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Unveiling the impact of GOLM1/GP73 on cytokine production in cancer and infectious disease

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Abstract

The Golgi membrane protein GOLM1/GP73/GOLPH2 has been found to impact cytokine production in both infectious disease and cancer. In viral infections, GOLM1 levels are increased, and this lowers the production of type I interferons and other inflammatory cytokines. However, elevated GOLM1 expression levels due to mutations are linked to a higher production of interleukin (IL)-6 during *Candida* infections, potentially explaining an increased susceptibility to candidemia in individuals carrying these mutations. In cancer, the protease Furin produces a soluble form of GOLM1 that has oncogenic properties by promoting the production of the chemokine CCL2 and suppressing the production of inflammatory cytokines such as IL-12 and interferon gamma. This review will focus on the role of GOLM1 in cytokine production, highlighting how it can both promote and inhibit cytokine production. It is crucial to understand this in order to effectively target GOLM1 for therapeutic purposes in diseases associated with abnormal cytokine production, including cancer and infectious disease.

INTRODUCTION

Cytokines and chemokines are small, secreted proteins that are released by various cell types and mediate signaling between cells. Inflammatory cytokines, which include interleukin (IL)-6, IL-12, interferon (IFN)-γ and tumor necrosis factor-alpha (TNF), activate the immune system in order to combat pathogens and cancer. Chemokines, such as C-C motif chemokine 2 (CCL2), are chemotactic compounds that recruit immune cells to sites of inflammation. Pro-inflammatory cytokines are counteracted by anti-inflammatory cytokines, such as IL-10, and thereby an immune response can be inhibited or blocked. The location, timing and magnitude of the production and release of cytokines and chemokines need to be tightly regulated, as these compounds can exert large effects.[1,2] When the production of pro-inflammatory cytokines is insufficient, this can result in an inability to clear infections and cancer. However, the production of excessive amounts of inflammatory cytokines is a hallmark of autoimmune diseases and sepsis.[3,4]

In immune cells, the production of most cytokines and chemokines is regulated at the transcriptional level.[1,2,5] Whereas mRNA coding for IL-6, IL-12 and TNF is only present at low levels in non-activated immune cells, the activation of immune cells by the recognition of pathogens or malignant cells results in transcription of the genes coding for these cytokines. Following their co-translational insertion into the rough endoplasmic reticulum (ER), the newly produced cytokines and chemokines are secreted by the so-called constitutive secretory pathway. In this pathway, these compounds are transported by continuous vesicular trafficking from the ER *via* the Golgi apparatus to the plasma membrane for secretion. The trafficking from the Golgi to the plasma membrane can occur *via* recycling endosomes, as shown for TNF and IL-6,[6] and *via* lysosome-related compartments, as shown for IL-12.[7] In the Golgi apparatus, the newly produced cytokines and chemokines are post-translationally modified and sorted into their cognate trafficking vesicles to ensure transport to the correct cellular destinations.[1,2]

Given that newly produced cytokines have to traffic through the Golgi network, it is no surprise that Golgi proteins are involved in diseases associated with cytokines. Indeed, in both cancer and infectious disease, aberrant cytokine production levels have been associated with Golgi membrane protein 1 (GOLM1), also called GP73 or GOLPH2. This review aims to provide an overview of the role of GOLM1 in cytokine and chemokine production, with the aim of gaining a molecular understanding of how this protein regulates these processes.

PROPERTIES AND FUNCTIONS OF GOLM1

GOLM1 is a 401-residue ubiquitously expressed type II membrane protein. Expression is higher in epithelial cells of various human tissues, including the kidneys, lungs, prostate and gut.[8–10] GOLM1 locates at the *cis* and *medial*-Golgi cisternae as was found by immunolabeling of epitope-tagged overexpressed GOLM1 in HEK-293 cells,[8] and later confirmed by immunolabeling of endogenously expressed GOLM1 in hepatocellular carcinoma (HCC) cell lines and the normal liver cell line L2.[11] GOLM1 is well conserved, and for example murine GOLM1 has a sequence identity of 66.5% with human GOLM1. According to structural predictions, GOLM1 has a short cytoplasmic N-terminus (residues 1–12) followed by a transmembrane domain (residues 13–35) and a large highly acidic C-terminal luminal region (residues 36–401). Mass spectrometry showed that the luminal domain of human GOLM1 is glycosylated at N109 (not conserved in mouse), N144 (conserved in mouse), and N398 (not conserved in mouse).[12–14] Removal of glycosylation at N144 enhances metastasis of human HCC cells.[14] In addition, human GOLM1 is phosphorylated at S187 (conserved in mouse) and S309 (not conserved),[15,16] but the functional significance of this luminal phosphorylation is unclear.

