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Role of GSTM1 in Resistance to Lung Inflammation

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Abstract

Lung inflammation resulting from oxidant/antioxidant imbalance is a common feature of many lung diseases. In particular, the role of enzymes regulated by the NF-E2-related factor 2 (Nrf2) transcription factor has recently received increased attention. Among these antioxidant genes, the glutathione S-transferase mu 1 (*GSTM1*) has been most extensively characterized since it has a null polymorphism which is highly prevalent in the population and associated with increased risk of inflammatory lung diseases. Present evidence suggests that *GSTM1* acts through interactions with other genes and environmental factors, especially air pollutants. Here, we review *GSTM1* gene expression and regulation and summarize the findings from epidemiological, clinical, animal and *in vitro* studies on the role played by GSTM1 in lung inflammation. We discuss limitations in the existing knowledge base and future perspectives and evaluate the potential of pharmacologic and genetic manipulation of the *GSTM1* gene to modulate pulmonary inflammatory responses.

Keywords

GSTM1 polymorphism; air pollution; lung inflammation; NrF2

1. Introduction

Chronic inflammation is a feature of many common lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD) [1,2]. There is now substantial evidence that oxidative stress plays an important role in the injurious and inflammatory responses central to many lung diseases. As a part of endogenous metabolism, as well as in response to challenge by inhaled environmental agents, the lung continuously generates reactive forms of oxygen, as well as free radical species [3]. Normally, moderate levels of oxidant species are thought to function as localized, transient and reversible signals to promote cell proliferation and survival. However, when the balance between oxidants and antioxidants shifts in favor of the former, from either an excess of oxidants, depletion of antioxidants, or decreased expression of antioxidant enzymes, oxidative stress occurs. Oxidative stress

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produces not only direct injurious effects in the lung through oxidation of proteins, DNA, and lipids, but some of these oxidized molecules (electrophils) also activate pro-inflammatory molecular mechanisms [4–6]. In addition, inflammation itself is an oxidative process that causes generation of reactive oxygen species (ROS) by activated cells. Inflammation and oxidative stress are thus intricately linked and a self-perpetuating cycle can occur when compensatory antioxidant processes are deficient.

The oxidant sources in the lungs include cell-derived endogenous and inhaled oxidants [7–9]. Lung cells are protected against oxidant challenge by well developed nonenzymatic and enzymatic antioxidant systems. The nonenzymatic antioxidants are low molecular weight compounds such as vitamins (vitamins C and E), beta carotene, uric acid, and glutathione (GSH). The enzymatic antioxidants include superoxide dismutases, catalase, glutathione peroxidase, heme oxygenase-1, small molecular weight redox proteins, and glutathione S-transferases (GSTs) [6].

The mammalian *GST* gene family consists of at least 16 genes assigned to eight protein enzyme classes based on their substrate specificity, structure, and kinetic behavior: alpha (GSTA), kappa (GSTK), mu (GSTM), omega (GSTO), pi (GSTP), sigma (*GSTS*), theta (GSTT), and zeta (GSTZ) [10–12]. The human *GST* genes are located on at least seven chromosomes [11]. They encode three major families of GST enzymes: cytosolic, mitochondrial, and microsomal proteins, of which the cytosolic GSTs constitute the largest family [13]. Most *GST* classes show a high degree of polymorphism and include several subtypes. Variant *GST* alleles have been identified within the general population and correlated with interindividual variations in protein level and enzymatic activity. The most extensively studied variant *GST*s include the *GSTM1* and *GSTT1* deletion (null) alleles and the *GSTP1* valine allele (Val/Val) [14]. The significance of *GSTM1* polymorphism in human was first recognized in cancer studies demonstrating that individuals carrying the *GSTM1* deletion allele were at increased risk for colon and lung cancers [15,16]. Other consequences of the genetic polymorphisms include potential differences in tolerance of toxic agents. To date, the GSTM1 is the most comprehensively studied among all GSTs, and is suggested to play an important role in the response to oxidative stress [17], particularly in the lung [18,19].

