Glutathione as a Marker for Human Disease

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Contents

Abstract

Glutathione (GSH), often referred to as "the master antioxidant," participates not only in antioxidant defense systems, but many metabolic processes, and therefore its role cannot be overstated. GSH deficiency causes cellular risk for oxidative damage and thus as expected, GSH imbalance is observed in a wide range of pathological conditions including tuberculosis (TB), HIV, diabetes, cancer, and aging. Consequently, it is not surprising that GSH has attracted the attention of biological researchers and pharmacologists alike as a possible target for medical intervention. Here, we discuss the role GSH plays amongst these pathological conditions to illuminate how it can be used as a marker for human disease.

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1. INTRODUCTION

The biological antioxidant glutathione (GSH) is present in virtually all mammalian tissues and participates in many essential aspects of cellular homeostasis. GSH is a pleiotropic tripeptide composed of the amino acids glycine, cysteine and glutamic acid. Its synthesis is largely regulated by the available quantity of antecedent cysteine and the total concentration of GSH present, which negatively feedbacks on the enzymes that regulate its synthesis [1]. GSH is synthesized in a two-step ATP dependent process catalyzed by glutamylcysteine synthase (GCL) and glutathione synthase (GSS) (Fig. 1) [2]. In the first step, GLCL forms a peptide bond between glutamate and cysteine, glycine is then added with the enzymatic support of GSS (Fig. 1) [3].

GSH is the most abundant non-protein intracellular thiol, present in millimolar concentrations (Table 1). The active thiol group is present as part of the cysteine residue and participates in antioxidant functioning either directly by detoxifying reactive oxygen species (ROS) and reactive nitrogen species (RNS) or indirectly via GSH-dependent peroxidase-catalyzed reactions [4]. Thus, GSH participates in many important detoxification reactions and has a high capacity for the prevention of oxidative stress-induced cellular damage. Therefore, the intracellular redox state characterized by the levels and ratio of oxidized (GSSG) and reduced (GSH) glutathione is considered to be an important indication of cellular health. This is largely because GSSG, is toxic and therefore must be rapidly

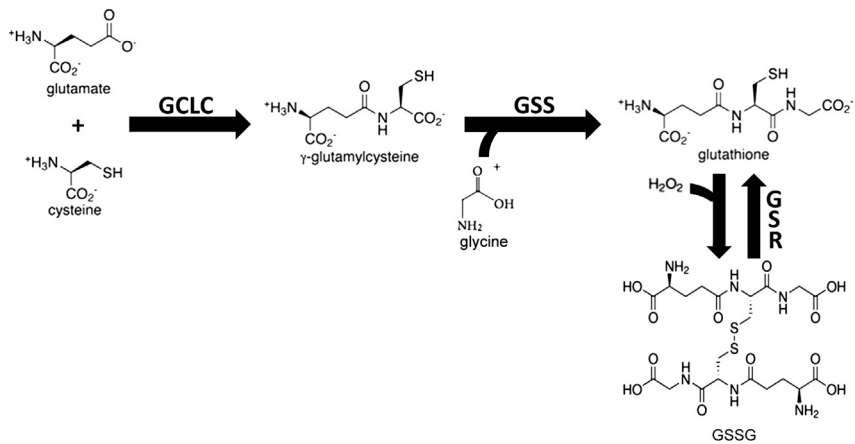

Figure 1 GSH synthesis pathways

Table 1 Human Intracellular Thiols

Thiol Name	Subcellular Localization	Concentration	Antioxidant
Cysteine (Cys)	Cytoplasm, Mitochondria	212 ± 23 μM	Yes
Cysteinylglycine (CysGly)	Cytoplasm	65.7 ± 4.6 μM	Yes
Homocysteine (Hcys)	Cytoplasm	9.4 ± 7.3 μM	No
Glutathione (GSH)	Cytoplasm, Mitochondria, Endoplasmic- reticulum	1–10 mM	Yes

converted back into GSH by the enzyme glutathione reductase (GSR). Subsequently, the ratio of GSSG to GSH under non-pathological conditions is typically about 1% [5].