GOLM1 can be cleaved at R55, located within the luminal coiled-coil domain (approximately residues 40–200), generating a soluble form of GOLM1, called sGOLM1, which is present in the sera of patients with liver and prostate cancer.[9,10] Recently, it was shown that GOLM1 also plays a role in type 2 diabetes mellitus (T2DM).[17] Circulating levels of sGOLM1 were increased in patients with type 2 diabetes mellitus, and this was found to stimulate liver glucose production and systemic glucose homeostasis.[17] Cleavage of GOLM1 is mediated by the endoprotease Furin, as it can be blocked by a Furin inhibitor.[18]

The luminal coiled-coil domain of GOLM1 is essential for binding and interacting with the extracellular chaperone Clusterin, as found by a yeast two-hybrid screen and confirmed by co-immunoprecipitation.[19] Co-immunoprecipitation also revealed other interacting partners of GOLM1: Using truncation mutants of GOLM1 lacking (part of) its cytosolic domain, transmembrane helix or luminal domain, it was shown that the cytosolic domain of GOLM1 interacts with the epithelial growth factor receptor (EGFR)[20] and the metalloproteases MMP2 and MMP7,[21,22] and these interactions play a role in HCC metastasis. The cytosolic region of GOLM1 also interacts with both full-length NOTCH2 and its intracellular N2ICD region, and this can regulate cell division.[23] Furthermore, it was found that GOLM1 mediates the selective autophagy of receptor tyrosine kinases (RTKs) by interacting with the autophagy adaptor LC3.[24] By mutagenesis it was shown that this interaction is mediated by a LC3-interacting region (LIR) located at residues 130–135,[24] which seems surprising since this is located at the luminal region of GOLM1, whereas LC3 is a cytosolic protein. Moreover, GOLM1 directly interacts with alpha-fetoprotein (AFP) and thereby facilitates its secretion, which promotes proliferation, metastasis and drug resistance of cancer cells.[25] By immunoprecipitation, it was shown that interactions of the immune checkpoint protein B7-H3 with GOLM1 mediate its trafficking to the surface of ovarian cancer cells, and thereby GOLM1 promotes the secretion of a soluble form of B7-H3 that drives cancer progression and metastasis.[26] Immunoprecipitation followed by Western blot indicated that GOLM1 also interacts with the Golgi component Golgin subfamily A member 2 (GOLGA2; also called GM130)[27] and BCL-2-like protein 1 (BCL2L1).[28] Moreover, a mass spectrometry screen identified many putative binding partners of GOLM1, including the SNARE protein GosR2, small-GTPases Rab19, Rab3d, Rab3d, Rab11 and Rab26, and trafficking protein particle complex subunit 3-like protein (Trappc3l), but these interactions still need to be confirmed with other methods.[23] Finally, molecular docking studies suggested that GOLM1 might interact with PTBP1 and E2F4, both involved in vascular epithelial growth factor (VEGF) signaling, but these interactions also need experimental confirmation.[29]

The function of GOLM1 has not been clearly defined. Transgenic mice expressing a truncated form of GOLM1 lacking 146 residues of the C-terminus display a shortened lifespan.[30] Moreover, the liver and kidney of these mice showed pathological changes, such as focal segmental glomerulosclerosis and hepatocyte nuclear membrane irregularities, which suggest that GOLM1 plays a role in the function of these organs.[30] At the cellular level, transient siRNA silencing of GOLM1 in Huh-7 cells (a HCC derived cell line) resulted in a scattered Golgi ultrastructure, a lower mitochondrial

oxygen consumption rate, an increased presence of ceramides and other sphingolipids, reduced cell proliferation, and increased apoptosis.[31] In line with this, overexpression of GOLM1 in PC9 cells promoted cell proliferation, migration and invasion.[32] Moreover, depletion of GOLM1 in intestinal epithelial cells led to aberrant NOTCH signaling that interfered with cell differentiation and maturation.[23] Transcriptomics in the HCC cell line MHCC97H with knockdown and overexpression of GOLM1 revealed that GOLM1 influences genes associated with oxidative stress, angiogenesis and the VEGF signaling pathway.[29]

