny, K. M., El-Sohemy, A., Cornelis, M., Sung, Y. K., Bae, S. C. (2005) Catalase and PPARγ2 genotype and risk of lupus erythematosus in Koreans. *Lupus* **14**, 351-355.

Esme, H., Cemek, M., Sezer, M., Saglam, H., Demir, A., Melek, H., Unlu, M. (2008) High levels of oxidative stress in patients with advanced lung cancer. *Respirology* **13**, 112-116.

Ezzikouri, S., El Feydi, A. E., Afifi, R., Benazzouz, M., Hassar, M., Pineau, P, Benjelloun, S. (2010) Polymorphisms in antioxidant defence genes and susceptibility to hepatocellular carcinoma in a Moroccan population. *Free Radic. Res.* **44**, 208-216.

Fabre, E. E., Raynaud-Simon, A., Golmard, J. L., Hebert, M., Dulcire, X., Succari, M., Myara, J., Durand, D., Nivet-Antoine, V. (2008) Gene polymorphisms of oxidative stress enzymes: prediction of elderly renutrition. *Am. J. Clin. Nutr.* **87**, 1504-1512.

Farawela, H., Khorshied, M., Shaheen, I., Gouda, H., Nasef, A., Abulata, N., Mahmoud, H. A., Zawam, H. M., Mousa, S. M. (2012) The association between hepatitis C virus infection, genetic polymorphisms of oxidative stress genes and B-cell non-Hodgkin's lymphoma risk in Egypt. *Infect. Genet. Evol.* **12**, 1189-1194.

Flekac, M., Skrha, J., Hilgertova, J., Lacinova, Z., Jarolimkova, M. (2008) Gene polymorphisms of superoxide dismutase and catalase in diabetes mellitus. *BMC Med. Genet.* **9**, 30-39.

Forsberg, L., Lyrenäs, L., de Faire, U., Morgenstern, R. (2001) A common functional C-T substitution polymorphism in the promoter region of the human catalase gene influences transcription factor binding, reporter gene transcription and is correlated to blood catalase levels. *Free Radic. Biol. Med*. **30**, 500-505.

Franko, A., Dolzan, V., Arnerić, N., Dodic-Fikfak, M. (2008) Asbestosis and catalase genetic polymorphism. *Arh. Hig. Rada Toksikol*. **59**, 233-240.

Fukui, M., Kanoh, M., Takamatsu, Y., Arakawa, Y. (2004) Analysis of serum catalase activities in pancreatic diseases. *J. Gastroenterol*. **39**, 469-474.

Funke, S., Risch, A., Nieters, A., Hoffmeister, M., Stegmaier, Ch., Seiler, Ch. M., Brenner, H., Chang-Calude, J. (2009a) Genetic polymorphisms in genes related to oxidative stress (GSTP1, GSTM1, GSTT1, CAT, MnSOD, MPO, eNOS) and survival of rectal cancer patients after radiotherapy. *J. Cancer Epidemiol.* **2009**, 1-6.

Funke, S., Hoffmeister, M., Brenner, H., Chang-Claude, J. (2009b) Effect modification by smoking on the association between genetic polymorphisms in oxidative stress genes and colorectal cancer risk. *Cancer Epidemiol. Biomarkers Prev*. **18**, 2336-2338.

Galecki, P., Szemraj, J., Zboralski, K., Florkowski, A., Lewinski, A. (2009a) Relation between functional polymorphism of catalase gene (-262C>T) and recurrent depressive disorder. *Neuro Endocrinol. Lett.* **30**, 357-362.

Gałecki, P., Szemraj, J., Bieńkiewicz, M., Florkowski, A., Gałecka, E. (2009b) Lipid peroxidation and antioxidant protection in patients during acute depressive episodes and in remission after fluoxetine treatment. *Pharmacol. Rep*. **61**, 436-447.

Gavalas, N. G., Akhtar, S., Gawkrodger, D. J., Watson, P. F., Weetman, A. P., Kemp, E. H. (2006) Analysis of allelic

variants in the catalase gene in patients with the skin depigmenting disorder vitiligo. *Biochem. Biophys. Res. Commun.* **345**, 1586-1591.

Ghaly, M. S., Ghattas, M. H., Labib, S. M. (2012) Association of catalase gene polymorphisms with catalase activity and susceptibility to systemic lupus erythematosus in the Suez Canal area, Egypt. *Lupus* **21**, 1244-1249.

Gil-del Valle, L., de la C Milian, L., Toledo, A., Vilaró, N., Tápanes, R., Otero, M. A. (2005) Altered redox status in patients with diabetes mellitus type I. *Pharmacol. Res*. **51**, 375-380.

Girnun, G. D., Domann, F. E., Moore, S. A., Robbins, M. E. (2002) Identification of a functional peroxisome proliferator-activated receptor response element in the rat catalase promoter. *Mol. Endocrinol.* **16**, 2793-801.

Glorieux, C., Dejeans, N., Sid, B., Beck, R., Calderon, P. B., Verrax, J. (2011) Catalase overexpression in mammary cancer cells leads to a less aggressive phenotype and an altered response to chemotherapy. *Biochem. Pharmacol.* **82**, 1384-90.