While an increase in GSH seems to be a universal cellular response to oxidative stress, some diseases appear to be exacerbated by decreased GSH levels. About 10%–15% of intracellular GSH is located within mitochondria, and dysfunction of the mitochondrial electron transport chain is often associated with abnormally low levels of GSH [6]. Consequently, mitochondrial GSH depletion will archetypically lead to increased levels of ROS, and categorical ATP depletion. As a consequence, cells may alter their prototypical apoptotic response in favor of necrosis [7]. Other than conditions associated with mitochondrial impairment, various additional diseases are also associated with dysregulated GSH synthesis or alterations in its concentration. Diminished GSH expression has been demonstrated a common feature among numerous pathological conditions including: diabetes, cancer, HIV, liver diseases, TB, uremia, pulmonary fibrosis, Friedreich ataxia, Alzheimer disease, Parkinson disease, amyotropic lateral sclerosis, and Rett syndrome (Table 2) [8–17]. Therefore, this article reviews various pathological conditions caused due to dysregulated levels of GSH which can have potential applications as a marker for human disease.

2. THE GLUTAMYLCYSTEINE SYNTHASE ENZYME

GCL is the rate limiting enzyme in the GSH synthesis pathway [18]. GCL comprises of the catalytic subunit (GCLC) and the modulating subunit, GCLM, and is responsible for linking glutamate and cysteine together to form γ–glutamylcysteine [19]. GCL deficiency has been implicated in hemolytic anemia, a disease in which red blood cells are prematurely destroyed and removed from the body [20–22]. Additionally, cholestasis, a disease that alters the flow of bile from the liver, has been

Table 2 Conditions With Altered GSH Concentrations

Condition	GSH Levels
Parkinson's Disease	Low
Alzheimer's Disease	Low
Friedreich Ataxia	Low
Rett Syndrome	Low
Myocardial Infarction	Low
Cancer	Low
HIV	Low
Ageing	Low
Pulmonary Fibrosis	Low
Uremia	Low
Tuberculosis	Low
Rheumatoid Arthritis	Low
Type 2 Diabetes Mellitus	Low

connected to decreased GCL levels [23]. Furthermore, after the research group restored the levels of GCL with ursodeoxycholic acid treatment, they observed notable disease regression [23]. In Diabetes Mellitus, GCL expression has been shown to be mediated by insulin release aiding in the protective effects against hyperglycemia induced apoptosis [24]. Although the exact mechanism has not yet been established, individuals suffering from alcoholic liver disease also show a marked decrease in GCL levels [25]. Additionally, it has also been demonstrated that patients going through dialysis due to uremia often present decreased levels of GSH, which is thought to be attributed to the diminished levels of GCL amongst these patients as well [8].

3. NRF2'S RELATION TO GLUTATHIONE VIA ANTIOXIDANT RESPONSE ELEMENTS

Compromised levels of GSH can be an important indicator of disease due to its significance in maintaining redox balance throughout the body. As ROS levels increase during metabolism and immune responses, antioxidant levels such as GSH, must likewise, escalate to compensate. Therefore, to ensure optimal levels of GSH, there needs to be upstream regulators to increase or decrease de novo synthesis and recycling of the molecule [26–28]. One of the most important of these antioxidant regulators is nuclear factor E2-related factor 2 (Nrf2).

Nrf2 is a transcription factor associated with the antioxidant response element (ARE), promoter region of various genes coding for antioxidant-associated enzymes [28]. At redox equilibrium, Nrf2 is restricted to the cytoplasm of cells by Kelch-like ECH-associated protein 1 (Keap1). Keap1, an E3 ubiquitin, facilitates proteasome-dependent degradation of Nrf2 [29–31]. Thus, in redox equilibrium, this mechanism prevents Nrf2 from enhancing the transcription of antioxidant-associated enzymes. However, during oxidative stress, Keap1's dissociation from Nrf2 is favored by various Keap1 inhibitors. Once dissociated from Keap1, Nrf2 is allowed to translocate into the nucleus of the cell and bind to the ARE of antioxidant-associated gene promoters [32–35]. The subsequent increase in transcription will consequently upregulate antioxidant levels, such as GSH, to re-establish the redox equilibrium. In a state of inflammation or disease, ROS levels will likely be elevated higher than normal. Subsequent to this systemic redox imbalance, Nrf2 will be allowed to translocate into the nucleus and promote transcription of GCL, GSS, and GSR, which will in turn not only increase the de novo synthesis of GSH but also increase the recycling of GSSG to GSH [36].

