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Diverse cellular and organismal functions of the lysosomal thiol reductase GILT

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Abstract

Gamma-interferon-inducible lysosomal thiol reductase (GILT) is the only enzyme known to catalyze disulfide bond reduction in the endocytic pathway. GILT facilitates the presentation of a subset of epitopes from disulfide bond-containing antigens. Enhanced presentation of MHC class II-restricted epitopes alters central tolerance and modulates CD4+ T cell-mediated autoimmunity. Improved cross-presentation of viral epitopes results in improved cross-priming of viral-specific CD8+ T cells. GILT regulates the cellular redox state. In GILT−/− cells, there is a shift from the reduced to the oxidized form of glutathione, resulting in mitochondrial autophagy, decreased superoxide dismutase 2, and elevated superoxide levels. GILT expression diminishes cellular activation, including decreased phosphorylated ERK1/2, and decreases cellular proliferation. GILT enhances the activity of bacterial hemolysins, such as listeriolysin O, and increases bacterial replication and infection. GILT expression in cancer cells is associated with improved patient survival. These diverse roles of GILT are discussed.

Keywords

GILT; IFI30; antigen presentation; autoimmunity; cancer; redox

Introduction

Gamma-interferon-inducible lysosomal thiol reductase (GILT; gene name: *IFI30*) catalyzes the reduction of disulfide bonds. The active site of GILT consists of a thioredoxin-like CXXC motif (Arunachalam et al., 2000). GILT is constitutively expressed by many antigen presenting cells, including B cells, bone marrow-derived dendritic cells and monocytes/macrophages (Arunachalam et al., 2000; Lackman et al., 2007; Maric et al., 2001; Phipps-

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Yonas et al., 2013a). In addition, low levels of constitutive GILT expression are detected in T cells and fibroblasts (Barjaktarevic et al., 2006; Bogunovic et al., 2008; Maric et al., 2009). GILT expression is upregulated by IFN-γ in these and other cell types, such as endothelial cells and tumor cell lines (Haque et al., 2002; Lackman et al., 2007; O'Donnell et al., 2004). IFN-γ engagement of it cell surface receptor results in the activation of JAKs and STAT1. STAT1 is responsible for IFN-γ-inducible GILT expression and negatively regulates constitutive GILT expression (O'Donnell et al., 2004; Srinivasan and Maric, 2011). Unlike MHC class II and other components of this pathway, neither constitutive nor inducible GILT expression is mediated by class II transactivator (CIITA) (O'Donnell et al., 2004). GILT is synthesized as a 35 kDa precursor, which is targeted to the endocytic pathway by the mannose-6-phosphate receptor (Arunachalam et al., 2000). In early endosomes, N- and C-terminal pro-peptides are cleaved to yield a 28 kDa mature form that resides in the late endosomes and lysosomes (Arunachalam et al., 2000). GILT is the only known reductase in the endocytic pathway. A portion of precursor GILT is secreted (Arunachalam et al., 2000; Lackman et al., 2007), but the biological functions of secreted GILT are poorly defined. This review will focus on the diverse roles of GILT in the endocytic compartments at the cellular and organismal levels, as summarized in Figure 1.

GILT in antigen presentation

GILT enhances the MHC class II-restricted presentation of a subset of epitopes from disulfide bond-containing antigens. Studies using T cell hybridomas have identified GILT-dependent class II epitopes in the model antigen, hen egg lysozyme (Maric et al., 2001), self and melanoma antigens, tyrosinase and tyrosinase-related protein 1 (TRP1) (Haque et al., 2002; Rausch et al., 2010), autoantigen myelin oligodendrocyte glycoprotein (MOG) (Bergman et al., 2012), HIV-1 gp120 envelope protein (Sealy et al., 2008), and dust mite allergen Der p 1 (West et al., 2013). An intact reductase active site of GILT is required to facilitate MHC class II-restricted antigen processing (Hastings et al., 2006). The GILT dependence of an epitope is not necessarily correlated with the presence or proximity of a disulfide bond in/near the epitope (Maric et al., 2001). Instead, GILT-independent epitopes tend to be surface exposed, and GILT-dependent epitopes tend to be buried, such that the requirement for GILT appears to depend on whether the epitope requires reduction to be exposed for MHC class II binding (Maric et al., 2001). A mass spectrometric analysis of MHC class II bound peptides from wild-type and GILT−/− resting splenocytes reveals that the bulk of the self peptide repertoire at steady state is GILT-independent with 5.5% of peptides more abundant in wild-type samples, 2% of peptides unique to GILT−/− samples, and 3.5% of peptides at least 10-fold more abundant in GILT−/− samples (Bogunovic et al., 2010).