2. Genetic polymorphisms and function of *GSTM1*

The *GSTM* gene class is one of the most highly evolved mammalian *GST* classes. In mice there are 7 *GSTM* genes [13,20]. *GSTM1* is the most abundantly expressed among all of the *GST* genes in mouse kidney [21]. In humans, five *GSTM* genes are encoded by a 100-kb gene cluster on chromosome 1p13.3 arranged as 5′-*GSTM4-GSTM2-GSTM1-GSTM5-GSTM3*-3′ and are known to be highly polymorphic [22–24]. The *GSTM1* gene contains four different alleles allowing for several M1 class polymorphisms, designated as *GSTM1**0*, *GSTM1**A, GSTM1**B* and *GSTM1**1x2* alleles [25–27]. *GSTM1**0 (*GSTM1* null allele) is deleted, and homozygotes express no protein [28], while *GSTM1**A* and *GSTM1**B* differ by a single base in exon 7. The products of these latter two genes combine to form active, homo- and hetero-dimeric, enzymes [11,29–31]. A unique *GSTM1* variant *dGSTM1**1x2*, containing a duplicated *GSTM1* gene was identified among a Saudi Arabian population [32]. The *GSTM1* null allele arose from a recombination event during evolution between 2 highly homologous regions flanking this locus, resulting in deletion of a 20-kb segment [23,33]. The prevalence of *GSTM1* deletion polymorphisms varies across ethnic groups, from 18% to 66% (median, 50%), with the exception of Asians, for whom it is 38%–58% [34,35]. The cDNAs encoded by *GSTM1* and *GSTM2* share a remarkable 99% sequence identity [36]. The fact that *GSTM1* and *GSTM2* are physically linked suggests that the frequent deletion of the *GSTM1* locus is caused by unequal crossing-over [22,23].

Moreover, *GSTM1*A* and *GSTM3*B* are in linkage disequilibrium suggesting that in some cases, links between clinical phenotype and *GSTM1* genotypes may reflect polymorphism in *GSTM3* or, indeed other mu class *GST* genes [11,37]. In addition to genetic polymorphisms, the tissue distribution of GSTs is subject to great individual variation. Quantitative analysis of GSTM1 protein in various human tissues revealed that the liver is the richest source of cytosolic GSTM1. The other sources include testis, lungs, stomach, brain, kidneys, heart, breast, colon, pituitary, and the lymphocytes [25,38].

The major function of all GSTs has been considered to be the catalysis of the conjugation of endogenous and xenobiotic electrophiles (e.g. products of oxidative stress, environmental pollutants, and carcinogens) with GSH, thereby neutralizing their electrophilic sites, and rendering the products more water-soluble and excretable [39]. GSTs function as homo- and hetero-dimeric combinations of subunits within a class, but not between classes [38]. Each subunit with an estimated molecular mass of ~25 kDa contains a catalytically independent GSH-binding site in the amino-terminal domain and a hydrophobic substrate binding site in the carboxy-terminal domain [40].

In recent years a great deal of evidence has shown that GSTs, and in particular GSTM1 and GSTP1, also have several nonenzymatic functions, in which they regulate a number of cellular processes that contribute to the intrinsic ability of cells to survive genotoxic, metabolic and oxidative stress [40–42]. The best-characterized of these properties is the interaction with other functional cellular proteins, such as c-Jun N-terminal kinase (JNK), tumor necrosis factor receptor associated factor, apoptosis-signal regulating kinase (ASK) [43,44], protein kinase C (PKC), and tissue transglutaminase, resulting in significant functional alteration of the binding partners or post-translational modification and functional alteration of the GST protein itself [45].

3. GSTM1 expression and regulation

The expression level of GSTs has been shown to be a factor that determines the cellular sensitivity to a broad spectrum of toxic chemicals. However, the regulation of the expression of the GST gene families is complex, as they exhibit sex-, age-, tissue-, and species-specific patterns of expression [38,40]. For example, GSTP1, originally isolated from placenta, is found mainly in brain, lung, and heart; its expression in liver decreases during embryonic development, becoming very low in adult tissue [46–48]. GSTM1 and GSTT1 are found in relatively low concentrations in many organs including the lungs [49]. The expression of *GSTM* genes in human lung tissue is most intense in the bronchial epithelium, decreasing in the distal airways [50–52].