Likely as a consequence of these GOLM1-associated cellular phenotypes, GOLM1 knockout mice had a higher susceptibility to mucosal inflammation, colitis induced epithelial damage and colon cancer.[23] Accordingly, the mRNA levels of the inflammatory cytokines IL-1β, IL-6, CCL2 and TNF were increased upon DSS (dextran sulfate sodium)-induced colitis.[23] Moreover, even untreated epithelial-specific GOLM1 knockout mice showed increased intestinal permeability, which is a hallmark of inflammation and colitis.[23] However, in another study no apparent developmental abnormalities nor decreased survival were found in complete GOLM1 knockout mice.[33] Nevertheless, these mice might be more suspectable to disease, since both liver-specific and whole-animal ablation of GOLM1 alleviated abnormal glucose metabolism in diet-induced obese mice.[17] In addition, another study found that the complete GOLM1 knockout mice are more susceptible to septic death induced by the bacterial immune stimulus lipopolysaccharide (LPS),[33] suggesting that GOLM1 plays a role in infectious disease.

GOLM1 AFFECTS CYTOKINES IN INFECTIOUS DISEASE

Other studies also show that GOLM1 is involved in infectious disease. First, it is firmly established that the expression of GOLM1 is upregulated in response to viral infections, as first shown in adenovirus-infected HepG2 cells and cultured amniotic cells infected with Newcastle disease virus.[8] This seems to be a general phenomenon, as increased GOLM1 expression has also been observed for other viral infections, including SARS-CoV-2,[34] Hepatitis B[35] and Hepatitis C virus (HCV).[36,37] By overexpression and shRNA silencing of GOLM1, it was shown that GOLM1 promotes the production of infectious HCV particles in infected Huh.7.5.1 cells,[37] at least partly by inhibiting the production of antiviral type I interferons.[36] GOLM1 overexpression also affects the production of other cytokines, since knockdown of GOLM1 in HCV infected Huh7 cells and Sendai virus

infected Thp1 cells resulted in increased levels of mRNA coding for inflammatory cytokines, including IL-6, TNF and IFN-β.[36] These effects are likely due to transcriptional regulation, as shRNA knockdown of GOLM1 in HEK293 cells expressing luciferase reporter constructs for the NF-κB promoter, IFN-β promoter and interferon-stimulated response element (ISRE) showed that GOLM1 reduces transcription of these promoters upon infection with Sendai virus.[36]

In line with this, IFN-γ and LPS stimulated bone marrow-derived macrophages from GOLM1 knockout mice showed higher levels of expression of *Ifnb*, the gene coding for IFN-β.[33] ELISA and qPCR showed that IL-12 secretion and *Il12a* and *Il12b* gene expression (code for the p35 and p40 subunits of IL-12, respectively) were also increased in GOLM1 knockout mice, although IL-10 and TNF production were not affected.[33] Recombinant sGOLM1 could also inhibit LPS and IFN-γ induced transcription of *Il12a* and *Il12b* in murine bone marrow-derived macrophages, whereas the production of IL-10 and TNF was not affected.[33] Transfecting the murine macrophage-like cell line RAW264.7 with a GOLM1 construct and a reporter construct consisting of the *Il12a* or *Il12b* promoter before the firefly luciferase reporter gene, also revealed that overexpression of GOLM1 inhibits the transcription of the IL-12 subunits.[38] By promoter truncation mutants and ChIP assays, it was shown that GOLM1 activates nuclear zinc finger protein GC-BP, which binds to the so-called apoptotic cell response element in the promoter region of *Il12a* in RAW264.7 cells.[33] However, GOLM1 not only inhibits cytokine production but also promotes the production of other factors, because expression of *Cxcl10*, coding for C-X-C motif chemokine 10 (CXCL-10), was reduced in the GOLM1 knockout mice.[33]

