Published in final edited form as:
Thorax. 2008 November ; 63(11): 956–961. doi:10.1136/thx.2007.086199.

Genetic Variation and Gene Expression in Antioxidant-Related Enzymes and Risk of Chronic Obstructive Pulmonary Disease: A Systematic Review

Amy R Bentley[‡], **Parastu Emrani**[‡], and **Patricia A Cassano**[‡]
[‡] Division of Nutritional Sciences, Cornell University, Ithaca, NY USA

Abstract

Observational epidemiologic studies of dietary antioxidant intake, serum antioxidant concentration, and lung outcomes suggest that lower levels of antioxidant defenses are associated with decreased lung function. Another approach to understanding the role of oxidant/antioxidant imbalance in risk of Chronic Obstructive Pulmonary Disease (COPD) is to investigate the role of genetic variation in antioxidant enzymes, and indeed family-based studies suggest a heritable component to lung disease. Many studies of the genes encoding antioxidant enzymes have considered COPD or COPD-related outcomes, and a systematic review is needed to summarise the evidence to date, and to provide insights for further research.

Genetic association studies of antioxidant enzymes and COPD/COPD-related traits, and comparative gene expression studies with disease or smoking as the exposure were systematically identified and reviewed. Antioxidant enzymes considered included enzymes involved in glutathione (GSH) metabolism, in the thioredoxin (TXN) system, superoxide dismutases (SOD), and catalase (CAT).

A total of 29 genetic association and 15 comparative gene expression studies met the inclusion criteria. The strongest and most consistent effects were in the genes *GCL*, *GSTM1*, *GSTP1*, and *SOD3*. This review also highlights the lack of studies for genes of interest, particularly *GSR*, *GGT*, and those related to *TXN*. There were limited opportunities to evaluate a gene's contribution to disease risk through a synthesis of results from different study designs, as the majority of studies considered either association of sequence variants with disease or effect of disease on gene expression. Network-driven approaches that consider potential interaction between genes and amoung genes, smoke exposure, and antioxidant intake are needed to fully characterise the role of oxidant/antioxidant balance in pathogenesis.

Keywords

Chronic Obstructive Pulmonary Disease (COPD); Antioxidants; Oxidative Stress

Address for correspondence: Dr. Patricia A. Cassano, Division of Nutritional Sciences, 209 Savage Hall, Cornell University, Ithaca, NY 14853 USA; ph 607-255-7551; fax 607-255-2608; pac6@cornell.edu.

Competing Interests: No conflict of interest exists.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterised by the development of airflow limitation that is not fully reversible. COPD is a major, and growing, public health burden.[1]

Smoking is the most important risk factor for COPD; however, there is considerable variation in the response to smoke exposure,[2] and it has been estimated that only 15% of the variation in lung function is explained by smoking parameters.[3] While not discounting the paramount importance of smoke exposure in the development of COPD, clearly other factors are significant. Genetic variation is a prime candidate, and many recent studies explore the contribution of genetic variation to inter-individual differences in the response to cigarette smoke.

This review focuses on genes related to antioxidant activity, as oxidant-rich cigarette smoke strains the antioxidant defenses of the lungs, leading to direct tissue damage and contributing to the inflammation and antiprotease inactivation seen in COPD. This hypothesis is supported by epidemiologic studies associating low dietary antioxidant intake and serum antioxidant concentration with decreased lung function[4–9] and increased COPD mortality risk.[10]

Many genetic association studies and comparative expression studies investigate the relation between genes coding for antioxidant enzymes and either COPD or associated traits. An overview of the evidence is warranted to ascertain whether the pattern of published results suggests directions for future research, or whether there are apparent gaps that need to be addressed. Both genetic association studies and gene expression studies were included: polymorphisms can affect disease risk in ways that may or may not be mediated by changes in expression, and expression studies can provide a snapshot of the adaptive response to an exposure. Thus, we conducted a systematic review of the literature to characterise the evidence that genes coding for antioxidant enzymes contribute to the aetiology of COPD and related traits.

METHODS

The selection of genes was based mainly on delineating important proteins and the networks of genes that may influence the amount or function of those proteins (Figure 1). As glutathione (GSH) is an antioxidant that plays a significant role in the lung, genes encoding GSH-associated enzymes were selected. Thioredoxin, which reduces oxidised glutathione and has an antioxidant function that overlaps GSH function, was included with genes encoding associated enzymes. Catalase and superoxide dismutase, two classical antioxidant enzymes of the lung, were also selected. Searches of PubMed were performed up to August 2007 (further details online). Published papers considering gene-disease association or differential gene expression in adult humans were selected. Association studies were included if the outcome was disease or lung function. Expression studies were included if the experimental exposure was disease status or smoking and if expression was measured in pulmonary tissues or cells.

RESULTS

A total of 29 genetic association studies and 14 expression studies were identified (online supplement table 1).