GILT facilitates the cross-presentation of exogenous viral antigens on MHC class I (Singh and Cresswell, 2010). GILT is required for the cross-presentation of an epitope from the herpes simplex virus-1 (HSV-1) integral membrane protein glycoprotein B (gB), but not direct MHC class I-restricted presentation of the gB epitope or cross-presentation of an epitope from an HSV-1 cytosolic protein. GILT's reductase activity is required to facilitate cross-presentation, and gB is a direct substrate for GILT. Furthermore, phagosomal proteolysis and proteosomal processing are required for cross-presentation. These data

suggest that GILT-mediated reduction may facilitate proteolysis in the phagosome and translocation from the phagosome into the cytosol.

GILT modulates the function of cathepsin S, a cysteine protease which mediates cleavage of invariant chain in MHC class II-restricted processing and proteolysis of large polypeptides in MHC class II-restricted presentation and cross-presentation on MHC class I. On one hand, we have shown that GILT's reductase activity facilitates the degradation of cathepsin S (Phipps-Yonas et al., 2013b). On the other hand, GILT maintains the proteolytic activity of cathepsin S (Balce et al., 2014). The impact on antigen presentation of these opposing roles for GILT on cathepsin S remains to be determined.

Thus, GILT facilitates the MHC class II-restricted presentation and cross-presentation of a subset of epitopes from disulfide bond-containing antigens.

GILT in cellular redox state

GILT maintains the cellular redox state which has implications on autophagy, cellular activation, and proliferation. The absence of GILT in fibroblasts and T cells decreases the expression, stability and activity of superoxide dismutase 2 (SOD2) (Bogunovic et al., 2008; Chiang and Maric, 2011; Maric et al., 2009), the mitochondrial enzyme which converts superoxide to hydrogen peroxide. GILT−/− cells have increased oxidative stress with higher levels of superoxide (Bogunovic et al., 2008; Chiang and Maric, 2011; Maric et al., 2009). Altered oxidation of the non-enzymatic antioxidant glutathione provides a link between lysosomal GILT and mitochondrial SOD2 (Chiang and Maric, 2011). In GILT−/− cells, there are decreased levels of reduced glutathione (GSH) and an increased ratio of the oxidized (GSSG) to reduced form. In the absence of GILT, mitochondrial membrane potential decreases and autophagy is increased, which may lead to diminished SOD2 and elevated superoxide. The absence of GILT in fibroblasts and T cells results in increased phosphorylation of the redox-sensitive extracellular signal-regulated kinase 1/2 (ERK1/2) and increased cellular proliferation (Barjaktarevic et al., 2006; Chiang and Maric, 2011; Maric et al., 2009).

GILT in infection

GILT's role in antigen presentation may alter the host response to infection. As discussed above, GILT is required for the presentation of certain epitopes from viral glycoproteins on MHC class II and cross-presentation on MHC class I (Sealy et al., 2008; Singh and Cresswell, 2010). In addition, GILT is required for cross-priming of viral-specific CD8+ T cells in vivo during HSV-1 and influenza A infections (Singh and Cresswell, 2010). The impact of GILT's alteration of MHC class I and II-restricted epitopes and CD4+ and CD8+ T cell responses on the overall host response to infection remains to be determined.