GOLM1 might promote the production of IL-6 as well. Genome-wide association studies (GWAS) identified GOLM1 as a key protein responsible for the large interindividual heterogeneity in cytokine production upon infection with the fungal pathogen *Candida albicans*.[39] In this study, which was performed with two independent cohorts from Belgium and the Netherlands, cytokine production of *in vitro* stimulated peripheral blood monocytic cells (PBMCs) was correlated with single nucleotide polymorphisms (SNPs), so-called expression quantitative trade loci (eQTL). A SNP increasing expression levels of GOLM1 was found to correlate with increased IL-6 production in cells stimulated with *Candida* and other pathogenic stimuli, whereas other cytokines were not significantly affected.[39] Moreover, SNPs that correlated with increased GOLM1 expression also correlated with increased IL-6 production from *in vitro* cultured immune cells.[39] This finding might

well have clinical relevance, as a SNP linked to higher GOLM1 expression was also found to be associated with increased susceptibility to candidemia, the bloodstream infection *C. albicans*.[39]

GOLM1 AFFECTS CYTOKINES IN CANCER

As HCV infections increase GOLM1 expression[36,37] and can cause HCC, it is no surprise that GOLM1 expression levels are increased in HCC.[29,37] However, GOLM1 protein and mRNA levels are also increased in other, non-virally induced cancer types, for example lung cancer, prostate cancer, gastric cancer, melanoma, breast cancer and testicular cancer.[9,10,20,38,40,41] Elevated GOLM1 levels have also been reported in other liver pathologies, specifically non-alcoholic steatohepatitis and alcoholic liver disease.[42] The higher expression of GOLM1 is associated with decreased survival in lung cancer, melanoma, colorectal cancer, uveal melanoma and HCC.[29,40,43,44] As recently reviewed elsewhere,[9] GOLM1 expression can be increased by multiple extracellular factors in the tumor microenvironment, including hypoxia,[22] various miRNAs,[45–47] and the cytokines IL-1β,[48] IL-6 and Oncostatin M.[49] However, the upregulation of GOLM1 is not a universal phenomenon in cancer, because lower levels of GOLM1 have been reported in colon cancer.[23]

Likely as a consequence of aberrantly high expression of GOLM1, cancer cells can secrete high levels of sGOLM1, as reported for HCC[18,50] and prostate cancer.[51] For example, healthy individuals have an average of about 20 ng mL^{-1} sGOLM1 detectable in their serum, compared with 166 ng mL^{-1} in patients with primary HCC.[52] Therefore, circulating levels of sGOLM1 are increasingly well established as a biomarker for hepatic cancers[18,50,53] and potentially also for prostate cancer.[51]

Multiple mechanisms of how GOLM1 promotes cancer progression have been shown.[9] For example, the elevated expression of GOLM1 inhibits tetramer formation, and thereby DNA binding, of the tumor antigen P53, and this increases non-small cell lung cancer aggressiveness.[32] However, most described mechanisms relate to a role of GOLM1 in organelle trafficking. First, elevated levels of GOLM1 increase cell surface recycling of the EGFR,[20] which in turn increases EGFR signaling and thereby promotes immune escape by elevating the expression of the immune checkpoint ligand PD-L1.[42] Similarly, GOLM1 mediates cell surface recycling of RTKs and thereby affects the expression of cancer-related proteins downstream of RTK signaling, including E-cadherin and the metalloprotease MMP9.[20] GOLM1 also directly regulates the trafficking of the other metalloproteases MMP2 and MMP7 through the Golgi network, as

knockdown of GOLM1 induces their intracellular accumulation.[21,22]