Glutathione Synthesis

Three enzymes that relate to glutathione synthesis were considered: gamma-glutamyl transpeptidase (GGT, no studies found), glutamate-cysteine ligase (GCL), and glutathione synthetase (GSS). A substitution in the promoter region of *GCLM* (GCL's modulatory subunit), leading to decreased glutathione levels,[11] was associated with a 3-fold increased risk of COPD in Chinese smokers.[12] In the single study of a substitution in GCL's catalytic subunit (GCLC) that results in decreased expression,[13] an increased prevalence was observed in patients vs. healthy controls (OR 1.83, 95% CI[1.00, 3.36]).[14]

Expression studies of glutathione synthesis compared expression in COPD patients with asymptomatic smokers and/or nonsmokers. Eight of the 9 comparisons of *GCLC* expression in lung epithelium found upregulation with disease.[15–18] Two comparisons of *GCLM* expression in lung epithelium of lung tumor patients with and without COPD showed decreased *GCLM* expression with disease,[17] while the single study of COPD patients without lung tumor found upregulation.[18]

There were 4 comparisons of *GCL* expression in lung epithelium of asymptomatic smokers and nonsmokers: expression of both subunits was increased in smokers who were healthy volunteers[18, 19] and unchanged or decreased in smokers with lung tumor.[17]

Expression of the *GCL* subunits in alveolar macrophages/inflammatory cells showed a more consistent pattern. Both *GCLC*[16, 17, 20] and *GCLM*[20] were increased in COPD patients vs. smokers, and smokers had lower expression of both subunits compared to nonsmokers.[17, 20] A 27% upregulation of the mRNA of *GSS*, the final step of GSH synthesis, was reported in smokers vs. nonsmokers ($p=0.08$),[19] but was not replicated in comparisons of nonsmokers with either asymptomatic smokers or COPD patients.[18, 19]

Antioxidant Activity of GSH and Recycling

Glutathione peroxidase (GPX), glutaredoxin (GLRX), glutathione reductase (GSR), and glucose-6-phosphate dehydrogenase (G6PD) were considered for their role in the antioxidant activity of GSH and in GSH recycling. There were no association studies of variants in these genes.

Two studies evaluated expression in COPD patients versus healthy controls. In the single study of *GPX2*, it was strongly upregulated in COPD patients at all stages compared to nonsmokers (and modestly upregulated compared to smokers).[18] *GPX3* was upregulated in COPD patients compared to nonsmokers, though this difference was not seen in comparison with asymptomatic smokers.[18, 21] There was little evidence of differential regulation of *GPX4*, *GPX5*, or *GPX7* by disease status.[18]

GPX2 showed a 3 to 5-fold upregulation in epithelial cells of smokers compared to nonsmokers.[18, 19] Each of the 4 studies of *GPX3* expression in epithelial cells reported upregulation in smokers: two studies found a 2-fold difference,[19, 22] and a study of alveolar macrophages reported similar differences.[22]

Two expression studies evaluated regulation of *GLRX*. A statistically significant downregulation was observed in the tissue homogenate of COPD patients compared to smokers (patients had either resection for lung tumor or lung transplantation for severe COPD),[23] but similar results were not observed in an analysis of bronchial epithelial cells.[18] A statistically significant upregulation of GLRX in the sputum of COPD patients in exacerbation was reported vs. nonsmokers.[23]

The sole comparison of GSR expression in epithelial cells by disease groups showed upregulation in COPD patients.[18] In the 2 comparisons by smoking status, upregulation was observed among smokers.[18, 19] Very similar results were found in the 3 studies of *G6PD* expression: 2-fold upregulation in epithelial cells [18, 19] and in alveolar macrophages.[24]

In agreement with biological networks, the 4 expression studies that considered *GPX* (*GPX1*, *GPX2*, and *GPX3*), *GSR*, and *G6PD* all showed upregulation of each of these genes with smoking.

GSH Conjugation and Export

There were 24 association and 4 expression studies of Glutathione S-Transferases (GSTs), which play a role in GSH conjugation and export.

A homozygous deletion of *GSTM1*, resulting in a complete lack of activity,[25] was associated with increased COPD risk in 3 of 7 association studies (range in OR: 2.2 to 8.0).[26–28] The prevalence of the deletion was increased in emphysema patients compared to non-diseased participants,[29, 30] though no association was observed with emphysematous changes in heavy smokers.[31] Both studies of chronic bronchitis reported a 3-fold increased risk associated with the null genotype.[32, 33]

Five studies investigated the association of the *GSTM1* deletion with COPD-related quantitative traits. Conflicting evidence was reported: 1 of 2 studies of rate of FEV_1 decline reported an association in men only[34] and 1 of 3 studies of FEV_1%predicted reported lower lung function with the null genotype.[35] In a single study of FVC %predicted, the null genotype was significantly associated with decreased lung function.[35] However, it was not associated with increased rate of FVC decline.[34] Null genotype was associated with a steeper rate of $FEF_{25–75}$ decline (among men) in one study.[34]

In *GSTP1*, the Ile105Val substitution, which causes altered affinity for specific substrates,[36] was associated with COPD-related outcomes. A protective effect of the heterozygous genotype was reported in 7 of 11 studies of COPD patients vs. asymptomatic participants; the magnitude of the effect varied and was statistically significant in 2 studies.[37, 38] A study of smokers with emphysematous changes (vs. normal smokers) reported a protective effect of heterozygosity.[31] However, 7 of 10 studies of the homozygous variant genotype in relation to COPD risk reported an increased risk: the difference was statistically significant in one study[39] and 4 estimates were based on small numbers.