GILT also alters microbial pathogenesis independent of antigen processing. GILT is a critical host factor that facilitates the activity of bacterial hemolysins (Singh et al., 2008). During infection with *Listeria monocytogenes*, the bacterium is phagocytosed by macrophages and evades destruction using the pore-forming listeriolysin O to escape into the cytosol. GILT-mediated reduction is required for listeriolysin O activity. In the absence

of GILT, bacterial replication in macrophages is diminished due to delayed phagosomal escape, and mice are resistant to *L. monocytogenes* infection. Secreted precursor GILT can activate streptolysin O, a virulence factor of *Streptococcus pyogenes*, suggesting that secreted GILT may enhance hemolysin-mediated tissue damage. Furthermore, GILT expression confers resistance to infection with dengue virus (Teramoto et al., 2013). Resistance to dengue viral translation and replication in GILT-expressing fibroblasts correlates with decreased autophagy.

GILT in T cell development, tolerance and autoimmunity

We have investigated the role of GILT in modulating CD4+ T cell development, tolerance and autoimmunity to a GILT-dependent epitope of the self and melanoma antigen TRP1, using the MHC class II-restricted TRP1-specific TCR transgenic (TRP1Tg) mouse strain. Transfer of naïve TRP1-specific T cells into GILT-deficient recipients results in autoimmune vitiligo with reduced severity and delayed onset compared with transfer into GILT-expressing recipients (Rausch et al., 2010). The onset of vitiligo in TRP1Tg mice is associated with an increased percentage of T cells with an effector memory phenotype, and there is a decrease in effector memory T cells in the absence of GILT. These data suggest that GILT expression in host antigen presenting cells improves the efficiency of MHC class II-restricted presentation of TRP1 resulting in enhanced T cell activation and autoimmunity.

GILT is required for the negative selection of TRP1-specific thymocytes in RAG1−/−TRP1Tg mice (Rausch and Hastings, 2012). CD4+ single positive thymocytes do not develop in RAG1−/−TRP1Tg mice, indicating that TRP1-specific T cells are deleted in these animals. An increased percentage of CD4+ single-positive thymocytes develop in GILT−/−RAG1−/−TRP1Tg mice, indicating that GILT is required for the deletion of TRP1-specific T cells. A similar percentage of CD4+ single positive thymocytes are present in TRP1-deficient RAG1−/−TRP1Tg mice and GILT−/−RAG1−/−TRP1Tg mice, demonstrating that GILT deficiency and absence of TRP1 have similar effects on thymic deletion. T cell development in the thymus depends on the presentation of self antigens by specialized cells of the thymic stroma, but GILT's role in antigen presentation by thymic stromal cells remains to be determined.

Although TRP1-specific T cells escape thymic deletion in GILT−/−RAG1−/−TRP1Tg mice, TRP1-specific T cells that develop in the absence of GILT lack autoimmune and anti-melanoma activity (Rausch and Hastings, 2012; Rausch and Hastings, 2015). TRP1-specific T cells from GILT−/−RAG1−/−TRP1Tg mice display diminished proliferation and decreased cytokine production in response to antigen presentation (Rausch and Hastings, 2012; Rausch and Hastings, 2015). Increased TRP1-specific regulatory T cells and PD-1 expressing T cells that develop in the absence of GILT mediate these phenotypes (Rausch and Hastings, 2012; Rausch and Hastings, 2015).

GILT expression alters the MHC class II peptidome and pathogenic mechanism of autoimmunity in experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis (Bergman et al., 2012). Immunization of wild-type mice with rat MOG protein results in EAE that is mediated by CD4+ T cells and depends on presentation of the

GILT-dependent epitope MOG35-55. MOG35-55 is the exclusive encephalitogenic epitope in MOG protein-induced EAE in wild-type mice. In contrast, T cells from GILT−/− mice immunized with MOG protein proliferate in response to several overlapping MOG peptides, but not MOG35-55. Consistent with the GILT-dependence of the MOG35-55 epitope, GILT −/− mice are resistant to EAE induced by MOG35-55. Surprisingly, GILT−/− mice develop more severe EAE following immunization with MOG protein compared to wild-type mice. This unanticipated finding is due to a switch in the pathogenic mechanism from T cell-mediated autoimmunity in wild-type mice to B cell-mediated disease in GILT−/− mice.