Although the Nrf2 pathway is a key component of oxidative relief, it is not the sole contributor, and thus must also be regulated. Other antioxidants such as Vitamin C, negatively correlate with and dictate the levels of intracellular Nrf2 [35]. Vitamin C has been shown to interrupt the localization of Nrf2 to the nucleus, preventing ARE binding. This leads to an increase in ubiquitin-mediated degradation of the transcription factor, and a subsequent reduction in the transcription of antioxidant-related intermediaries [37]. Therefore, the inhibition of the Nrf2 pathway ultimately modulates the levels of GSH production.

4. GLUTATHIONE RELATION TO VITAMIN D

Vitamins are a form of micronutrient needed for regular biological functionality. Vitamin deficiency will often lead to increased susceptibility to medical conditions such as TB, cardiovascular disease, and even cancer. Historically, Vitamin C and Vitamin D were used during the pre-antibiotic era to help treat myriad medical conditions. Recently however, vitamins have been re-investigated to further understand their potentiality in disease acquisition and prevention.

Vitamin D, a fat-soluble molecule, is used to regulate calcium and phosphate metabolism. While Vitamin D itself does not possess any direct

antimicrobial mechanisms it can however, modulate host defense machinery, inflammation, and repair through two suggested mechanisms. The first mechanism suggests Toll-like Receptor (TLR) mediate the upregulation of the Vitamin D receptor (VDR) allowing for activated macrophages to produce the active form of Vitamin D, 1,25-dihydroxy vitamin D (DHVD) [38–40]. As a result, DHVD will interact with VDR and activate the antimicrobial peptide cathelicidin [38–40]. In addition, DHVD enhances intracellular GSH quantities and significantly reduces nitrite production induced by lipopolysaccharides [41]. DHVD has been reported to inhibit the synthesis of inducible nitric oxide synthase (iNOS), an enzyme induced during various diseases, such as AIDS and infections [42]. Vitamin D is an important factor in the upregulation of GSH pools as well. The specific activity of gamma-glutamyl transpeptidase (gamma-GT), an enzyme involved in GSH metabolism, is also regulated by DHVD [41]. The second proposed antimicrobial mechanism is that Vitamin D can downregulate tryptophan-aspartate-phagosome coat protein (TACO). TACO permits infectious agents such as *Mycobacterium tuberculosis* (*M. tb*) to avoid phagolysosomal fusion within macrophages [43]. The result of Vitamin D regulated TACO downregulation thus promotes intracellular pathogenic degradation via increased lysosomal fusion with infested phagosomes. Furthermore, recent research suggests Vitamin D can upregulate GCLC and GSR production, thereby enzymatically eliciting the upregulation of GSH biosynthesis [44]. Therefore, not only is Vitamin D a beneficial micronutrient in regards to parthenogenic diseases and infections, it also upregulates levels of available and usable GSH as well.

5. GLUTATHIONE'S ROLE IN TUBERCULOSIS

It is reported that GSH levels are significantly diminished among the peripheral blood mononuclear cells (PBMCs) and red blood cells (RBCs) of individuals with pulmonary tuberculosis (TB) compared to their healthy counterparts [45]. This decrease in GSH is also significantly correlated with increased levels of free radicals, production of pro-inflammatory cytokines and intracellular *M. tb* viability [36,46–50]. GSH possesses direct anti-mycobacterial effects which assists in infection control [46]. It is well established that macrophages are the major innate immune cell type responsible for combating an *M. tb* infection. Once macrophages are activated, they release antimicrobial molecules such as RNS, which is toxic to *M. tb*. Nitric

oxide (NO), an essential member of the RNS family has been shown to significantly inhibit *M. tb* growth, however, its activity is short lived as it becomes detoxified rapidly [51–55]. Interestingly, GSH can become a carrier molecule for NO by forming S-nitrosoglutathione (GSNO), which previous studies have demonstrated has direct mycobactericidal effects [56–58].