The Ile105Val genotype had little or no relation to the rate of decline in FEV_1, although the direction of effect was consistent with the hypothesis: risk was increased in those homozygous for the variant allele.[34] Greater effect sizes were found for risk of being in the tails of the FEV_1%predicted distribution,[40] but there was little or no continuous relation with FEV_1%predicted.[41]

A *GSTP1* polymorphism with unknown biological effect (Ala114Val) was investigated in 3 studies. One study of Indian smokers observed a statistically significant graded increase in prevalence of COPD with the variant allele,[39] but a similar association with emphysema risk was not observed in an American population.[30] In 3 comparisons of lung function within disease groups, statistically significantly lower lung function was observed with the variant allele in COPD patients,[39] but not in emphysema patients[41] or asymptomatic smokers.[39]

There was little or no association of a homozygous deletion of *GSTT1* with COPD risk; 3 of 4 studies reported a slightly decreased risk of disease with the null genotype, but the interval estimates of the effect were wide. There was no association of *GSTT1* null and risk of

emphysematous changes in smokers.[31] Three of 4 studies of lung function reported an association: null genotype was associated with a steeper decline in FEV_1 in a general population,[42] with steeper decline in FEV_1, FVC, and $FEF_{25–75}$ among men,[34] and with an increased risk of being in the lowest compared to the highest group of %predicted FEV_1.[40] The only study of mGST1 found no association between 4 markers and FEV_1 %predicted.[41]

There were 3 studies of gene expression differences by disease group. Upregulation of *GSTM3* and *mGST1* expression was observed in COPD patients.[18] *GSTO1* was significantly downregulated in the single study of lung tissue and sputum from COPD patients with lung tumor,[43] but was upregulated in the epithelial cells of patients with COPD only (less severe stages).[18] Four studies investigated the expression of *GSTs* by smoking status. Both studies of *GSTA1* expression showed upregulation among smokers in lung tissue.[18, 21] Statistically significant upregulation was associated with smoking in a single study of *GSTA2*.[19] *GSTM3* expression was increased among smokers to the same extent (approximately 50%) in both studies of epithelial cells.[18, 19] There was some evidence of upregulation of *mGST1* among smokers in 2 studies.[18, 19] In 6 of 7 comparisons of *GSTO1* expression in various lung tissues, expression was unrelated to smoking.

Thioredoxin Metabolism

Thioredoxin metabolism was evaluated by considering the enzymes thioredoxin (TXN), thioredoxin reductase (TXNRD), and peroxiredoxin (PRDX). No association studies and 2 expression studies were found. A single study considering epithelial cell expression in COPD vs. non-diseased reported upregulation of *TXN*, *TXNRD1*, and *PRDX1* with disease, and downregulation of *PRDX5* with disease.[18] Both studies of expression by smoking status reported increased expression of *TXN* and *TXNRD1* with smoking.[18, 19] In the study that also evaluated peroxiredoxins, *PRDX1* was upregulated and *PRDX3* and *PRDX5* were both downregulated in smokers.[18]

Other Enzymes

Two classic antioxidants, superoxide dismutase (SOD) and catalase (CAT), were considered. Three association studies (evaluating 5 variants) and 6 expression studies were identified.

There was no association between an intronic SNP in *SOD1* and COPD. *SOD2* Val16Ala was associated with disease in a Chinese population,[44] but not in persons of European descent.[45] The association between *SOD3* Arg213Gly and COPD was studied in 2 large populations.[45, 46] Heterozygosity was associated with a strong, statistically significant decreased risk of disease (~40–75% reduction) [45, 46] and a 70% reduction in risk of COPD hospitalization or death during follow-up.[46] Genotype was not associated with lung function in a general population, but FEV_1/FVC ratio was higher among smokers with the heterozygous genotype ($p=0.04$).[46] There were no homozygous variants among diseased individuals in either study, precluding odds ratio calculation.

Three studies of SOD expression compared COPD patients to healthy controls. SOD activity was increased in the bronchial lavage fluid of nonsmokers with COPD compared to smokers with COPD and healthy controls.[47] No evidence for differential expression by disease status was seen in 3 studies of SOD1.[18, 21, 48] In the 6 comparisons of *SOD2* in lung tumor patients with COPD versus controls, COPD was associated with increased *SOD2* concentration.[21, 48] An increase in expression was not observed in the single study of COPD patients without lung tumor.[18] Neither of the studies of *SOD3* expression in disease groups provided strong evidence for differential regulation by disease.[18, 21]

Little or no evidence of differential expression of *SOD1* and *SOD3* by smoking status was observed. *SOD2* was upregulated in smokers vs. nonsmokers in 3 comparisons of epithelial cells (with one showing strong, significant upregulation) and downregulated in 3 other comparisons. *SOD2* was also upregulated in lung tissue homogenate and alveolar macrophages, but downregulated in the pulmonary blood vessels of smokers vs. nonsmokers.

Two studies evaluated polymorphisms in *CAT*, but provided no strong evidence for an association of two promoter region SNPs with disease risk.[44, 45] Two studies compared *CAT* expression in disease groups, with little evidence for differential regulation by COPD status, though statistically significant downregulation was observed in lung tumor patients with COPD in 1 study.[21] Three studies compared *CAT* expression by smoking status, with inconsistent results.