Góth, L., Mészáros, I., Németh, H. (1982) Serum catalase enzyme activity in acute pancreatitis. *Clin. Chem.* **28**, 1999-2000.

Góth, L. (1989) Origin of serum catalase activity in acute pancreatitis. *Clin. Chim. Acta* **186**, 39-44.

Góth, L., Shemirani, A., Kalmar, T. (2000) A novel catalase mutation (a GA insertion) causes the Hungarian type of acatalasemia. *Blood Cells Mol. Dis.* **26**, 151-154.

Góth, L. (2001a) A new type of inherited catalase deficiencies: its characterization and comparison to the Japanese and Swiss type of acatalasemia. *Blood Cells Mol. Dis.* **27**, 512-517.

Góth, L. (2001b) A novel catalase mutation (a G insertion in exon 2) causes the type B of the Hungarian acatalasemia. *Clin. Chim. Acta* **311**, 161-163.

Góth, L., Rass, P., Madarasi, I. (2001) A novel catalase mutation detected by polymerase chain reaction-single strand conformation polymorphism, nucleotide sequencing, and Western blot analyses is responsible for the type C of Hungarian acatalasemia. *Electrophoresis* **22**, 49-51.

Góth, L., Rass, P., Páy, A. (2004) Catalase enzyme mutations and their association with diseases. *Mol. Diagn*. **8**, 141-149.

Góth, L., Rass, P., Madarasi, I. (2005) Detection of a novel familial catalase mutation (Hungarian type D) and the possible risk of inherited catalase deficiency for diabetes mellitus. *Electrophoresis* **26**, 1646-1649.

Góth, L., Nagy, T. (2012) Acatalasemia and diabetes mellitus. *Arch. Biochem. Biophys*. **525**, 195-200.

Góth, L., Nagy, T. (2013) Inherited catalase deficiency: is it benign or a factor in various age related disorders? *Mutat. Res.* **753**, 147-54.

Goulas, A., Fidani, L., Kotsis, A., Mirtsou, V., Petersen, R. C., Tangalos, E., Hardy, J. (2002) An association study of a functional catalase gene polymorphism, -262C/T, and patients with Alzheimer's disease. *Neurosci. Lett.* **330**, 210-212.

Grabar, P. B., Logar, D., Tomšic, M., Rozman, B., Dolzan, V. (2009) Genetic polymorphisms modifying oxidative stress are associated with disease activity in rheumatoid arthritis patients. *Dis. Markers* **26**, 41-48.

Guemouri, L., Artur, Y., Herbeth, B., Jeandel, C., Cuny, G., Siest, G. (1991) Biological variability of superoxide dismutase, glutathione peroxidase, and catalase in blood. *Clin. Chem*. **37**, 1932-1937.

Halliwell, B., Gutteridge, J. M. C. (2007) *Free Radicals in Biology and Medicine.* Fourth edition. Oxford University Press Inc., New York.

Hebert-Schuster, M., Cottart, C. H., Laguillier-Morizot, C., Raynaud-Simon, A., Golmard, J. L., Cynober, L., Beaudeux, J. L., Fabre, E. E., Nivet-Antoine, V. (2011) Catalase rs769214 SNP in elderly malnutrition and during renutrition: is glucagon to blame? *Free Radic. Biol. Med.* **51**, 1583-1588.

Hebert-Schuster, M., Fabre, E. E., Nivet-Antoine, V. (2012) Catalase polymorphisms and metabolic diseases. *Curr. Opin. Clin. Nutr. Metab. Care* **15**, 397-402.

Heck, D. E., Vetrano, A. M., Mariano, T. M., Laskin, J. D. (2003) UVB light stimulates production of reactive oxygen species. *J. Biol. Chem.* **278**, 22432-22436.

Hillar, A., Nicholls, P. (1992) A mechanism for NADPH inhibition of catalase compound II formation. *FEBS Lett.* **314**, 179-182.

Ho, J. C., Mak, J. C., Ho, S. P., Ip, M. S., Tsang, K. W., Lam, W. K., Chan-Yeung, M. (2006) Manganese superoxide dismutase and catalase genetic polymorphisms, activity levels, and lung cancer risk in Chinese in Hong Kong. *J. Thorac. Oncol.* **1**, 648-53.

Hussain, S. P., Amstad, P., He, P., Robles, A., Lupold, S., Kaneko, I., Ichimiya, M., Sengupta, S., Mechanic, L., Okamura, S., Hofseth, L. J., Moake, M., Nagashima, M., Forrester, K. S., Harris, C. C. (2004) p53-induced up-regulation of MnSOD and GPx but not catalase increases oxidative stress and apoptosis. *Cancer Res*. **64**, 2350-2356.

Hsueh, Y. M., Lin, P., Chen, H. W., Shiue, H. S., Chung, Ch. J., Tsai, Ch. T., Huang, Y. K., Chiou, H. Y., Chen, Ch. J. (2005) Genetic polymorphisms of oxidative and antioxidant enzymes and arsenic related hypertension. *J. Toxicol. Environ. Health A* **68**, 1471-1484.