Natural killer (NK) cells perform a critical role in the innate immune response to intracellular bacterial infections, especially *M. tb*. Research has shown that the cytolytic activity of NK cells can become critically impaired due to low levels of GSH [59,60]. Studies have also demonstrated that NK cells treated with N-acetyl cysteine (NAC), a precursor molecule to GSH synthesis, can cause significant recovery of cytolytic activity, which indicates that GSH plays an important role in enhancing NK functionality against *M. tb* [59,60].

GSH has been shown to modulate cytokine profile expression [45,60–63]. It has been reported that the in vitro treatment of whole blood with NAC results in increased IFN-γ production, thereby enhancing the Th1 cell response against *M. tb* [64–66]. Studies have demonstrated that higher Th1 and lower Th2 responses help control *M. tb* growth [65,67–69]. This indicates that intracellular GSH levels are important in modulating Th1 cytokines and aid in *M. tb* clearance.

Dendritic cells (DCs) are potent antigen presenting cells (APCs) which act as a bridge between innate and adaptive immunity. GSH has also been revealed to play a role in promoting DC maturation. Experimental evidence from murine model suggests that the down regulation of GSH results in decreased IL-12 production by DCs [70]. IL-27 another cytokine released by DCs is responsible for native T-cells differentiation. It has been indicated that there is a correlation between the intracellular levels of GSH and the production of IL-27 [71]. Accordingly, GSH can regulate many cytokines and cell types in response to an *M. tb* infection.

6. GLUTATHIONE DEFICIENCY AMONG HIV INFECTED INDIVIDUALS

HIV-mediated immune suppression increases susceptibility to acquiring opportunistic infections, one of which being TB. According to the World Health Organization, the risk of developing TB is estimated to be anywhere from 16 to 27 times greater in people living with HIV than among those without HIV infection [72]. TB is the most common illness presented

among individuals living with HIV [73]. This phenomenon is especially evident in developing countries where the rate of HIV infection is significant. There were an estimated 1.2 million new TB cases among HIV positive individuals, in 2014, and roughly 74% of these individuals live in sub-Saharan Africa [73]. There is also an increased risk of developing drug-resistant TB among individuals living with an HIV co-infection [73]. An adequate response to TB requires functioning host defense mechanisms. HIV primarily targets host CD4+ T cells and macrophages, resulting in immune suppression, characterized by gradually decreasing CD4 T cell counts.

One of the mechanisms associated with this immunosuppression is a decrease in the levels of GSH. Studies have shown that the levels of GSH are significantly compromised in the immune cells derived from the peripheral blood of HIV-infected individuals [46,48,51,64,68,74,79]. This decrease in the levels of GSH was also shown to correlate with increased intracellular *M. tb* survival [46,48,51,64,68,74,79]. Similar findings i.e., diminished levels of GSH were noted upon analysis of brain tissue isolated from HIV-infected individuals [74]. The proposed mechanism for this decrease in GSH levels is a decline in the levels of enzymes involved in the synthesis of GSH [51]. With decreased levels of GSH, an HIV infected individual has an increased risk for developing an active *M. tb* infection. Additionally, significant decreases have been observed in the levels of immune-stimulatory cytokines (IL-2, IL-12, and IFN-γ) as well as increased levels of immune-suppressing cytokines (TGF-β, IL-6, IL-10) among HIV-positive individuals [64]. Furthermore, liposomal GSH (Readisorb) supplementation for 3 months resulted in restoration in the levels of immune-stimulatory and a significant decrease in the levels of immune-suppressing cytokines among these individuals [64]. Furthermore, another recentstudy demonstrated that liposomal GSH supplementation in AIDS patients can restore redox and cytokine balance thereby improving their immune functionality [75].

7. GLUTATHIONE DEFICIENCY AMONG DIABETIC INDIVIDUALS

The incidence of diabetes has increased worldwide due to population ageing, urbanization, changes in diet and reduced physical activity patterns resulting in obesity, especially in populations where TB is most prevalent [76]. Diabetes is the leading worldwide cause of blindness, end-stage renal

diseases, and amputations, as well as macrovascular complications including myocardial ischemia and strokes. A common feature of these pathways that mediate tissue damage is increased oxidative stress marked by elevated levels of ROS [77].