GILT may prevent autoimmunity by diminishing T cell sensitivity to self-antigens, independent of antigen processing. GILT expression in T cells decreases proliferation and cytotoxic activity (Barjaktarevic et al., 2006). GILT expression levels increase with T cell development from double positive to single positive thymocytes to peripheral T cells (Maric et al., 2009). GILT expression results in diminished ERK1/2 phosphorylation following TCR stimulation. GILT−/− mice develop earlier onset and more severe hyperglycemia in streptozotocin-induced diabetes, a CD8+ T cell-mediated model of autoimmunity.

Gene expression profiling studies in human autoimmune diseases support the clinical significance of GILT in autoimmunity. GILT mRNA expression is significantly upregulated in the blood and skin of patients with chronic cutaneous lupus erythematosus and in the glomeruli of patients with lupus nephritis and systemic lupus erythematosus (Dey-Rao and Sinha, 2015; Peterson et al., 2004). A meta-analysis of mRNA expression in the saliva and salivary glands in Sjogren’s syndrome reveals significant upregulation of GILT expression (Song et al., 2014). Increased differential expression of GILT in tissues affected with autoimmunity compared with healthy controls supports a role for GILT in pathogenesis of autoimmune disease.

GILT in cancer survival

Low GILT expression in tumor cells is associated with poor patient survival. We investigated the association of GILT expression with patient survival in diffuse large B cell lymphoma (DLBCL), because expression of MHC class II (HLA-DR, DP, DQ) and other class II pathway components including HLA-DM and invariant chain is associated with improved patient survival in DLBCL (Phipps-Yonas et al., 2013a). Since GILT is critical for the presentation of a subset of MHC class II-restricted epitopes and unlike the other members of this pathway GILT expression is not regulated by the transcription factor class II CIITA, we hypothesized that GILT expression may provide further prognostic information in DLBCL. Low GILT mRNA expression is associated with poor overall survival in DLBCL patients in each of four independent gene expression profiling cohorts with a total of 585 patients. The association of GILT expression with poor survival is independent of known prognostic factors, including the International Prognostic Index and the cell of origin classification. Immunohistochemical analysis of 96 DLBCL specimens reveals variable GILT protein levels in tumor cells which correlate with the overall GILT mRNA expression in specimens, suggesting that GILT expression in tumor cells correlates with improved patient survival. Subsequently, an immunohistochemical analysis of 218 patients with breast cancer demonstrated that loss of GILT protein expression in tumor cells

is associated with poor disease-free survival (Xiang et al., 2014). Low GILT staining is associated with advanced tumor stage and is an independent predictor of poor three-year disease-free survival in breast cancer. These studies establish the clinical significance of GILT expression in cancer.

How might GILT expression in tumor cells improve cancer survival? One possibility is that improved processing and presentation of tumor antigens by cancer cells may result in enhanced anti-tumor T cell responses that ultimately improve patient survival. Support for this hypothesis comes from studies in melanoma. Melanoma cells are capable of presenting endogenous membrane bound and cytoplasmic antigens on MHC class II and stimulating melanoma-specific CD4+ T cells (Robila et al., 2008; Tsuji et al., 2012). An analysis of human MHC class II-expressing melanoma cell lines showed that GILT expression facilitates the presentation of a naturally-occurring epitope from the melanoma antigen tyrosinase (Haque et al., 2002). We have demonstrated that GILT is required for optimal presentation of the melanoma antigen TRP1 (Rausch et al., 2010). Given that other melanoma antigens, such as gp100, TRP2 and NY-ESO-1, contain disulfide bonds, GILT is likely to facilitate the presentation of epitopes from multiple melanoma antigens. These studies support the hypothesis that GILT expression in tumor cells improves the presentation of tumor antigens and T cell recognition. It remains to be determined whether GILT expression in tumor cells is associated with improved T cell-mediated anti-tumor responses and patient outcome in melanoma.