Islam, T., McConnell, R., Gauderman, W. J., Avol, E., Peters, J. M., Gilliland, F. D. (2008) Ozone, oxidant defense genes, and risk of asthma during adolescence. *Am. J. Respir. Crit. Care Med.* **177**, 388-395.

Jiang, Z., Akey, J. M., Shi, J., Xiong, M., Wang, Y., Shen, Y., Xu, X., Chen, H., Wu, H., Xiao, J., Lu, D., Huang, W., Jin, L. (2001) A polymorphism in the promoter region of catalase is associated with blood pressure levels. *Hum. Genet.* **109**, 95-98.

Jozwiak, Z., Jasnowska, B. (1985) Changes in oxygen-metabolizing enzymes and lipid peroxidation in human erythrocytes as a function of age of donor. *Mech. Aging Dev*. **32**, 77-93.

Kang, M. Y., Kim, H. B., Piao, C., Lee, K. H., Hyun, J. W., Chang, I. Y., You, H. J. (2013) The critical role of catalase in prooxidant and antioxidant function of p53. *Cell Death Differ*. **20**, 117-29.

Kapoor, K., Basu, S., Das, B. K., Bhatia, B. D. (2006) Lipid peroxidation and antioxidants in neonatal septicemia. *J. Trop. Pediatr*. **52**, 372-375.

Kedziora-Kornatowska, K. Z., Luciak, M., Blaszczyk, J., Pawlak, W. (1998) Lipid peroxidation and activities of an-

tioxidant enzymes in erythrocytes of patients with non-insulin dependent diabetes with or without diabetic nephropathy. *Nephrol. Dial. Transplant.* **13**, 2829-2832.

Kesavulu, M. M., Giri, R., Kameswara Rao, B., Apparao, C. (2000) Lipid peroxidation and antioxidant enzyme levels in type 2 diabetics with microvascular complications. *Diabetes Metab*. **26**, 387-392.

Kesavulu, M. M., Rao, B. K., Giri, R., Vijaya, J., Subramanyam, G., Apparao, C. (2001) Lipid peroxidation and antioxidant enzyme status in type 2 diabetics with coronary heart disease. *Diabetes Res. Clin. Pract*. **53**, 33-39.

Khodayari, S., Salehi, Z., Fakhrieh Asl, S., Aminian, K., Mirzaei Gisomi, N., Torabi Dalivandan, S. (2013) Catalase gene C-262T polymorphism: importance in ulcerative colitis. *J. Gastroenterol. Hepatol*. **28**, 819-822.

Kim, T. H., Hong, J. M., Oh, B., Cho, Y. S., Lee, J. Y., Kim, H. L., Shin, E. S., Lee, J. E., Park, E. K., Kim, S. Y. (2008) Genetic association study of polymorphisms in the catalase gene with the risk of osteonecrosis of the femoral head in the Korean population. *Osteoarthr. Cartil.* **16**, 1060-1066.

Kirkman, H. N., Gaetani, G. F. (1984) Catalase: a tetrameric enzyme with four tightly bound molecules of NADPH. *Proc. Natl. Acad. Sci. USA* **81**, 4343-4347.

Kirkman, H. N., Galiano, S., Gaetani, G. F. (1987) The function of catalase-bound NADPH. *J. Biol. Chem.* **262**, 660-666.

Kirkman, H. N., Rolfo, M., Ferraris, A. M., Gaetani, G. F. (1999) Mechanisms of protection of catalase by NADPH. *J. Biol. Chem.* **274**, 13908-13914.

Kirkman, H. N., Gaetani, G. F. (2007) Mammalian catalase: venerable enzyme with new mysteries. *Trends Biochem. Sci.* **32**, 44-50.

Ko, T. P., Safo, M. K., Musayev, F. N., Di Salvo, M. L., Wang, C., Wu, S. H., Abraham, D. J. (2000) Structure of human erythrocyte catalase. *Acta Crystallogr. D Biol. Crystallogr.* **56**, 241-245.

Kodydková, J., Vávrová, L., Zeman, M., Jirák, R., Macásek, J., Stanková, B., Tvrzická, E., Zák, A. (2009) Antioxidative enzymes and increased oxidative stress in depressive women. *Clin. Biochem*. **42**, 1368-1374.

Kodydkova, J., Vavrova, L., Stankova, B., Macasek, J., Krechler, T., Zak, A. (2013) Antioxidant status and oxidative stress markers in pancreatic cancer and chronic pancreatitis. *Pancreas* **42**, 614-621.

Koistinen, P., Ruuska, S., Saily, M., Kakko, S., Siitonen, P., Siitonen, T., Savolainen. M. J., Kinnula, V. L., Savolainen, E. R. (2006) An association between manganese superoxide dismutase polymorphism and outcome of chemotherapy in acute myeloid leukemia. *Haematologica* **91**, 829-832.

Komosińska-Vassev, K., Olczyk, K., Olczyk, P., Winsz-Szczotka, K. (2005) Effects of metabolic control and vascular complications on indices of oxidative stress in type 2 diabetic patients. *Diabetes Res. Clin. Pract.* **68**, 207-216.