Oxidative stress and ROS formation are significantly increased by uncontrolled hyperglycemia [78]. A characterization of diabetes mellitus includes hyperglycemia caused by insulin resistance, which accounts for roughly 90%–95% of the total prevalence of diabetes [79]. There is growing evidence that diabetes mellitus is an important risk factor for TB and might affect disease presentation and treatment response [80]. Individuals with Type 2 Diabetes Mellitus (T2DM) have three times the risk of developing TB, and there are now more individuals with TB-T2DM co-morbidity than TB-HIV co-infection [81,82].

These conditions point to a compromised immune system, and patient predisposition to infections for which cell-mediated immunity has a pivotal role. Decreased levels of GSH is likewise, associated with diabetes.

8. GLUTATHIONE DEFICIENCY AS A RESULT OF AGEING

Ageing is characterized as the gradual dysfunction of molecular and cellular mechanisms that culminate in diminished physiological functioning and an increased susceptibility to disease [83–85]. Mitochondrial dysfunction is a hallmark of the ageing process that is associated with an increase in oxidative stress and a decrease in antimicrobial defenses [83,86–89]. Mitochondrial capacity to mitigate damage due to oxidative stress and attenuate microbial invasion is dependent upon its ability to produce endogenous antioxidants, among which GSH is the most abundant [87]. However, intracellular GSH concentrations have been shown to decline with age [90–93]. Therefore, GSH deficiency can potentiate the underlying mechanisms which contribute to the age-induced elevation of oxidative stress as well as increased susceptibility to microbial infections [87,93].

Evidence suggests that the GSH deficiency which occurs in ageing cells is attributed to a lack of GSH precursor amino acids, cysteine and glycine [85,90,93]. This implies that the decreased availability of cysteine and glycine is a potential consequence of the deceleration of the overall protein turnover which occurs with ageing [94]. However, the exact metabolic mechanisms responsible for the diminished concentrations of non-essential amino acids among ageing cells is not fully understood and needs further

elucidation. Additionally, GCL experiences a decrease in its affinity (increased Km) for its cognate substrates due to an age-related accumulation of homocysteine, a toxic trans-sulfuration/GSH biosynthesis pathway intermediate [85]. Consequently, the combination of the age-related deficiency of GSH precursors and a loss in GCL catalytic activity results in a reduction of de novo GSH biosynthesis which ultimately inhibits mitochondrial defense. Thus, ageing cells which synthesize inadequate amounts of GSH will experience irreversible cell damage in consequence [87,93]. Furthermore, studies have shown that inducing an acute GSH deficiency can not only causes mitochondrial damage but ultimately result in cell death, substantiating the protective role of GSH among aging cells [95,96].

In addition to elevated oxidative stress, ageing is associated with an altered abundance of circulating inflammatory cytokines, immune cell dysfunction, and impaired microbial clearance mechanisms [89,97,98]. Collectively, these cellular changes contribute to an age-related decline in immune cell response to microorganisms, such as *M. tb* [89]. Due to a diminution in T cell and macrophage functioning, ageing correlates with an increased risk of developing TB stemming from primary infection or from reactivation of a latent infection [87]. Given the abundance of evidence substantiating the role of GSH in mediating an *M. tb* infection, the natural age-related deficiency of GSH is a plausible explanation for the increased susceptibility to TB among the elderly.

9. SMOKING RELATION TO GLUTATHIONE DEPLETION AND CANCER SUSCEPTIBILITY

Cigarette smoking still remains the leading avoidable cause of morbidity and mortality and is attributed to roughly 12% of global deaths among adults aged 30 years and over [99]. Moreover, cigarette smoke (CS) is credited as a top risk factor for cancer, cardiovascular disease, and respiratory diseases [99–101]. Inhaled CS induces oxidant imbalance by release of free radicals, ROS, and RNS in the lungs. These oxidative agents have the capacity to overwhelm the normal redox balance, causing decreases in antioxidant levels which promotes more oxidative stress and eventually tissue damage [102]. Additionally, CS in combination with low levels of GSH has also been shown to increase pro-inflammatory cytokine synthesis [103]. GSH in lung epithelial tissue is among the first-line defenses against a large number of the reactive species found in CS [103]. Long term tobacco exposure can cause GSH levels in multiple tissues to become significantly

decreased, leaving the individual susceptible to a myriad of illnesses including *M. tb* infection and cancer [48,103,104].