Recently, it was found that GOLM1 levels correlate with the expression of B7-H3 in human ovarian cancer samples, and that this correlated with patient survival.[26] In line with this, overexpression of GOLM1 increased B7-H3 levels in the ovarian cancer cell line SKOV3, while knockdown reduced this. Although GOLM1 affects mRNA transcript levels of *CD276* (coding for B7-H3), this effect was small and could not fully explain its effects on B7-H3 expression. Instead, it was found that GOLM1 traffics B7-H3 to the membrane by direct interaction. This promotes the secretion of a soluble form of B7-H3, and it was confirmed in a murine breast cancer model that GOLM1 knockdown resulted in lower soluble B7-H3 levels and reduced metastasis. In line with this, *in vitro* cancer cell migration assays showed that both GOLM1 and B7-H3 knockdown reduced cancer cell migration, and this could be restored for both knockdowns by the addition of soluble B7-H3. These findings indicate that GOLM1 can increase ovarian cancer cell invasion and migration by upregulating soluble B7-H3 production.[26]

Another mechanism of how GOLM1 promotes cancer progression involves the cytokine IL-12. In gastric cancer tissues, it was found by PCR that *IL12A* was downregulated and *GOLM1* was upregulated compared with adjacent non-cancerous tissue.[38] Overexpression of GOLM1 in human gastric cancer SGC7901 cells showed that GOLM1 suppresses transcription of *IL12A* by co-cultured human peripheral blood lymphocytes. Transwell assays showed that sGOLM1 also reduces the production of IFN-γ, TNF and IL-12p35 by the co-cultured lymphocytes.[38] These findings are in line with a later study in B cell leukemia. Using a transwell culturing system, it was found that peripheral B cells from chronic lymphocytic leukemia patients produce sGOLM1 and this inhibits the production of IL-12 by human monocyte-derived dendritic cells, whereas the production of IL-10 was not affected.[33] Thus, sGOLM1 inhibits the expression of IL-12 and thereby cancer cells can suppress anti-cancer immune responses.

However, GOLM1 seems to exert the opposite effect on the expression of CCL2, because overexpression of GOLM1 can promote the transcription of *CCL2*, and this contributes to tumor metastasis and progression by recruiting myeloid-derived suppressor cells (MDSCs).[43] MDSCs are premature myeloid cells that can induce immunosuppression and are pro-tumorigenic. Migration and invasion of MDSCs are promoted by overexpression of GOLM1, as shown *in vitro* by Transwell assays with colorectal cancer cell lines and *in vivo* in a orthotopic mouse model of colorectal cancer.[43] In SW480 human adenocarcinoma cells, PCR showed that the

overexpression of GOLM1 upregulated *CCL2* expression.[43]

DISCUSSION

Although it is increasingly clear that GOLM1 regulates the production of cytokines and chemokines, the reported effects are contradictory as GOLM1 can both increase and decrease their production (Table 1). For example, in LPS-stimulated human and mouse dendritic cells and macrophages, GOLM1 inhibits the production of IL-12, whereas it promotes the production of CXCL-10 and does not affect TNF and IL-10 production.[33] However, GOLM1 not only inhibits IL-12 production but also TNF production by human lymphocytes.[38] Moreover, GOLM1 inhibits the production IFN-β, TNF and IL-6 in virally infected Huh7 and Thp1 cells,[36] but in SW480 human adenocarcinoma cells it promotes the production of CCL2.[43] Finally, in PBMCs stimulated with *Candida* and other microbial stimuli, there is a positive correlation between GOLM1 expression levels and IL-6 production, but not of other cytokines.[39]

Likely, these differential effects of GOLM1 on cytokine production depend on the precise stimulus, the presence of co-stimuli and the cell type. As described above, GOLM1 can directly mediate NOTCH signaling,[23] and indirectly affects RTK and EGFR signaling by altering receptor surface levels.[20] As these (and other) signaling pathways have different contributions in different cell types, these pathways likely contribute to the observed differences among cell types and stimuli. Moreover, as

GOLM1 affects the production of cytokines and chemokines, their autocrine signaling will likely also be affected, which in turn will affect downstream transcriptional processes. Indeed, overexpression of GOLM1 leads to increased signaling of JAK and STAT3 in the lung adenocarcinoma cell line A549,[46] possibly due to alterations in autocrine cytokine signaling. All these mechanisms likely contribute to the effects of GOLM1 on gene expression,[29] including downregulation of *IFNB*,[33,36] *IL12A*,[33,38] and upregulation of *CXCL10*[33] and *CCL2*.[43]