Kósa, Z., Fejes, Z., Nagy, T., Csordás, M., Simics, E., Remenyik, E, Góth L. (2012) Catalase -262C>T polymorphisms in Hungarian vitiligo patients and in controls: further acatalasemia mutations in Hungary. *Mol. Biol. Rep*. **39**, 4787-4795.

Koziróg, M., Poliwczak, A. R., Duchnowicz, P., Koter-Michalak, M., Sikora, J., Broncel, M. (2011) Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. *J. Pineal Res*. **50**, 261-266

Lai, C. C., Peng, M., Huang, L., Huang, W. H., Chiu, T. H. (1996) Chronic exposure of neonatal cardiac myocytes to hydrogen peroxide enhances the expression of catalase. *J. Mol. Cell. Cardiol.* **28**, 1157-1163.

Leff, J. A., Parsons, P. E., Day, C. E., Moore, E. E., Moore, F. A., Oppegard, M. A., Repine, J. E. (1992) Increased serum catalase activity in septic patients with the adult respiratory distress syndrome. *Am. Rev. Respir. Dis*. **146**, 985-989.

Leff, J. A., Parsons, P. E., Day, C. E., Taniguchi, N., Jochum, M., Fritz, H., Moore, F. A., Moore, E. E., McCord, J. M., Repine, J. E. (1993) Serum antioxidants as predictors of adult respiratory distress syndrome in patients with sepsis. *Lancet* **341**, 777-780.

Li, Y., Ambrosone, B., McCullough, M. J., Ahn, J., Stevens, V. L., Thun, M. J., Hong, C. C. (2009) Oxidative stress-related genotypes, fruit and vegetable consumption and breast cancer risk. *Carcinogenesis* **30**, 777-784.

Lightfoot, T. J., Skibola, C. F., Smith, A. G., Forrest, M. S., Adamson, P. J., Morgan, G. J., Bracci, P. M., Roman, E., Smith, M. T., Holly, E. A. (2006) Polymorphisms in the oxidative stress genes, superoxide dismutase, glutathione peroxidase and catalase and risk of non-Hodgkin's lymphoma. *Haematologia* **91**, 1222-1227.

Liles, M. R., Newsome, D. A., Oliver, P. D. (1991) Antioxidant enzymes in the aging human retinal pigment epithelium. *Arch. Ophthamol*. **109**, 1285-1288.

Liu, L., Li, Ch., Gao, J., Li, K., Zhang, R., Wang, G., Li, Ch., Gao, T. (2010) Promoter variant in the catalase gene is associated with vitiligo in Chinese people. *J. Invest. Dermatol*. **130**, 2647-2653.

Loew, O. (1900) A new enzyme of general occurrence in organisms. A preliminary note. *Science* **11**, 701-702.

Lubkowska, A., Dolegowska, B., Szygula, Z., Klimek, A. (2009) Activity of selected enzymes in erythrocytes and level of plasma antioxidants in response to single whole-body cryostimulation in humans. *Scand. J. Clin. Lab. Invest.* **69**, 387-394.

Lv, Y. J., Liao, W. J., Luan, Q., Wang, H., Wang, L., Li, Q. (2011) The polymorphism of catalase T/C codon 389 in exon 9 and vitiligo susceptibility: a meta-analysis. *J. Eur. Acad. Dermatol. Venereol.* **25**, 955-958.

Mak, J. C. W., Leung, H. C. M., Ho, S. P., Ko, F. W. S., Cheung, A. H. K., Ip, M. S. M., Chan-Yeung, M. M. W. (2006) Polymorphisms in manganese superoxide dismutase and catalase genes: functional study in Hong Kong Chinese asthma patients. *Clin. Exp. Allergy.* **36**, 440-447.

Mak, J. C. W., Ho, S. P., Yu, W. C., Choo, K. L., Chu, C. M., Yew, W. W., Lam, W. K., Chan-Yeung, M. W. (2007) Polymorphisms and functional activity in superoxide dismutase and catalase genes in smokers with COPD. *Eur. Respir. J.* **30**, 684-690.

Mansego, M. L., Solar Gde, M., Alonso, M. P., Martínez, F, Sáez, G. T., Escudero, J. C., Redón, J., Chaves, F. J. (2011) Polymorphisms of antioxidant enzymes, blood pressure and risk of hypertension. *J. Hypertens.* **29**, 492-500.

Margoliash, E., Novogrodsky, A., Schejter, A. (1960) Irreversible reaction of 3-amino-1,2,4-triazole and related in-

hibitors with the protein of catalase. *Biochem. J.* **74**, 339-348.

Maté, M. J., Ortíz-Lombardía, M., Marina, A., Fita, I. (1999) Crystallization and preliminary structural results of catalase from human erythrocytes. *Acta Crystallogr. D Biol. Crystallogr.* **55**, 1066-1068.

Meilhac, O., Zhou, M., Santanam, N., Parthasarathy, S. (2000) Lipid peroxides induce expression of catalase in cultured vascular cells. *J. Lipid Res.* **41**, 1205-1213.