Total glutathione (TGSH) levels, which includes GSSG, are higher among individuals who smoke as is an increase in GSH peroxidase activity. This suggests a greater demand for GSH to sacrifice itself into GSSG, hence the elevated amounts of TGSH [105]. In young smokers, below age 50, adaptive compensation allows for GSH levels to respond by upregulating to meet the oxidative demand in response to CS. However, as aforementioned, older individuals experience a significant depletion in GSH with age and are more susceptible to the adverse effects caused by CS. Once endogenous protective mechanisms are compromised such as the depletion of GSH, cells are left vulnerable to damage and infections. After being engulfed by macrophages, cell mediated immunity is important for preventing an active *M. tb* infection, and any conditions which weaken the immune system cause greater susceptibility to opportunistic pathogens including *M. tb* [106]. An estimated 7% of all deaths due to TB can be attributed to the effects of tobacco [99].

In addition to the role GSH levels have in regard to tobacco related susceptibility to *M. tb* infection, it is also implicated in cancer susceptibility as well [99–101]. In Hepatocellular Carcinoma (HCC) GSH acts as an endogenous mitochondrial antioxidant by scavenging ROS in order to maintain a balanced mitochondrial redox state. Additionally, CS and nicotine can upregulate the activity of CYP2E, a metabolic liver enzyme whose induction is also associated with ROS generation [104]. Long term tobacco exposure decreases hepatic GSH, which increases the likelihood of developing HCC [104]. Accordingly, an improper redox state due to decreased levels of GSH can lead to carcinogenesis.

10. CURRENT GLUTATHIONE DETECTION METHODS

In vivo detection of GSH has been demonstrated in a variety of ways. One of these methods involves measuring the levels of GSH within the brain by proton (^{1}H) magnetic resonance spectroscopy (MRS). Due to overlap of ^{1}H resonance peaks of GSH in addition, to other metabolites, spectral editing techniques such as J-difference spectroscopy, point-resolved spectroscopy localization sequence (PRESS), MEshcher-GArwood-PRESS (MEGA-PRESS), and double quantum coherence filtering (DQF) have been developed to allow for more reliable quantification of GSH [107–110]. Furthermore, the linear combination model (LCModel) analysis

provides an unbiased quantification of signal contribution from such editing [111]. The quality of DQF combined with PRESS is thought to be less sensitive to patient motion as it utilizes a single shot nature in contrast to DQF alone, J-difference spectroscopy, and MEGA-PRESS [110]. MRS imaging detection of stable isotope-labeled GSH has also been used to track GSH metabolism and heterogeneity within tumor tissue following infusion of [2−13C] glycine in rats [112]. Electron paramagnetic resonance imaging is another imaging technique that has been utilized for the detection of GSH through a redox map with the use of a nitroxide imaging probe, 3-methoxycarbonyl-2,2,5,5-tetramethyl-piperidine-1-oxyl (MCP) [113]. In the presence of ascorbates, GSH increases the ascorbate-induced reduction of nitroxides, and therefore GSH levels can be estimated [113]. Another method involved in the in vivo detection of GSH is through the use of a galactose-appended naphthalimide, a targetable ligand for hepatic thiol imaging through its display of a fluorescence emission feature that is induced by exposure to free endogenous GSH [114]. Similar to the highly sensitive in vitro biosensor of GSSG in plasma samples, the in vivo biosensor of GSSG was developed using glutathione reductase (GR) and NADPH immobilized onto a nanocomposite conducting polymer film and inserted into the liver of rats. While this method requires incision and insertion within the liver, it has attractive features in that this detection method does not require a specific label and is relatively cost efficient [115]. Finally, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) has been used to detect single nucleotide polymorphisms of the glutamate-cysteine ligase subunit catalytic (GCLC) gene, particularly 129C/T, which has been reported to have an association with an increased risk factor for oxidative stress [116].

11. CONCLUSION

GSH depletion contributes to pro-inflammatory cytokine release, free radical formation, inhibition of macrophage and natural killer cell functionality along with disease susceptibility and progression. Furthermore, GSH can regulate a vast array of cytokines and other biological molecules related to the immune system. It is evident that GSH participates in numerous intracellular homeostatic roles and thus, its use as a biomarker has tremendous potential. Therefore, further investigation should be pursued to evaluate GSH as an early detection method for human disease and pathology.

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