GST expression can be induced by a structurally diverse range of xenobiotics and, to date, at least 100 chemicals have been identified that induce GSTs [53,54]. Many of the GST inducers are themselves substrates for these enzymes, or are metabolized to compounds that can serve as GST substrates [38]. These inducers effect transcriptional activation of *GST* genes through either the antioxidant-responsive element (ARE) [55], a Barbie box element, the xenobiotic-responsive element, the GST P enhancer 1, or the glucocorticoid-responsive element, which may involve interactions with many transcription factors including aryl hydrocarbon receptor, CCAAT-enhancer binding protein-β, Maf, Nrl, Jun, Fos, hepatic nuclear factor-1, peroxisome proliferator–activated receptors, and nuclear factor kB (NFkB) [38,54]. The most significant development in this field has been the recent identification of a transcriptional factor, NF-E2-related factor 2 (Nrf2) that appears to bind to the ARE sequences and enhance transcription of GSTs [56–60]. Nrf2 is ubiquitously expressed in a wide range of tissues and cell types. Under normal conditions, Keap1 anchors the Nrf2 transcription factor within the cytoplasm targeting it for ubiquitination and proteasomal

degradation. When cells are exposed to chemopreventive agents and oxidative stress, a signal involving phosphorylation and/or redox modification of critical cysteine residues in Keap1 inhibits the enzymatic activity of the E3 ubiquitin ligase complex, resulting in decreased Nrf2 ubiquitination and degradation. As a consequence, free Nrf2 translocates into the nucleus and in combination with other transcription factors transactivates the AREs/electrophile response elements of many cytoprotective genes including *GSTM1*as well as Nrf2 itself [61]. In addition to transcriptional regulation, *GST* expression can also be controlled by posttranscriptional modulation of mRNA stability and protein modification [38,54]. Posttranslational modification of protein can also affect the GST activity and may, therefore, represent another mechanism of control. The activity of GSTM enzymes can be increased by treatment with ROS [38].

4. Association of GSTM1 with lung inflammation

Oxidant/antioxidant imbalance is a hallmark of lung inflammation [62]. Genetic polymorphisms associated with reduced activity of antioxidant enzymes including GSTs are therefore relevant to studies of lung inflammatory disease susceptibility. Moreover, the etiology of inflammatory lung diseases involves a complex interplay between genetic background and exposure to multiple environmental stimuli [63]. *GSTM1* gene has been a natural candidate in studies of susceptibility to inflammatory airway diseases with environmental components because of the high prevalence of the null polymorphism and its role in detoxification [64–68].

4.1 Epidemiological studies

Asthma and chronic obstructive pulmonary disease (COPD) are two common inflammatory lung diseases the incidence of which is increasing globally [9,69]. The association of *GSTM1* polymorphism with the risk of these two diseases has been widely investigated [67]. Asthma is a polygenetic or multifactorial illness characterized by chronic airway inflammation leading to reversible airflow obstruction [70,71]. *GSTM1* has been listed as one of at least 118 genes to date associated with an asthma-related phenotype [72]. Two common deletion polymorphisms of *GSTM1* and *GSTT1* genes have been associated with asthma in children and adults [73–76]. In addition, a single nucleotide polymorphism in *GSTM1* was also associated significantly with asthma in an African American urban population [77]. In this study, *GSTM1* rs412543 C carriers were almost 3 times as likely to have asthma compared to individuals without the C allele. *GSTM1* CCG haplotype was associated with a 3 fold increase in the odds of asthma. However, a negative association between the *GTSM1* null genotype and asthma phenotypes was also reported [75,78–82]. To resolve these conflicting results, a meta-analysis of *GSTM1* effects has been conducted but the conclusion did not favor a substantial role of *GSTM1* gene by itself in the development of asthma, likely due to extreme between-study heterogeneity and publication bias [83]. In a subsequent meta-analysis of antioxidant genes, the same authors concluded that the *GSTM1* association with asthma risk needs to consider gene-gene and gene-environment interactions [66]. The GSTM1 enzyme has overlapping substrate specificities with other GST enzymes, a deficiency in one isoform may be compensated by another. Thus, it is perhaps not surprising that children and adults with combined deletion polymorphisms of the *GSTM1* and *GSTT1* genes were found to be at a higher risk of developing asthma [73–76,84–86]. In addition, *GSTM1* can act as a modifier gene of *GSTP1*NAD(P)H:quinine oxidoreductase 1 (NQO1), or nitric oxide synthase genes for the risk of childhood asthma [87–92]. Besides gene-gene interaction, failure to account for environmental exposures might partly explain not only the heterogeneity of results across studies, but also the overall negative findings. Strong environmental effects on asthma phenotypes could mask modest genetic effects and, more importantly, gene-environment interactions could make the effects of *GSTM1* gene