GILT may also influence cancer survival through functions outside of antigen presentation, such as regulation of the cellular redox state and proliferation. This possibility is supported by the finding that the association of GILT expression with patient outcome in DLBCL is observed in three cohorts in which HLA-DRA expression is not associated with patient outcome (Phipps-Yonas et al., 2013a). Altered expression of genes that regulate the cellular redox state, including low SOD2, is associated with poor patient survival in DLBCL. The absence of GILT in fibroblasts and T cells leads to increased levels of reactive oxygen species, decreased SOD2, and an increased ratio of oxidized glutathione (GSSG) to reduced glutathione (GSH) (Bogunovic et al., 2008; Chiang and Maric, 2011; Maric et al., 2009). Thus, regulation of the cellular redox state may contribute to the effect of GILT expression on cancer survival. Alternatively, the absence of GILT may increase tumor growth. Consistent with this hypothesis, low GILT staining in breast cancer is associated with a higher Ki67 proliferation index (Xiang et al., 2014). Similarly, GILT−/− fibroblasts and T cells exhibit increased cellular proliferation (Barjaktarevic et al., 2006; Bogunovic et al., 2008). Thus, low GILT expression in tumor cells may contribute to poor patient survival through altered cellular redox state and increased proliferation.

Conclusion

The lysosomal thiol reductase GILT catalyzes the reduction of disulfide bonds in the endocytic compartments. Facilitating antigen presentation is the most established function for GILT. Emerging roles for lysosomal GILT include modulating cysteine protease stability and activity, controlling the cellular redox state and redox-sensitive cellular processes, and regulating T cell tolerance. The mechanisms responsible for the association of low GILT

expression with poor cancer survival, the impact of GILT on the overall host response to infection, and the role of secreted GILT remain to be determined.

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Abbreviations

GILT	Gamma-interferon-inducible lysosomal thiol reductase
CIITA	class II transactivator
TRP1	tyrosinase-related protein 1
MOG	myelin oligodendrocyte glycoprotein
HSV1	herpes simplex virus-1
gB	glycoprotein B
SOD2	superoxide dismutase 2
EAE	experimental autoimmune encephalomyelitis
DLBCL	diffuse large B cell lymphoma

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- GILT catalyzes disulfide bond reduction in endocytic compartments
- GILT facilitates antigen presentation via MHC class I and II
- GILT regulates the cellular redox state impacting autophagy and proliferation
- GILT enhances the activity of bacterial hemolysins
- GILT modulates T cell tolerance, autoimmunity, cancer survival and infection

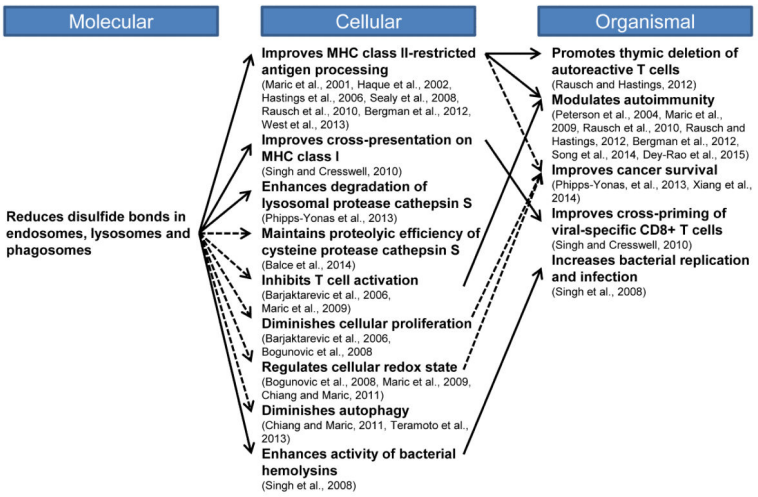

Figure 1. Diverse roles of GILT

Reduction of disulfide bonds is the only known molecular function of GILT. GILT has been shown to have a number of functions at the cellular level. A solid arrow connecting the molecular and cellular function indicates that the cellular role of GILT is dependent on an intact reductase active site. A number of these cellular functions have been shown to result in functions at the organismal level (connected by solid arrows). Possible mechanisms of other organismal functions are indicted with dashed arrows.