Gene-Gene Interaction

Increased risk of COPD, and decreased FEV_1 %predicted among COPD patients, was reported for various genotype combinations that included either *GSTP1* 105Val or 114Val vs. wildtype for both polymorphisms (OR 1.99 for COPD risk; 95% CI 1.28, 3.09).[39] In an analysis of *GSTM1* null, *GSTT1* null, and *GSTP1* Ile105Val, most combinations of the "higher risk" genotypes were associated with an increased risk of disease, with the strongest associations observed with the *GSTP1* 105Ile allele and the null genotype for either *GSTM1* (OR 11.3; 95% CI 1.3, 98.6) or *GSTT1* (OR 12.1; 95% CI 1.3, 116.96).[37] Although the combination of *GSTM1* null, *GSTT1* null, and *GSTP1* 105Ile was not associated with COPD risk in another study,[49] it was associated with steeper lung function decline ($p=0.026$)[40] and risk of rapid decline in lung function (OR 2.83; 95% CI 1.1, 7.2).[42] Men with the null genotype for both *GSTM1* and *GSTT1* had 8.3 ml/year greater decline in FEV_1 vs. those with at least one copy of both ($p<0.001$), with similar results reported for both FVC and $FEF_{25–75}$.[34] The National Emphysema Treatment Trial reported little or no association between combinations of *GSTM1* null and *GSTP1* 105Ile and disease.[30] There was little or no association of *GSTM1* and *GSTT1* null genotypes and emphysematous changes in Japanese heavy smokers.[31] The combination of *GSTM1* null, *GSTP1* 105 Ile/Ile, and at least one slow allele for *microsomal epoxide hydrolase* increased risk of COPD (OR 6.8; 95% CI 1.6, 17.2).[26] The combination of *GSTM1* null and a *matrix metalloproteinase 9* polymorphism increased COPD risk by about 8-fold (OR 7.7; 95% CI 1.1, 53.3).[27]

DISCUSSION

Observational epidemiologic evidence suggests a role for nutrients contributing to antioxidant function in the prevention of lung disease.[4–9] Whether these findings reflect underlying biological mechanisms or methodologic bias (e.g., confounding) is unclear. The consideration of genetic variants that affect antioxidant/oxidant balance and that may be sensitive to dietary intake of antioxidants can help address this question. The study of genetic variants affecting antioxidant capacity allows an unbiased approach, in comparison to observational studies of diet, based in part on the principles of Mendelian randomisation.[50] Thus, this review was designed to evaluate the evidence that antioxidant enzyme function and/or regulation is related to COPD risk.

This systematic review included studies that addressed gene-disease associations as well as those that evaluated differences in gene expression. There were limited opportunities to synthesise results from both approaches as genes were often considered *either* in association studies *or* in expression studies, yet such synthesis may reveal complementary data.[51] For example, a variant allele that leads to decreased glutathione was associated with an increased risk of COPD among smokers,[12] and an expression study of *GCLM* reported

upregulation in smokers.[19] The combined results support the hypothesis that increasing available glutathione in persons with a high oxidant load may protect against lung damage. A lack of agreement between association and gene expression studies may also be informative. While association studies suggest a protective effect of heterozygosity for the *GSTP1* Ile105Val polymorphism in COPD, no differences in expression of *GSTP1* were reported in smokers compared to nonsmokers, suggesting that the effect of the genotype is not mediated through mRNA quantity.

Comparisons with animal studies provide an additional context in which to interpret the findings from human studies, but caution is warranted. Mice and adult rats (in contrast to humans) synthesise ascorbate,[52] which protects GSH from oxidation and reduces it from its disulphide form.[53] The interaction between ascorbate and other antioxidants suggests that animal studies of genetic manipulation or oxidant insult may not be predictive of results in humans. While two human studies of *GSR* expression reported significantly increased mRNA expression in the airway epithelial cells of asymptomatic smokers,[18, 19] findings in smoke-exposed rats were mainly negative.[54–56] Reduction of GSSG by endogenously formed ascorbate may blunt the rat's need for GSR to perform the same function.

This review reveals very few instances where the evidence base contains enough information to make a strong statement of effect, but a few examples deserve mention. The *GSTM1* null genotype (no enzyme activity) was consistently associated with increased COPD risk.[26–29, 32–35, 37, 57] A substitution in another GST, *GSTP1* Ile105Val, which affects catalytic activity and binding affinity for particular substrates, was consistently inversely associated with disease.[31, 34, 37, 38, 40, 58–60] A rare substitution in *SOD3*, which increases plasma SOD levels, was also associated with a significantly decreased COPD risk,[45, 46] a result supported by an animal study: transgenic mice overexpressing human *SOD3* had attenuated lung damage and inflammatory response in hyperoxic conditions.[61] In addition, there was simultaneous upregulation of *GSR*, *GPX*, and *G6PD* in the airway epithelial cells of smokers,[19] highlighting the importance of a network of genes in the lung's response to oxidative stress.

Several elements of the selected interrelated pathways have received minimal or no attention in human studies to date. For example, targeted disruption of the TXN gene produced early embryo lethality in mice,[62, 63] and transgenic mice over-expressing human *TXN1* had increased survival and decreased hydroxyl radical production during exposure to diesel exhaust particles.[64] The two studies of TXN-related enzymes in humans reported upregulation of *TXNRD1* and *TXN* in the airway epithelial cells of smokers and those with COPD[18, 19]: further investigation is warranted. Other understudied genes of interest include *GGT*, *PRDX6*, and *GLRX*. GGT is the key enzyme in one pathway for the intracellular supply of cysteine for GSH synthesis: *GGT*-deficient mice show a reduced ability for *de novo* synthesis[65] and decreased intracellular GSH concentration.[66] Furthermore, pulmonary *GGT* activity was increased during hyperoxia in rats,[67] and *GGT*-deficient mice had worse survival in hyperoxic conditions.[65, 66] PRDX6 is a peroxiredoxin that uses GSH as a cofactor. *PRDX6* null mice had more severe lung injury and significantly decreased survival in conditions of hyperoxia vs. wildtype.[68] Transgenic mice over-expressing *PRDX6* had greater survival and attenuated lung damage in hyperoxia.[69] Finally, GLRX comprises part of a major thiol-disulphide redox buffer in the cell. The activity of this enzyme suggests a possible role in relation to the oxidation of GSH and the redox status of the cell, recommending it for further study.