Merzouk, S., Hichami, A., Madani, S., Merzouk, H., Berrouiguet, A. Y., Prost, J., Moutairou, K., Chabane-Sari, N., Khan, N. A. (2003) Antioxidant status and levels of different vitamins determined by high performance liquid chromatography in diabetic subjects with multiple complications. *Gen. Physiol. Biophys*. **22,** 15-27.

Metnitz, P. G., Bartens, C., Fischer, M., Fridrich, P., Steltzer, H., Druml, W. (1999) Antioxidant status in patients with acute respiratory distress syndrome. *Intensive Care Med*. **25**, 180-185.

Michaeloudes, C., Chang, P. J., Petrou, M., Chung, K. F. (2011a) Transforming growth factor-β and nuclear factor E2-related factor 2 regulate antioxidant responses in airway smooth muscle cells: role in asthma. *Am. J. Respir. Crit. Care Med.* **184**, 894-903.

Michaeloudes, C., Sukkar, M. B., Khorasani, N. M., Bhavsar, P. K., Chung, K. F. (2011b) TGF-β regulates Nox4, MnSOD and catalase expression, and IL-6 release in airway smooth muscle cells. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **300**, L295-304.

Miller, E., Mrowicka, M., Malinowska, K., Mrowicki, J., Saluk-Juszczak, J., Kędziora, J. (2011) Effects of whole-body cryotherapy on a total antioxidative status and activities of antioxidative enzymes in blood of depressive multiple sclerosis patients. *World J. Biol. Psychiatry* **12**, 223-227.

Min, J. Y, Lim, S. O., Jung, G. (2010) Downregulation of catalase by reactive oxygen species via hypermethylation of CpG island II on the catalase promoter. *FEBS Lett.* **584**, 2427-2432.

Mostowska, A., Hozyasz, K. K., Lianeri, M., Piwowar, W., Jagodzinski, P. P. (2007) Polymorphic variants of genes encoding main antioxidant enzymes and the risk of CL/P-affected pregnancies. *Clin. Biochem.* **40**, 416-419.

Nadif, R., Mintz, M., Jedlicka, A., Bertrand, J. P., Kleeberger, S. R., Kauffmann, F. (2005) Association of CAT polymorphisms with catalase activity and exposure to environmental oxidative stimuli. *Free Radic. Res*. **39**, 1345-1350.

Nahon, P., Sutton, A., Rufat, P., Ziol, M., Akouche, H., Laguillier, Ch., Charnaux, N., Ganne-Carrié, N., Grando-Lemaire, V., N'Kontchou, G., Trinchet, J. C., Gattegno, L., Pessayre, D., Beaugrand M. (2009) Myeloperoxidase and superoxide dismutase 2 polymorphisms comodulate the risk of hepatocellular carcinoma and death in alcoholic cirrhosis. *Hepatology* **50**, 1484-1493.

Nemoto, M., Nishimura, R., Sasaki, T., Hiki, Y., Miyashita, Y., Nishioka, M., Fujimoto, K., Sakuma, T., Ohashi, T., Fukuda, K., Eto, Y., Tajima, N. (2007) Genetic association of glutathione peroxidase-I with coronary artery calcification in type 2 diabetes: a case control study with multi-slice computed tomography. *Cardiovasc. Diabetol.* **6**, 23-30.

Ngoka, L. C. (2008) Dramatic down-regulation of oxidoreductases in human hepatocellular carcinoma hepG2 cells: proteomics and gene ontology unveiling new frontiers in cancer enzymology. *Proteome Sci.* **6**, 29.

Nishikawa, M., Hashida, M., Takakura, Y. (2009) Catalase delivery for inhibiting ROS-mediated tissue injury and tumor metastasis. *Adv. Drug Deliv. Rev*. **61**, 319-26.

Ogata, M., Wang, D. H., Ogino, K. (2008) Mammalian acatalasemia: the perspectives of bioinformatics and genetic toxicology. *Acta Med. Okayma* **62**, 345-361.

Oh, B., Kim, S. Y., Kim, D. J., Lee, J. Y., Lee, J. K., Kimm, K., Park, B. L., Shin, H. D., Kim, T. H., Park, E. K., Koh, J. M., Kim, G. S. (2007) Associations of catalase gene polymorphisms with bone mineral density and bone turnover markers in postmenopausal women. *J. Med. Genet*. **44**, e62-68.

Okuno, Y., Matsuda, M., Miyata, Y., Fukuhara, A., Komuro, R., Shimabukuro, M., Shimomura, I. (2010) Human catalase gene is regulated by peroxisome proliferator activated receptor-gamma through a response element distinct from that of mouse. *Endocr. J.* **57**, 303-309.

Olson, L. P., Bruice, T. C. (1995) Electron tunneling and ab initio calculations related to one-electron oxidation of NADPH bound to catalase. *Biochemistry* **34**, 7335-7347.

Ozcan, M. E., Gulec, M., Ozerol, E., Polat, R., Akyol, O. (2004) Antioxidant enzyme activities and oxidative stress in affective disorders. *Int. Clin. Psychopharmacol*. **19**, 89-95.