However, at least part of the different effects of GOLM1 on cytokine and chemokine production might be caused by differences between full-length GOLM1 and the secreted form sGOLM1. Overexpression of GOLM1 promotes the release of sGOLM1, and only low levels of sGOLM1 are detected in the circulation in healthy individuals (i.e. with non-increased GOLM1 expression).[52] Moreover, coculturing experiments with transwells and experiments with conditioned medium and recombinant sGOLM1 showed that sGOLM1 inhibits the production of IL-12 by both mouse and human dendritic cells, macrophages and lymphocytes.[33,38] All together this suggests that the differential effects on cytokine expression by GOLM1 might be explained by the production of sGOLM. In this model (Figure 1), full-length membrane-incorporated GOLM1 acts as a chaperone and traffics receptors and other cargo molecules, including potentially cytokines, through the Golgi network, thereby promoting their release at the cell surface. This chaperone role of GOLM1 would be similar to its trafficking role in EGFR, RTK, MMP2, MMP7 and B3-H7 trafficking.[20–22,26] However, the overexpression of GOLM1 in cancer and (virus) infected cells promotes the release of sGOLM1, which might inhibit cytokine and chemokine production by other cells, possibly by competing with full-length GOLM1 for binding to the cargo molecules. This model might explain how intraindividual variations in GOLM1 expression levels among healthy individuals can correlate with IL-6 production,[39] whereas the overexpression in virus-infected and cancer cells inhibits the production of other cytokines.[33,36,38] However, this mechanism is an untested hypothesis that needs to be tested experimentally.

In any case, current data support the concept that both full-length GOLM1 and the secreted sGOLM1 are targets for cancer, infectious diseases and other diseases associated with aberrant cytokine and chemokine production. Thus, GOLM1 is not only a biomarker for hepatic cancers,[18,50,53] but also has important functional roles as it affects the production of cytokines involved in tumor progression and infectious disease. These effects seem to relate to GOLM1-mediated trafficking of signaling receptors through the Golgi, because GOLM1

Table 1. Overview of GOLM1 affected cytokines.

Cyto/chemokine	Gene	Protein	Regulation	Reference
TNF		X	−	33
		X	↓	36,38
IL-6		X	↓	36
		X	↑	39
IL-10		X	−	33
IFN-β	X		↓	33,36
		X	↓	36
IFN-γ		X	↓	38
IL-12p70		X	↓	33
IL-12p35	X		↓	33,38
		X	↓	38
IL-12p40	X		↓	33,38
CXCL10	X		↑	33
CCL2	X		↑	43