Several methodological considerations deserve mention. COPD aetiology is expected to include gene-environment interactions, given the clear role of smoking in this disease and the inter-individual differences in response to cigarette smoke. Thus, comparison groups

must be carefully selected with regard to smoke exposure. In association studies in which the non-diseased group is comprised of non-smokers and the diseased group of smokers, for instance, the estimate of a true effect may be diluted. Similarly, in expression studies, a comparison between individuals with equivalent exposures, but whose disease outcome differed may be most informative. Studies published in other languages were included to avoid the "Tower of Babel error".[70] A comprehensive set of enzymes based on biological networks were the starting point for the review, however our selections may have led to inadvertent omission of relevant enzymes. Disturbances in a broad range of redox-related enzymes are likely to affect disease risk, suggesting that complex interactions cannot be ignored. A broader network approach may ultimately lead to more robust epidemiologic findings.

In conclusion, the evidence summarised in this review supports the continued investigation of the hypothesis that variation in genes that code for enzymes that can alter the redox environment of the lungs may contribute to COPD risk. Future directions suggested by this summary are: more network-driven approaches that include broader consideration of enzymes whose related, redundant and linked activities might alter disease risk, further integration of association and expression studies to determine the nature of the biological relationships that may lead to disease, and careful consideration, in both study design and analysis, of environmental exposures (e.g., smoking and nutritional status) that are likely to modify the gene-disease associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: Supported by USDA (CSREES) Subproject on grant number 2003-34324-13135 and by NIH R01 HL 0701022; ARB supported in part by NIH training grant T32 DK007158-31.

Abbreviations used

ABCC1	ATP-binding cassette C1
CAT	catalase
COPD	chronic obstructive pulmonary disease
G6PD	glucose-6-phosphate dehydrogenase
GCL	glutamate-cysteine ligase
GCLC	GCL catalytic subunit
GCLM	GCL modulatory subunit
GGT	gamma-glutamyl transpeptidase
GPX	glutathione peroxidase
GLRX	glutaredoxin
GSH	glutathione
GSR	glutathione reductase
GSS	glutathione synthetase
GSSG	oxidised glutathione

GST	glutathione S-transferase
H_20_2	hydrogen peroxide
PRDX	peroxiredoxin
SOD	superoxide dismutase
TXN	thioredoxin
TXNRD	thioredoxin reductase

References

1. Lopez AD, Murray CC. The global burden of disease, 1990–2020. Nat Med 1998;4:1241–1243. [PubMed: 9809543]
2. Fletcher, CM. The Natural History of Chronic Bronchitis and Emphysema : An Eight-Year Study of Early Chronic Obstructive Lung Disease in Working Men in London. Oxford ; New York: Oxford University Press; 1976. p. xixp. 272
3. Beck GJ, Doyle CA, Schachter EN. Smoking and lung function. Am Rev Respir Dis 1981;123:149–155. [PubMed: 7235353]
4. Butland BK, Fehily AM, Elwood PC. Diet, lung function, and lung function decline in a cohort of 2512 middle aged men. Thorax 2000;55:102–108. [PubMed: 10639525]
5. Ochs-Balcom HM, Grant BJ, Muti P, Sempos CT, Freudenheim JL, Browne RW, et al. Antioxidants, oxidative stress, and pulmonary function in individuals diagnosed with asthma or COPD. Eur J Clin Nutr. 2006
6. Grievink L, Smit HA, Ocke MC, van 't Veer P, Kromhout D. Dietary intake of antioxidant (pro)-vitamins, respiratory symptoms and pulmonary function: the MORGEN study. Thorax 1998;53:166–171. [PubMed: 9659349]
7. Hu G, Zhang X, Chen J, Peto R, Campbell TC, Cassano PA. Dietary vitamin C intake and lung function in rural China. Am J Epidemiol 1998;148:594–599. [PubMed: 9753014]
8. Tabak C, Smit HA, Heederik D, Ocke MC, Kromhout D. Diet and chronic obstructive pulmonary disease: independent beneficial effects of fruits, whole grains, and alcohol (the MORGEN study). Clin Exp Allergy 2001;31:747–755. [PubMed: 11422134]
9. McKeever TM, Scrivener S, Broadfield E, Jones Z, Britton J, Lewis SA. Prospective study of diet and decline in lung function in a general population. Am J Respir Crit Care Med 2002;165:1299–1303. [PubMed: 11991883]
10. Walda IC, Tabak C, Smit HA, Rasanen L, Fidanza F, Menotti A, et al. Diet and 20-year chronic obstructive pulmonary disease mortality in middle-aged men from three European countries. Eur J Clin Nutr 2002;56:638–643. [PubMed: 12080403]
11. Nakamura S, Kugiyama K, Sugiyama S, Miyamoto S, Koide S, Fukushima H, et al. Polymorphism in the 5'-flanking region of human glutamate-cysteine ligase modifier subunit gene is associated with myocardial infarction. Circulation 2002;105:2968–2973. [PubMed: 12081989]
12. Hu RC, Tan SX, Dai AG. The relationship between the polymorphism of glutamate cysteine ligase modulatory subunit gene and the susceptibility to chronic obstructive pulmonary disease. Zhonghua Jie He He Hu Xi Za Zhi 2006;29:100–103. [PubMed: 16677451]
13. Koide S, Kugiyama K, Sugiyama S, Nakamura S, Fukushima H, Honda O, et al. Association of polymorphism in glutamate-cysteine ligase catalytic subunit gene with coronary vasomotor dysfunction and myocardial infarction. J Am Coll Cardiol 2003;41:539–545. [PubMed: 12598062]
14. Liu S, Li B, Zhou Y, Zhong N, Ran P. Genetic analysis of CC16, OGG1 and GCLC polymorphisms and susceptibility to COPD. Respirology 2007;12:29–33. [PubMed: 17207022]
15. Rahman I, van Schadewijk AA, Hiemstra PS, Stolk J, van Krieken JH, MacNee W, et al. Localization of gamma-glutamylcysteine synthetase messenger rna expression in lungs of smokers and patients with chronic obstructive pulmonary disease. Free Radic Biol Med 2000;28:920–925. [PubMed: 10802223]