Panduru, N. M., Moţa, E., Moţa, M., Cimponeriu, D., Serafinceanu, C., Cheţa, D. M. (2010) Polymorphism of catalase gene promoter in Romanian patients with diabetic kidney disease and type 1 diabetes. *Rom. J. Intern. Med*. **48**, 81-88.

Park, H. H., Ha, E., Uhm, Y. K., Jin, S. Y., Kim, Y. J., Chung, J. H., Lee, M. H. (2006) Association study between catalase gene polymorphisms and the susceptibility to vitiligo in Korean population. *Exp. Dermatol.* **15**, 377-380.

Pask, R., Cooper, J. D., Walker, N. M., Nutland S., Hutchings, J., Dunger, D. B., Nejentsev, S., Todd, J. A. (2006) No evidence for major effect of two common polymorphisms of the catalase gene in type 1 diabetes susceptibility. *Diabetes Metab. Res. Rev.* **22**, 356-360.

Perianayagam, M. C., Liangos, O., Kolyada, A. Y., Wald, R., MacKinnon, R. W., Li, L., Rao, M, Balakrishnan, V. S., Bonventre, J. V., Pereira, B. J., Jaber, B. L. (2007) NADPH oxidase p22phox and catalase gene variants are associated with biomarkers of oxidative stress and adverse outcomes in acute renal failure. *J. Am. Soc. Nephrol.* **18**, 255-263.

Pizent, A., Pavlovic, M., Jurasovic, J., Dodig, S., Pasalic, D., Mujagic, R. (2010) Antioxidants, trace elements and metabolic syndrome in elderly subjects. *J. Nutr. Health Aging* **14**, 866-871.

Podgoreanu, M. V., White, W. D., Morris, R. W., Mathew, J. P., Stafford-Smith, M., Welsby, L. J, Grocott, H. P., Milano, C. A., Newman, M. F., Schwinn, D. A. (2006) Inflammatory gene polymorphism and risk of postoperative myocardial infarction after cardiac surgery. *Circulation* **114(Suppl 1)**, I275-281.

Polonikov, A. V., Ivanov, V. P., Solodilova, M. A., Kozhuhov, M. A., Panfilov, V. I. (2009) Tobacco smoking, fruit and vegetable intake modify association between -21A/T poly-

morphism of catalase gene and risk of bronchial asthma. *J. Asthma* **46**, 217-224.

Quan, F., Korneluk, R. G., Tropak, M. B., Gravel, R. (1986) Isolation and characterization of human catalase gene. *Nucleic Acids Res.* **14**, 5321-5335.

Quan, X., Lim, S. O., Jung, G. (2011) Reactive oxygen species downregulate catalase expression via methylation of a CpG island in the Oct-1 promoter. *FEBS Lett.* **585**, 3436-3441.

Quick, S. K, Shields, P. G., Nie, J., Platek, M. E., McCann, S. E., Hutson, A. D., Trevisan, M., Vito, D., Lehman, T. A., Seddon, M., Edge, S. B., Marian, C., Muti, P., Freudenheim, J. L. (2008) Effect modifications by catalase genotype suggest a role for oxidative stress in the association of hormone replacement therapy with postmenopausal breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.* **17**, 1082-1087.

Quilliot, D., Walters, E., Bonte, J. P., Fruchart, J. C., Duriez, P., Ziegler, O. (2005) Diabetes mellitus worsens antioxidant status in patients with chronic pancreatitis. *Am. J. Clin. Nutr*. **81**, 1117-1125.

Rajaraman, P., Hutchinson, A., Rothman, N., Black, P. M., Fine, H. A., Loeffler, J. S., Selker, R. G., Shapiro, W. R., Linet, M. S., Inskip, P. D. (2008) Oxidative response gene polymorphisms and risk of adult brain tumors. *Neuro-Oncology* **10**, 709-715.

Rajić, V., Aplenc, R., Debeljak, M., Prestor, V. V., Karas-Kuzelicki, N, Mlinaric-Rascan, I., Jazbec, J. (2009) Influence of the polymorphism in candidate genes on late cardiac damage in patients treated due to acute leukemia in childhood. *Leuk. Lymphoma* **50**, 1693-1698.

Ramakrishna, V., Jailkhani, R. (2008) Oxidative stress in non-insulin-dependent diabetes mellitus (NIDDM) patients. *Acta Diabetol*. **45**, 41-46.

Rodrigo, R., Prat, H., Passalacqua, W., Araya, J., Guichard, C., Bächler, J. P. (2007) Relationship between oxidative stress and essential hypertension. *Hypertens. Res*. **30**, 1159-1167.

Rovira, C. (2005) Structure, protonation state and dynamics of catalase compound II. *Chemphyschem.* **6**, 1820-1826.

Sailaja, Y. R., Baskar, R., Saralakumari, D. (2003) The antioxidant status during maturation of reticulocytes to erythrocytes in type 2 diabetics. *Free Radic. Biol. Med*. **35**, 133-139.