become substantial only in the presence of oxidant exposures and not detectable at a population level [83].

Diisocyanate-induced occupational asthma is a dramatic example of gene–environment interactions causing lung inflammation [67]. The asthma risk related to diisocyanate exposure was associated with the *GSTM1* null genotype [93], which also involved the interaction between *GSTM1* null genotype and *N*-acetyltransferases [94]. The underlying mechanism might be due to the deficiency of biotransformation of isocyanates and excretion of metabolic products in the *GSTM1* null workers [95]. Aside from occupational exposure, air pollution has attracted much attention in its contribution to the development of asthma and asthma exacerbations [96,97]. Environmental tobacco smoke (ETS) or secondhand smoke, ambient air pollutants, such as ozone and diesel exhaust particles (DEPs), and endotoxin and/or other pathogen-associated molecular patterns are the ambient exposures studied most frequently for interactions with *GSTM1* polymorphisms in asthma [98–100]. Ozone is a gaseous air pollutant associated with an increased risk of asthma [97,101,102]. Asthmatic children with *GSTM1* null and *GSTP1* (Val/Val) genotypes appear more susceptible to developing respiratory symptoms related to ozone exposure [103]. ETS is an extremely potent oxidant mixture and important in the etiology of childhood asthma [8,98]. In the Children's Health Study cohort [104], the effects of in utero exposure to maternal smoking on asthma and wheezing occurrence were largely restricted to children with *GSTM1* null genotype. Among *GSTM1* null children, in utero exposure was associated with increased prevalence of early onset asthma, asthma with current symptoms, persistent asthma, lifetime history of wheezing, wheezing with exercise, wheezing requiring medication, and emergency room visits in the past year. Among children with *GSTM1* sufficient genotype, in utero exposure was not associated with asthma or wheezing. Others have shown that children who either had the *GSTM1* null genotype or were homozygous for the *GSTP1* (Val/Val) allele had increased risk of asthma at younger ages related to ETS, with an increased risk for decreased lung function in adolescence [105]. In addition, *GSTM1* deficiency was also shown to increase the adverse health effects including asthma and atopy of in utero and current ETS exposure [106]. In a recent study *GSTM1* null genotype itself was not significantly associated with asthma. However, the *GSTM1* null genotype could modify the association of the *NQO1* polymorphism with asthma in children exposed to ETS [91]. It should be noted that, to date, evidence for gene-air pollution interactions on asthma have been reported only in children [107,108]. Susceptibility to air pollution in early life may differ from that in adulthood [109]. For example, a recent study in adults showed no significant associations of *GSTM1* polymorphism with asthma either alone or in combination with *NQO1* SNPs. The lack of consistence with previous analyses could be related to the heterogeneity of effects in adults compared with children [109]. Intriguingly, there is emerging evidence that the risk conferred by *GSTM1* may be hereditable. The Children's Health Study cohort found that children of non-smoking mothers but with maternal grand-mother who smoked had a two-fold risk of asthma. A further study by the same group demonstrated that smoking-related effects on LINE1 methylation could be seen in *GSTM1* null children exposed to cigarette smoke [110].