16. Lin SD, Dai AG, Xu P. Changes of the activity and expression of gamma-glutamylcysteine synthetase in patients with chronic obstructive pulmonary disease. Zhonghua Jie He He Hu Xi Za Zhi 2005;28:97–101. [PubMed: 15854390]

17. Harju T, Kaarteenaho-Wiik R, Soini Y, Sormunen R, Kinnula VL. Diminished immunoreactivity of gamma-glutamylcysteine synthetase in the airways of smokers' lung. Am J Respir Crit Care Med 2002;166:754–759. [PubMed: 12204877]

18. Pierrou S, Broberg P, O'Donnell RA, Pawlowski K, Virtala R, Lindqvist E, et al. Expression of genes involved in oxidative stress responses in airway epithelial cells of smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007;175:577–586. [PubMed: 17158281]

19. Hackett NR, Heguy A, Harvey BG, O'Connor TP, Luettich K, Flieder DB, et al. Variability of antioxidant-related gene expression in the airway epithelium of cigarette smokers. Am J Respir Cell Mol Biol 2003;29:331–343. [PubMed: 12702543]

20. Neurohr C, Lenz AG, Ding I, Leuchte H, Kolbe T, Behr J. Glutamate-cysteine ligase modulatory subunit in BAL alveolar macrophages of healthy smokers. Eur Respir J 2003;22:82–87. [PubMed: 12882455]

21. Tomaki M, Sugiura H, Koarai A, Komaki Y, Akita T, Matsumoto T, et al. Decreased expression of antioxidant enzymes and increased expression of chemokines in COPD lung. Pulm Pharmacol Ther 2007;20:596–605. [PubMed: 16919984]

22. Comhair SA, Thomassen MJ, Erzurum SC. Differential induction of extracellular glutathione peroxidase and nitric oxide synthase 2 in airways of healthy individuals exposed to 100% O(2) or cigarette smoke. Am J Respir Cell Mol Biol 2000;23:350–354. [PubMed: 10970826]

23. Peltoniemi MJ, Rytila PH, Harju TH, Soini YM, Salmenkivi KM, Ruddock LW, et al. Modulation of glutaredoxin in the lung and sputum of cigarette smokers and chronic obstructive pulmonary disease. Respir Res 2006;7:133. [PubMed: 17064412]

24. Heguy A, O'connor TP, Luettich K, Worgall S, Cieciuch A, Harvey BG, et al. Gene expression profiling of human alveolar macrophages of phenotypically normal smokers and nonsmokers reveals a previously unrecognized subset of genes modulated by cigarette smoking. J Mol Med 2006;84:318–328. [PubMed: 16520944]

25. Xu S, Wang Y, Roe B, Pearson WR. Characterization of the human class Mu glutathione S-transferase gene cluster and the GSTM1 deletion. J Biol Chem 1998;273:3517–3527. [PubMed: 9452477]

26. Cheng SL, Yu CJ, Chen CJ, Yang PC. Genetic polymorphism of epoxide hydrolase and glutathione S-transferase in COPD. Eur Respir J 2004;23:818–824. [PubMed: 15218992]

27. Yanchina ED, Ivchik TV, Shvarts EI, Kokosov AN, Khodzhayantz NE. Gene-gene interactions between glutathione-s transferase M1 and matrix metalloproteinase 9 in the formation of hereditary predisposition to chronic obstructive pulmonary disease. Bull Exp Biol Med 2004;137:64–66. [PubMed: 15085249]

28. Dialyna IA, Miyakis S, Georgatou N, Spandidos DA. Genetic polymorphisms of CYP1A1, GSTM1 and GSTT1 genes and lung cancer risk. Oncol Rep 2003;10:1829–1835. [PubMed: 14534704]

29. Harrison DJ, Cantlay AM, Rae F, Lamb D, Smith CA. Frequency of glutathione S-transferase M1 deletion in smokers with emphysema and lung cancer. Hum Exp Toxicol 1997;16:356–360. [PubMed: 9257159]

30. Hersh CP, Demeo DL, Lange C, Litonjua AA, Reilly JJ, Kwiatkowski D, et al. Attempted replication of reported chronic obstructive pulmonary disease candidate gene associations. Am J Respir Cell Mol Biol 2005;33:71–78. [PubMed: 15817713]

31. Budhi A, Hiyama K, Isobe T, Oshima Y, Hara H, Maeda H, et al. Genetic susceptibility for emphysematous changes of the lung in Japanese. Int J Mol Med 2003;11:321–329. [PubMed: 12579334]

32. Baranova H, Perriot J, Albuisson E, Ivaschenko T, Baranov VS, Hemery B, et al. Peculiarities of the GSTM1 0/0 genotype in French heavy smokers with various types of chronic bronchitis. Hum Genet 1997;99:822–826. [PubMed: 9187680]