Safo, M. K., Musayev, F. N., Wu, S. H., Abraham, D. J., Ko, T. P. (2001) Structure of tetragonal crystals of human erythrocyte catalase. *Acta Crystallogr. D Biol. Crystallogr.* **57**, 1-7.

Sato, K., Ito, K., Kohara, H., Yamaguchi, Y., Adachi, K., Endo, H. (1992) Negative regulation of catalase gene expression in hepatoma cells. *Mol. Cell. Biol*. **12**, 2525-33.

Sergeeva, T. V., Chistiakov, D. A., Kobalava, Z. D., Moiseev, V. S. (2001) Polymorphism of the catalase and glutathione peroxidase genes and macrovascular complications in non-insulin-dependent diabetic hypertensives. *Russ. J. Genet.* **37**, 329-331.

Shajil, E. M., Laddha, N. C., Chatterjee, S., Gani, A. R., Malek, R. A., Shah, B. J., Begum, R. (2007) Association of catalase T/C exon 9 and glutathione peroxidase codon 200 polymorphisms in relation to their activities and oxidative stress with vitiligo susceptibility in Gujarat population. *Pigment Cell Res*. **20**, 405-407.

Shin, M. J., Park, E. (2006) Contribution of insulin resistance to reduced antioxidant enzymes and vitamins in nonobese Korean children. *Clin. Chim. Acta*. **365**, 200-205.

Shuvalova, Y. A., Kaminnyi, A. I., Meshkov, A. N., Shirokov, R. O., Samko, A. N. (2012) Association between polymorphisms of eNOS and GPx-1 genes, activity of free-radical processes and in-stent restenosis. *Mol. Cell. Biochem*. **370**, 241-249.

Sözmen, B., Delen, Y., Girgin, F. K., Sözmen, E. Y. (1999) Catalase and paraoxonase in hypertensive type 2 diabetes mellitus: correlation with glycemic control. *Clin. Biochem*. **32**, 423-427.

St Clair, D. K., Wan, X. S., Oberley, T. D., Muse, K. E., St Clair, W. H. (1992) Suppression of radiation-induced neoplastic transformation by overexpression of mitochondrial superoxide dismutase. *Mol. Carcinog*. **6**, 238-242.

Steenport, M., Eom, H., Uezu, M., Schneller, J., Gupta, R., Mustafa, Y., Villanueva, R., Straus, E. W., Raffaniello, R. D. (2007) Association of polymorphisms in myeloperoxidase and catalase genes with precancerous changes in the gastric mucosa of patients at inner-city hospitals in New York. *Oncol. Rep.* **18**, 235-240.

Switala, J., Loewen, P. C. (2002) Diversity of properties among catalases. *Arch. Biochem. Biophys*. **401**, 145-154.

Szelestei, T., Bähring, S., Wagner, Z., Aydin, A., Molnár, G. A., Kocsis, B., Nagy, J., Wittmann, I. (2005) Serum levels of L-arginine analogues and glutathione peroxidase and catalase gene variants in type 2 diabetes mellitus patients. *Diabet. Med*. **22**, 356-357.

Szuster-Ciesielska, A., Słotwińska, M., Stachura, A., Marmurowska-Michałowska, H., Dubas-Slemp, H., Bojarska-Junak, A., Kandefer-Szerszeń, M. (2008) Accelerated apoptosis of blood leukocytes and oxidative stress in blood of patients with major depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **32**, 686-694.

Szuster-Ciesielska, A., Daniluk, J., Kandefer-Szerszeń, M. (2001a) Oxidative stress in blood of patients with alcohol-related pancreatitis. *Pancreas* **22**, 261-266.

Szuster-Ciesielska, A., Daniluk, J., Kandefer-Szerszeń, M. (2001b) Alcohol-related cirrhosis with pancreatitis. The role of oxidative stress in the progression of the disease. *Arch. Immunol. Ther. Exp. (Warsz)* **49**, 139-146.

Tang, H., Dong, X., Day, R. S., Hassan, M. M., Li, D. (2010) Antioxidant genes, diabetes and dietary antioxidants in association with risk of pancreatic cancer. *Carcinogenesis* 31, 607-613.

Tarnai, I., Csordás, M., Sükei, E., Shemirani, A. H., Káplár, M., Góth, L. (2007) Effect of C111T polymorphism in exon 9 of the catalase gene on blood catalase activity in different types of diabetes mellitus. *Free Radic. Res.* **41**, 806-811.

Tate, D. J. Jr., Miceli, M. V., Newsome, D. A. (1995) Phagocytosis and H_2O_2 induce catalase and metallothionein gene expression in human retinal pigment cells. *Invest. Ophthalmol. Vis. Sci.* **36**, 1271-1279.

Toda, H., Takeuchi, T., Hori, N., Ito, K., Sato, K. (1997) Inverted repeats in the TATA-less promoter of the rat catalase gene. *J. Biochem.* **121**, 1035-1040.

Touyz, R. M., Montezano, A. C. (2012) Vascular Nox4: a multifarious NADPH oxidase. *Circ. Res.* **110**, 1159-1161.