COPD is another major inflammatory lung disease attributable to environmental exposures, especially cigarette smoking, and genetic susceptibility [69,111–113]. Candidate susceptibility genes have been selected in terms of putative pathogenesis of COPD such as the protease-antiprotease imbalance, oxidative stress and antioxidants, and cytokines and chemokines related to airway inflammation [114]. Most studies on these candidate genes have not been consistently replicated possibly due to genetic heterogeneity between different study populations, phenotypic differences, population stratification, multiple statistical testing, small sample sizes, and random error [111,115,116]. However, longitudinal studies of decline in lung function, meta-analyses of candidate gene studies, and family-based

linkage analyses suggest that variants in *GSTM1* and other candidate genes are associated with susceptibility to COPD [114,117–120]. Again, it is likely that *GSTM1* acts in an epistatic fashion. For example, although the polymorphism of *GSTM1, GSTT1* or *GSTP1* genes was found unlikely to be individually involved in the pathogenesis of COPD in a Chinese population [121], the combined *GSTM1* and *GSTT1* null genotype was a significant risk factor for developing COPD in Chinese smokers [122]. The co-existence of the *GSTM1* null allele with other genetic polymorphisms, such as the microsomal epoxide hydrolase exon-3 and homozygous *GSTP1* (Val/Val) alleles, also plays a significant role in the development of COPD [118,119,123–125]. In addition, the expression levels of *GSTM1* mRNA was significantly decreased in the COPD lung tissues compared with those in non-COPD tissues, and most of these decreases were significantly correlated with the degree of airflow limitation and cigarette smoking [126]. In a study on patients with non-small-cell lung cancer the presence of at least one active allele in *GSTM1* gene had a protective effect against the development of COPD [127].

4.2 Controlled human studies

An earlier study examining the effects of GSTM1 on ozone-induced serum clara cell protein CC16 (a biomarker of lung injury) release showed that increases in levels of CC16 and decreases in lung function were more pronounced in subjects with the combined *GSTM1* null and *NQO1* CC (wild-type) genotype in healthy volunteers [128]. In a controlled ozone exposure study (0.1 ppm for 2 h), the same group observed that subjects with the combined *GSTM1* null plus *NQO1* CC genotype had greater increases in biomarkers of inflammation and oxidative stress relative to subjects with other genotypes [129]. Our studies with healthy young adult volunteers also demonstrated that the *GSTM1* null genotype is associated with increased airways neutrophilic inflammation 24 hours after ozone exposure (0.4 ppm for 2 h) [130]. Interestingly, this association between the *GSTM1* null genotype and neutrophilic lung inflammation was not observed in healthy volunteers exposed to 0.06 ppm ozone [131]. In addition, no difference in inflammatory response (sputum neutrophil count) to ozone was observed between asthmatic patients with or without the combined *GSTM1* null and *NQO1* wild-type genotypes [132]. These results suggest that exposure conditions and subject health status can influence the evaluation on the role of *GSTM1* in lung inflammation.

In a separate study, we investigated whether the *GSTM1* null genotype is a risk factor for the development of exacerbated inflammatory responses to inhaled endotoxin [133]. It was shown that *GSTM1*-null healthy volunteers had significantly elevated neutrophil counts in their sputum after endotoxin challenge (20,000 endotoxin units). In contrast, *GSTM1* sufficient volunteers showed statistically significant, but blunted increases in neutrophils/mg sputum, suggesting that the *GSTM1* null genotype is a risk factor for the increased acute respiratory inflammatory response to inhaled endotoxin.

Particulate pollution, such as DEPs, is associated with the occurrence of asthma and allergy [134]. Individuals with the *GSTM1* null genotype showed enhanced nasal allergic responses in the presence of DEPs [100], indicating that GSTM1 could modify the adjuvant effect of DEPs on allergic inflammation. In addition, GSTM1 has been shown to be an important cytoprotective factor that reduces allergen-induced airway responses upon exposure to second hand smoke [135]. It should be noted however, that these studies on DEP and secondhand smoke only examined nasal responses and the upper airways and further verification of the results in the lung or lower airways is expected.