CCL2, C-C motif chemokine 2; CXCL-10, C-X-C motif chemokine 10; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; −, no effects upon GOLM1 ablation and/or overexpression; ↓, downregulation by GOLM1; ↑, upregulation by GOLM1.
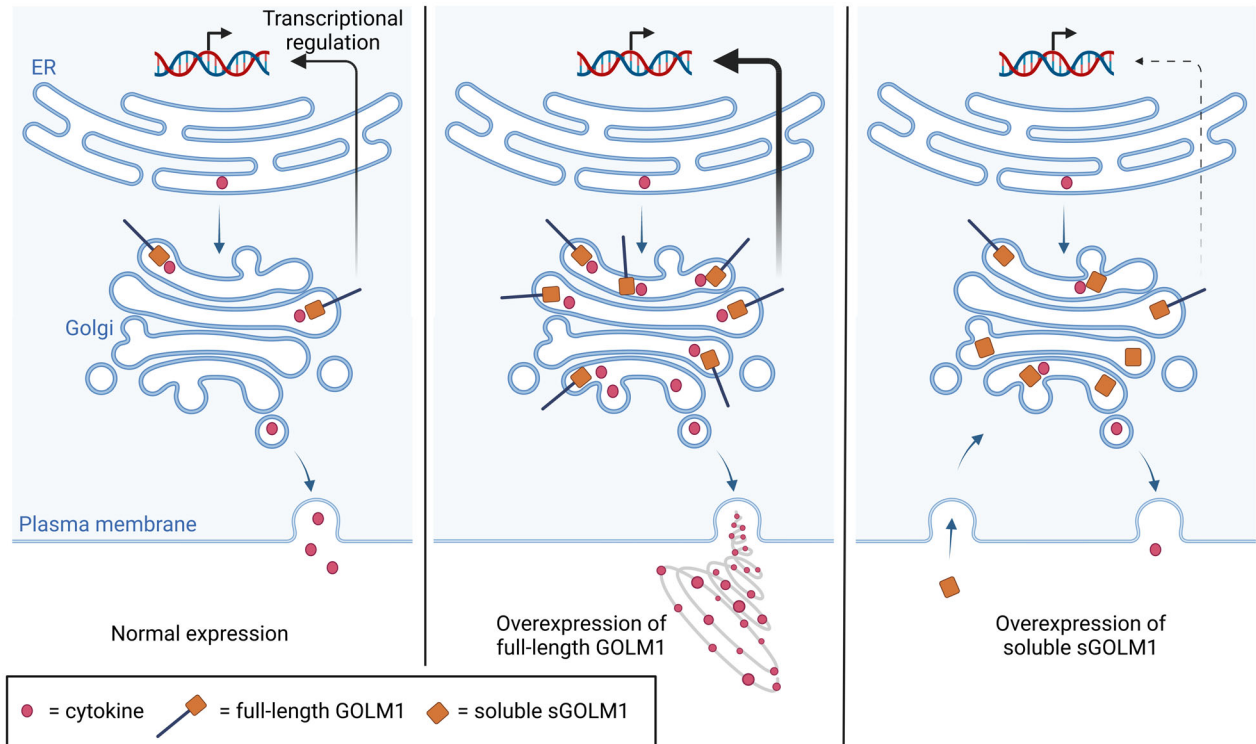
Figure 1. Hypothetical model for the contrasting roles of GOLM1 in cytokine production. Membrane-bound full-length GOLM1 chaperones receptors and/or newly synthesized inflammatory cytokines through the Golgi network (left panel). This chaperoning is rate-limiting for cytokine production. Therefore, cells with elevated expression levels of full-length GOLM1 can produce more cytokines, for example upon pathogenic stimulation (middle panel). However, upon very high expression of GOLM1 in cancer and viral infections, a soluble form (sGOLM1) is produced, which inhibits cytokine transport through the Golgi network by competing for cargo binding with full-length GOLM1 (right panel). ER, endoplasmic reticulum. The figure was created with BioRender.com.

affects cytokine production both at the transcriptional and protein level. Indeed, GOLM1 has been shown to (either directly or indirectly) bind to various receptors including EGFR,[20] NOTCH2,[23] RTKs[24] and B7-H3,[26] and more receptors will likely be identified in the future. Moreover, it cannot be excluded that GOLM1 regulates the trafficking of the cytokines themselves through the Golgi network. Although no interactions of GOLM1 with cytokines have been reported, it seems possible that GOLM1 affects their trafficking indirectly for two reasons. First, the ablation of GOLM1 has been shown to result in a scattered Golgi ultrastructure,[31] which is highly likely to impact Golgi trafficking.[54] Second, GOLM1 was found by mass spectrometry to interact with SNAREs, small-GTPases of the Rab family, and other trafficking proteins with well-known roles in Golgi transport,[23] and this can also be expected to broadly impact Golgi trafficking.

The effects of GOLM1 on cytokine and chemokine production warrant testing its therapeutic targeting. In mouse models of type 2 diabetes mellitus, it was shown that the glucose metabolism could be improved by

neutralizing sGOLM1 with antibodies.[17] As explained in this review, neutralization of sGOLM1 and/or full-length GOLM1 by the same approach could also be a promising therapeutic strategy in cancer and infectious disease.

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AUTHOR CONTRIBUTIONS

Myrthe T Frans: Conceptualization; writing – original draft. **Ella M Kuipers:** Conceptualization; writing – original draft. **Frans Bianchi:** Conceptualization; writing – review and editing. **Geert van den Bogaart:** Conceptualization; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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