33. Baranov VS, Ivaschenko T, Bakay B, Aseev M, Belotserkovskaya R, Baranova H, et al. Proportion of the GSTM1 0/0 genotype in some Slavic populations and its correlation with cystic fibrosis and some multifactorial diseases. Hum Genet 1996;97:516–520. [PubMed: 8834254]
34. Imboden M, Downs SH, Senn O, Matyas G, Brandli O, Russi EW, et al. Glutathione S-transferase genotypes modify lung function decline in the general population: SAPALDIA cohort study. Respir Res 2007;8:2. [PubMed: 17217536]
35. Tkacova R, Salagovic J, Ceripkova M, Tkac I, Stubna J, Kalina I. Glutathione S-transferase M1 gene polymorphism is related to COPD in patients with non-small-cell lung cancer. Wien Klin Wochenschr 2004;116:131–134. [PubMed: 15038404]
36. Zimniak P, Nanduri B, Pikula S, Bandorowicz-Pikula J, Singhal SS, Srivastava SK, et al. Naturally occurring human glutathione S-transferase GSTP1–1 isoforms with isoleucine and valine in position 104 differ in enzymic properties. Eur J Biochem 1994;224:893–899. [PubMed: 7925413]
37. Calikoglu M, Tamer L, Ates Aras N, Karakas S, Ercan B. The association between polymorphic genotypes of glutathione S-transferases and COPD in the Turkish population. Biochem Genet 2006;44:307–319. [PubMed: 16977512]
38. Ishii T, Matsuse T, Teramoto S, Matsui H, Miyao M, Hosoi T, et al. Glutathione S-transferase P1 (GSTP1) polymorphism in patients with chronic obstructive pulmonary disease. Thorax 1999;54:693–696. [PubMed: 10413721]
39. Vibhuti A, Arif E, Deepak D, Singh B, Qadar Pasha MA. Genetic polymorphisms of GSTP1 and mEPHX correlate with oxidative stress markers and lung function in COPD. Biochem Biophys Res Commun 2007;359:136–142. [PubMed: 17532303]
40. He JQ, Connett JE, Anthonisen NR, Pare PD, Sandford AJ. Glutathione S-transferase variants and their interaction with smoking on lung function. Am J Respir Crit Care Med 2004;170:388–394. [PubMed: 15184197]
41. Hersh CP, Demeo DL, Lazarus R, Celedon JC, Raby BA, Benditt JO, et al. Genetic association analysis of functional impairment in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006;173:977–984. [PubMed: 16456143]
42. He JQ, Ruan J, Connett JE, Anthonisen NR, Pare PD, Sandford AJ. Antioxidant gene polymorphisms and susceptibility to a rapid decline in lung function in smokers. Am J Respir Crit Care Med 2002;166:323–328. [PubMed: 12153964]
43. Harju TH, Peltoniemi MJ, Rytila PH, Soini Y, Salmenkivi KM, Board PG, et al. Glutathione S-transferase omega in the lung and sputum supernatants of COPD patients. Respir Res 2007;8:48. [PubMed: 17617905]
44. Mak JC, Ho SP, Yu WC, Choo KL, Chu CM, Yew WW, et al. Polymorphisms and functional activity in SOD and catalase genes in smokers with COPD. Eur Respir J. 2007
45. Young RP, Hopkins R, Black PN, Eddy C, Wu L, Gamble GD, et al. Functional variants of antioxidant genes in smokers with COPD and in those with normal lung function. Thorax 2006;61:394–399. [PubMed: 16467073]
46. Juul K, Tybjaerg-Hansen A, Marklund S, Lange P, Nordestgaard BG. Genetically Increased Antioxidative Protection and Decreased Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2006
47. Yigla M, Berkovich Y, Nagler RM. Oxidative stress indices in COPD--Broncho-alveolar lavage and salivary analysis. Arch Oral Biol 2007;52:36–43. [PubMed: 17092480]
48. Harju T, Kaarteenaho-Wiik R, Sirvio R, Paakko P, Crapo JD, Oury TD, et al. Manganese superoxide dismutase is increased in the airways of smokers' lungs. Eur Respir J 2004;24:765–771. [PubMed: 15516670]
49. Chan-Yeung M, Ho SP, Cheung AH, So LK, Wong PC, Chan KK, et al. Polymorphisms of glutathione S-transferase genes and functional activity in smokers with or without COPD. Int J Tuberc Lung Dis 2007;11:508–514. [PubMed: 17439673]
50. Davey Smith G, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol 2003;32:1–22. [PubMed: 12689998]
51. Li J, Burmeister M. Genetical genomics: combining genetics with gene expression analysis. Hum Mol Genet 2005;14(Spec No 2):R163–9. [PubMed: 16244315]