4.3 Animal studies

The use of knockout mice with a single disrupted gene, such as *GSTM1*, is expected to pinpoint the role of *GSTM1* in the pathogenesis of lung inflammation. To date, no studies

using *GSTM1* knockout mice have been reported in this field although *GSTM1* knockout mice have been used for other studies [136,137]. However, in a mouse model of acute lung injury, the transcription factor *Nrf2* was identified as a candidate gene that protected against oxidant injury via upregulation of antioxidant and phase II enzyme genes including *GSTM1* [138]. In another study the DEP-induced DNA adduct formation was enhanced in the lung of *Nrf2* knockout mice [139].

4.4 *In vitro* studies

The association of GSTM1 with inflammatory responses has not been extensively investigated *in vitro*. In a recent study, we showed that knockdown of *GSTM1* expression in a human bronchial epithelial cell line (BEAS-2B) enhances ozone-induced NFκB activation and interleukin 8 (IL-8) production [140]. This finding was confirmed in primary human bronchial epithelial cells from healthy subjects with *GSTM1*-sufficient or -null genotypes. Another study with human nasal epithelial cells showed that *Nrf2* knockdown correlated with a significant increase in influenza virus entry and replication [141].

5. Possible mechanisms of GSTM1-modulated lung inflammation

The possible mechanisms underlying GSTM1-modulated lung inflammation are largely unknown. It has been well recognized that oxidants initiate lung inflammation through their direct and/or indirect activation of stress kinases and redox-sensitive transcription factors, such as NFκB, leading to increased expression of a battery of distinct pro-inflammatory mediators [142].

As described previously, GSTM1 detoxifies electrophilic compounds by catalyzing their conjugation with reduced GSH. It is presumed that intermediate electrophilic metabolites, arising in the first phase of detoxification, are not metabolized in *GSTM1*-null asthmatic patients and are not excreted. These intermediate metabolites may damage cells and generate oxidative stress, and thereby contribute to the pathogenesis of asthma [85]. In addition to this well-characterized catalytic activity, recent evidence has suggested that GSTM1 may control oxidative stress and inflammation through the regulation of intracellular signaling pathways by its effects on certain small molecules or by protein-protein interactions with critical kinases [143]. The ligand-binding capacity of GSTM1 results in the negative regulation of signaling pathways through sequestration of signaling kinases [144]. For example, GSTM1 can interact with the N-terminal portion of ASK1, inhibiting oxidative stress-induced ASK1-dependent apoptosis [43]. ASK1 is a mitogen-activated protein kinase (MAPK) kinase kinase that activates the JNK and p38 pathways leading to cytokine- and stress-induced apoptosis [42,145]. Under normal conditions, ASK1 exhibits low activity because of its sequestration by GSTM1. This protein/protein interaction forms a GSTM1/ASK1 complex, which is dissociated under oxidative stress, leading to the release and activation of ASK1 [146,147]. Overexpression of GSTM1 has been shown to repress ASK1 activity and ASK1-induced apoptosis [44]. Mitogen-activated protein kinase/extracellular signal-regulated kinase kinase kinase 1 (MEKK1) is an important component in the stress-activated protein kinase pathway. GSTM1 has been shown to inhibit MEKK1 activity induced by cellular stresses through direct binding of MEKK1 [148], leading to suppression of MEKK1-mediated apoptosis. Recent evidence also showed GSTM1 could facilitate the addition of glutathione to cysteine residues in target proteins (*S*-glutathionylation) [149], regulating lung inflammation [150].

Knockdown of *GSTM1* could increase the production of ROS [151], and enhance the activity of inflammation-related transcription factor NFkB in ozone-exposed human bronchial epithelial cells, leading to IL-8 upregulation [140]. Interestingly, the interaction between broccoli consumption and *GSTM1* genotype resulted in complex changes to

transforming growth factor beta 1 and epidermal growth factor signaling pathways associated with inflammation [152].