Tsao, S. M., Yin, M. C., Liu, W. H. (2007) Oxidant stress and B vitamins status in patients with non-small cell lung cancer. *Nutr. Cancer* **59**, 8-13.

Twardowska-Saucha, K., Grzeszczak, W., Lacka, B., Froehlich, J., Krywult, D. (1994) Lipid peroxidation, antioxidant enzyme activity and trace element concentration in II and III trimester of pregnancy in pregnant women with diabetes. *Pol. Arch. Med. Wewn*. **92**, 313-321. (in Polish)

Ukkola, O., Erkkilä, P. H., Savolainen, M. J., Kesäniemi, Y. A. (2001) Lack of association between polymorphisms of catalase, copper-zinc superoxide dismutase (SOD), extracellular SOD and endothelial nitric oxide synthase genes and macroangiopathy in patients with type 2 diabetes mellitus. *J. Intern. Med.* **249**, 451-459.

Vávrová, L., Kodydková, J., Macášek, J., Ulrych, J., Žák, A. (2012) Oxidative stress in the course of acute pancreatitis. *Klin. Biochem. Metab.* **20**, 188-193. (in Czech)

Vávrová, L., Kodydková, J., Zeman, M., Dušejovská, M., Macášek, J., Staňková, B., Tvrzická, E., Zák, A. (2013) Altered activities of antioxidant enzymes in patients with metabolic syndrome. *Obes. Facts* **6**, 39-47.

Viroonudomphol, D., Pongpaew, P., Tungtrongchitr, R., Phonrat, B., Supawan, V., Vudhivai, N., Schelp, F. P. (2000) Erythrocyte antioxidant enzymes and blood pressure in relation to overweight and obese Thai in Bangkok. *Southeast Asian J. Trop. Med. Public Health* **31**, 325-334.

Warchol, T., Lianeri, M., Wudarski, M., Łącki, J. K., Jagodzinski, P. P. (2008) Catalase -262C/T polymorphism in systemic lupus erythematosus in Poland. *Rheumatol. Int.* **28**, 1035-1039.

Warner, A., Bencosme, A., Healy, D., Verme, C. (1995) Prognostic role of antioxidant enzymes in sepsis: preliminary assessment. *Clin. Chem*. **41(6 Pt 1)**, 867-871.

Watanabe, Y., Metoki, H., Ohkubo, T., Katsuya, T., Tabara, Y., Kikuya, M., Hirose, T., Sugimoto, K., Asayama, K., Inoue, R., Hara, A., Obara, T. (2010) Accumulation of common polymorphisms is associated with development of hypertension: a 12-year follow-up from the Ohasama study. *Hypertens. Res*. **33**, 129-134.

Way, J. M., Harrington, W. W., Brown, K. K., Gottschalk, W. K., Sundseth, S. S., Mansfield, T. A., Ramachandran, R. K., Willson, T. M., Kliewer, S. A. (2001) Comprehensive messenger ribonucleic acid profiling reveals that peroxisome proliferator-activated receptor γ activation has coordinate effects on gene expression in multiple insulin-sensitive tissues. *Endocrinology* **142**, 1269-1277.

Wenten, M., Gauderman, W. J., Berhane, K., Lin, P. C., Peters, J., Gilliland, F. (2009) Functional variants in the catalase and myeloperoxidase genes, ambient air pollution, and respiratory-related school absences: an example of epistasis in gene-environment interactions. *Am. J. Epidemiol.* **170**, 1494-1501.

Yang, W., Zhang, J., Wang, H., Shen, W., Gao, P., Singh, M., Fang, N. (2011) Peroxisome proliferator-activated receptor γ regulates angiotensin II-induced catalase downregulation in adventitial fibroblasts of rats. *FEBS Lett*. **585**, 761-766.

Yanping, L., Xin, Z., Zhimin, W., Daru, L., Wei, H., Li, J. (2004) An SNP polymorphism (-844C/T) in the promoter gene leads to differential expression. *Chin. Sci. Bull.* **49**, 1777-1778.

Young, R. P., Hopkins, R., Black, P. N., Eddy, C., Wu, L., Gamble, G. D., Mills, G. D., Garrett, J. E., Eaton, T. E., Rees, M. I. (2006) Functional variants of antioxidant genes in smokers with COPD and in those with normal lung function. *Thorax* **61**, 394-399.

Zámocký, M., Koller, F. (1999) Understanding the structure and function of catalases: clues from molecular evolution and in vitro mutagenesis. *Prog. Biophys. Mol. Biol.* **72**, 19-66.

Zarbock, R., Hendig, D., Szliska, C., Kleesiek, K., Götting, C. (2007) Pseudoxanthoma elasticum: Genetic variations in antioxidant genes are risk factors for early disease onset. *Clin. Chem.* **53**, 1734-1740.

Zhou, X. F., Cui, J., DeStefano, A. L., Chazaro, I., Farrer, L. A., Manolis, A. J., Gavras, H., Baldwin, C. T. (2005) Polymorphisms in the promoter region of catalase gene and essential hypertension. *Dis. Markers* **21**, 3-7.