52. Banhegyi G, Braun L, Csala M, Puskas F, Mandl J. Ascorbate metabolism and its regulation in animals. Free Radic Biol Med 1997;23:793–803. [PubMed: 9296457]
53. Meister A. Glutathione-ascorbic acid antioxidant system in animals. J Biol Chem 1994;269:9397–9400. [PubMed: 8144521]
54. York GK, Peirce TH, Schwartz LW, Cross CE. Stimulation by cigarette smoke of glutathione peroxidase system enzyme activities in rat lung. Arch Environ Health 1976;31:286–290. [PubMed: 999340]
55. Joshi UM, Kodavanti PR, Mehendale HM. Glutathione metabolism and utilization of external thiols by cigarette smoke-challenged, isolated rat and rabbit lungs. Toxicol Appl Pharmacol 1988;96:324–335. [PubMed: 3194918]
56. Gupta MP, Khanduja KL, Sharma RR. Effect of cigarette smoke inhalation on antioxidant enzymes and lipid peroxidation in the rat. Toxicol Lett 1988;41:107–114. [PubMed: 3368925]
57. Korytina GF, Iaibaeva DG, Viktorova TV. Polymorphism of glutathione-S-transferase M1 and P1 genes in patients with cystic fibrosis and chronic respiratory tract diseases. Genetika 2004;40:401–408. [PubMed: 15125256]
58. Lu B, He Q. Correlation between exon5 polymorphism of glutathione S-transferase P1 gene and susceptibility to chronic obstructive pulmonary disease in northern Chinese population of Han nationality living in Beijing, China. Zhonghua Nei Ke Za Zhi 2002;41:678–681. [PubMed: 12485534]
59. Rodriguez F, de la Roza C, Jardi R, Schaper M, Vidal R, Miravitlles M. Glutathione S-transferase P1 and lung function in patients with alpha1-antitrypsin deficiency and COPD. Chest 2005;127:1537–1543. [PubMed: 15888825]
60. Yim JJ, Yoo CG, Lee CT, Kim YW, Han SK, Shim YS. Lack of association between glutathione S-transferase P1 polymorphism and COPD in Koreans. Lung 2002;180:119–125. [PubMed: 12172904]
61. Folz RJ, Abushamaa AM, Suliman HB. Extracellular superoxide dismutase in the airways of transgenic mice reduces inflammation and attenuates lung toxicity following hyperoxia. J Clin Invest 1999;103:1055–1066. [PubMed: 10194479]
62. Matsui M, Oshima M, Oshima H, Takaku K, Maruyama T, Yodoi J, et al. Early embryonic lethality caused by targeted disruption of the mouse thioredoxin gene. Dev Biol 1996;178:179–185. [PubMed: 8812119]
63. Nonn L, Williams RR, Erickson RP, Powis G. The absence of mitochondrial thioredoxin 2 causes massive apoptosis, exencephaly, and early embryonic lethality in homozygous mice. Mol Cell Biol 2003;23:916–922. [PubMed: 12529397]
64. Kaimul Ahsan M, Nakamura H, Tanito M, Yamada K, Utsumi H, Yodoi J. Thioredoxin-1 suppresses lung injury and apoptosis induced by diesel exhaust particles (DEP) by scavenging reactive oxygen species and by inhibiting DEP-induced downregulation of Akt. Free Radic Biol Med 2005;39:1549–1559. [PubMed: 16298680]
65. Barrios R, Shi ZZ, Kala SV, Wiseman AL, Welty SE, Kala G, et al. Oxygen-induced pulmonary injury in gamma-glutamyl transpeptidase-deficient mice. Lung 2001;179:319–330. [PubMed: 11976899]
66. Jean JC, Liu Y, Brown LA, Marc RE, Klings E, Joyce-Brady M. Gamma-glutamyl transferase deficiency results in lung oxidant stress in normoxia. Am J Physiol Lung Cell Mol Physiol 2002;283:L766–76. [PubMed: 12225953]
67. Van Klaveren RJ, Dinsdale D, Pype JL, Demedts M, Nemery B. Changes in gamma-glutamyltransferase activity in rat lung tissue, BAL, and type II cells after hyperoxia. Am J Physiol 1997;273:L537–47. [PubMed: 9316487]
68. Wang Y, Feinstein SI, Manevich Y, Ho YS, Fisher AB. Lung injury and mortality with hyperoxia are increased in peroxiredoxin 6 gene-targeted mice. Free Radic Biol Med 2004;37:1736–1743. [PubMed: 15528033]
69. Wang Y, Phelan SA, Manevich Y, Feinstein SI, Fisher AB. Transgenic Mice Overexpressing Peroxiredoxin 6 Show Increased Resistance to Lung Injury in Hyperoxia. Am J Respir Cell Mol Biol. 2006

70. Gregoire G, Derderian F, Le Lorier J. Selecting the language of the publications included in a meta-analysis: is there a Tower of Babel bias? J Clin Epidemiol 1995;48:159–163. [PubMed: 7853041]

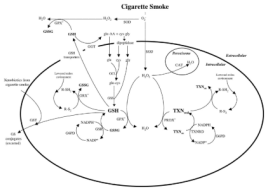

Figure 1.

Interaction of antioxidant enzymes in response to oxidative stress

*: this reaction also occurs without the listed enzyme

Abbreviations are as follows:

cys: Cysteine

CAT: Catalase

G6PD: Glucose-6-phosphate dehydrogenase

GCL: Glutamate-cysteine ligase

GGT: Gamma-glutamyl transferase

glu: Glutamate

GPX: Glutathione Peroxidase

GRX: Glutaredoxin

GSH: Reduced Glutathione

GSR: Glutathione reductase

GSS: Glutathione synthetase

GSSG: Oxidised Glutathione

GST: Glutathione S-transferase

$NADP^+$: Oxidised nicotinamide adenine dinucleotide phosphate

NADPH: Reduced nicotinamide adenine dinucleotide phosphate

PRDX: Peroxiredoxin

$R\text{-}SH_2$: Reduced thiol

$R\text{-}S_2$: Disulphide (could be mixed disulphides or glutathionylated proteins)

SOD: Superoxide dismutase

TXN_{red}: Reduced thioredoxin

TXN_{ox}: Oxidised thioredoxin

TXNRD: Thioredoxin reductase