6. Clinical implications of *GSTM1* manipulation and antioxidant supplementation

Given the critical role that oxidative stress plays in lung inflammation, induction of antioxidant enzymes could constitute a powerful potential chemopreventive approach against initiation and progression of lung inflammation. Sulforaphane is an isothiocyanate that activates the transcription factor Nrf2. The richest source of sulforaphane is from cruciferous vegetables and it is the most potent known naturally occurring inducer of the phase II enzyme genes [153]. It has been shown that sulforaphane significantly augmented expression of GSTM1 and its enzymatic activity, and sulforaphane pretreatment inhibited DEP-induced production of pro-inflammatory cytokines by human bronchial epithelial cells [154]. In animal models, it can reduce inflammation induced by agents such as cigarette smoke [155]. The induction of GSTM1 by sulforaphane could also block DEP-induced enhancement of immunoglobulin (Ig) E production in B cells [156]. Promisingly, in a human study, we showed that dietary sulforaphane safely and effectively induced expression of Phase II enzymes including GSTM1 in the upper airway of human subjects, suggesting the potential of enhancement of Phase II enzyme expression as a novel therapeutic strategy for oxidant induced lung diseases [157].

In either the presence or absence of GSTM1 enzyme, supplementation of antioxidants remains a therapeutic option to lung inflammation treatment. As the specific substrate of GSTM1, GSH is the predominant non-protein thiol in the cells and is a key player in the maintenance of the cellular redox status [158]. However, GSH is not well absorbed across the gastrointestinal tract [159]. Thus, oral supplementation does not improve glutathione status, nor reduce markers of oxidative stress in healthy adults, and thus routine supplementation may not offer health benefits in the absence of disease or oxidative challenge [160]. In contrast, supplementation of other antioxidants including vitamins C and E has been shown to have protective effects in asthmatic children with the *GSTM1* null genotype in Mexico City [18].

7. Conclusion and perspectives

In summary, from the overview of epidemiological studies, controlled inhalation studies, and the limited animal and *in vitro* studies currently available, GSTM1 appears to play an important role in the pathogenesis of lung inflammation. The inconsistent epidemiological results may be, on the one hand, due to limited sample size, ambiguous definition of clinical and pathological phenotypes, ethnic population grouping, population admixture (diversity), publication bias and other factors contributing to the large heterogeneity of studies [66,161,162]. On the other hand, intragenic, gene-environment, and gene-diet interactions also significantly confounds the evaluation of the association of GSTM1 with lung inflammation [65]. Thus, the approaches that consider potential interaction between and among genes, smoke exposure and antioxidant intake are needed to fully characterize the role of oxidant/antioxidant balance in pathogenesis [163]. In reorganization of the overlapping substrate specificities, simultaneous determination of all *GST* genotypes appears to be a prerequisite for reliable interpretation of the role of the GSTM1 in lung inflammation [29]. In addition, the role of epigenetic mechanisms needs to be considered along with gene-environment interactions, since epigenetic changes may have profound effects on disease susceptibility [1]. The completion of the Human Genome Project, the HapMap project, technological advances in genotyping and the potential of genome-wide association analysis has led to a rapid increase in the number of susceptibility candidate

genes for asthma and other environmentally induced inflammatory pulmonary diseases. Most of the studies, however, lack information on the mechanisms by which the polymorphisms could affect individual's susceptibility to these lung diseases. Confirmation of the functional consequences of specific genetic polymorphisms ultimately depends on performing functional studies [1,67]. In this case, *GSTM1* knockout mice and lung cells will provide unique tools for characterization of the role of GSTM1 in lung inflammation.

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List of Abbreviations

GSTM1	glutathione S-transferase mu 1
IL-8	interleukin 8
ROS	reactive oxygen species
IκBα	inhibitory protein
NFκB	nuclear factor κB
COPD	chronic obstructive pulmonary disease
GSH	glutathione
JNK	c-Jun N-terminal kinase
Ask	apoptosis-signal regulating kinase
PKC	protein kinase C
ARE	antioxidant-responsive element
NFkB	nuclear factor kB
NrF2	NF-E2-related factor 2
NQO1	NAD(P)H:quinine oxidoreductase 1
DEPs	diesel exhaust particles
ETS	environmental tobacco smoke
MAPK	mitogen-activated protein kinase
MEKK1	mitogen-activated protein kinase/extracellular signal-regulated kinase kinase kinase 1

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Highlights

- *GSTM1* gene expression, function, and regulation are reviewed.
- *GSTM1* acts through interactions with other genes and environmental factors.
- Pharmacologic and genetic manipulation of the *GSTM1* gene was discussed.