The conserved oligomeric Golgi (COG) complex, a window into plant-pathogen interactions

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ABSTRACT

The endomembrane system, functioning in secretion, performs many roles relating to eukaryotic cell physiological processes and the Golgi apparatus is the central organelle in this system. An essential associated Golgi component is the conserved oligomeric Golgi (COG) complex, maintaining correct Golgi structure and function during retrograde trafficking. In animals, naturally occurring cog mutants provide a window into understanding its function(s). Eliminating even one COG component impairs its function. In animals, COG mutations lead to severe cell biological and developmental defects and death while far less is understood in plants which is changing. The plant genetic model Arabidopsis thaliana COG complex functions in growth, cell expansion and other processes, involving direct interactions with other secretion system components including the exocyst, soluble N-Ethylmaleimide-Sensitive Factor Attachment Protein Receptor (SNARE), and the microtubule cytoskeleton. Recent experiments have identified a defense role for the COG complex in plants, the focus of this review.

Backdrop

The Golgi apparatus is positioned at the nexus of vesicle transport. Materials arrive at, pass through, and exit the Golgi apparatus. During this time, important interactions are occurring with cargo processed in various ways employing proteins and complexes that are crucial to their proper function (Khakurel et al. 2021). More specifically, the Golgi apparatus is a dynamic membranous compartment composed of a series of cisternae derived from the endoplasmic reticulum (ER) having polarity with the cis face oriented toward the nucleus and the trans face opposite of it. The Golgi cisternal maturation model describes newly synthesized secretory and membrane molecules moving in an anterograde (biosynthetic) manner (cis to trans) cisternae mostly within the cisternae (Emr et al. 2009; Glick and Luini 2011; Luini 2011). In contrast, recycling molecules (Golgi enzymes, SNAREs, cargo receptors) moving in a retrograde (recycling) manner occurring from trans to cis cisternae and happening within small membrane intermediates, mostly vesicles (Emr et al. 2009; Glick and Luini 2011; Luini 2011). The conserved oligomeric Golgi (COG) complex specifically regulates the intra-Golgi vesicle recycling pathway. This pathway is essential for the proper localization and function of the Golgi glycosylation machinery as well as cargo receptors. Consequently, aberrant COG function results in the disruption of its major functions including the glycosylation of proteins and lipids and protein sorting.

The discovery of protein components that would later become known as the COG complex that facilitate retrograde transport occurred with the identification of the low density lipoprotein (LDL) receptor-deficient phenotype in Chinese hamster ovary (CHO) cells (Kingsley et al. 1986; Bonifaccio and Rojas 2006). While these ldlB, ldlC, and ldlD mutants synthesized a normal amount of precursor LDL receptor they were unable to process it into its mature form. The mutant receptor exhibited defective N- and O-linked carbohydrate chain processing among other glycosylation defects (Kingsley et al. 1986). Furthermore, a ldlC revertant, RevC-13, was identified providing additional knowledge on the regulation of the receptor (Reddy and Krieger 1989). Curiously, the cloning of a human LDLC cDNA corrected the ldlC mutant phenotype in CHO cells but did not restore the ldlB cells’ function, indicating a
level of specificity of the gene’s protein product (Podos et al. 1994). The IdICp protein was shown to be a peripheral Golgi protein and that the Golgi association was sensitive to brefeldin A, a lactone isolated from the
Penicillium brefeldianum
fungus that inhibits protein transport from the endoplasmic reticulum (ER) to the Golgi complex (Hutchinson et al. 1983; Helms and Rothman 1992; Podos et al. 1994). A
Caenorhabditis elegans
IdICp sequence was also identified in the analysis, demonstrating the conserved nature of the receptor’s structure (Podos et al. 1994). Subsequent cloning of a mouse LDLB cDNA and experimentation showed it corrected the mutant phenotypes of the IdLB cells with homologous sequences identified in human, C. elegans, Drosophila melanogaster, and Arabidopsis thaliana (Chatterton et al. 1999). The outcomes of these experiments presaged the results obtained from unicellular organisms, and ultimately those made prior to the cloning of the genes functioning in retrograde transport in human cells and the designation of the COG complex (Survorova et al. 2002; Ungar et al. 2002). Subsequent crystalline work on the
Saccharomyces cerevisiae
homolog of IdICp, Secretion 35 protein (Sec35p)–conserved oligomeric Golgi (Cog) 2 protein (Cog2p) yielded important knowledge on this tethering complex component that as a part of the COG complex mediates the contact between the physical interfaces of target and vesicle membranes that relates to other large proteinaceous complexes that also function broadly in vesicle transport (i.e. the exocyst) (Cavanaugh et al. 2007). Further studies of congenital disorders of glycosylation (CDGs) identified a human cog4 mutant whose crystalline structure (Cog4-[525–785]) analysis at 1.9 Å resolution revealed the R729W domain D missense mutation or its E764 domain E salt bridge partner causes severe glycosylation defects but did not impair its incorporation into the COG complex (Richardson et al. 2009). Consequently, neither the D nor the E domains are important for COG complex formation but are likely the sites mediating important functional Golgi trafficking machinery interactions (Richardson et al. 2009). Additional structural work on reconstituted
S. cerevisiae
Cogs1-4p performed via single-particle electron microscopy provided numerous insights into the COG complex’s structure, suggesting the Cog1–Cog4 complex’s central region, and distal regions of at least two legs participating in the intracellular trafficking machinery through interactions with various other components (Lees et al. 2010). This work allowed for the inference of the interaction sites for the human Syntaxin5 (STX5), the homolog of the
S. cerevisiae
suppressors of the erd2-deletion 5 (Sed5p), and Suppressor of loss of YPT1 protein 1 (Sly1) (Dascher et al. 1991; Shestakova et al. 2007; Lees et al. 2010). Notably, the human homolog of Sec17p is alpha soluble N-Ethylmaleimide-Sensitive Factor Attachment Protein (α-SNAP) whose Glycine max (soybean) homolog is found in its major resistance to
heterodera glycines
(rlg1) locus and is widely believed to be the rlg1
Heterodera glycines
e (soybean cyst nematode) parasitic nematode resistance gene (Matsye et al. 2011, 2012; Cook et al. 2012; Liu et al. 2017; Lakshssasi et al. 2020a, 2020b). Ultimately, negative-stain electron microscopy of the entire
S. cerevisiae
COG complex (Cogs1-8) elucidated its architecture revealing 4 or 5 flexible legs positioning it well for vesicle capture and membrane fusion (Ha et al. 2016).

The subsequent sections in this review will begin by introducing the importance of the COG complex, beginning with providing context through its role in plant defense and how it relates to the delivery of a specific locally-expressed, hemicellulose-modifying, putatively-glycosylated protein (xyloglucan endotransglycosylase/hydrolase 43 [XTH43]) that functions in ways that are different than typically thought for proteins in this evolutionarily conserved family (Pant et al. 2014; Niraula et al. 2021). The balance of the review places those observations into the broader context of the COG complex and bring attention to an urgent need for more study of it and associated proteins and complexes that underlie its functions.

**Plant COG complex function during defense as it relates to hemicellulose modification**

The plant cell wall is a structural element that is modified for growth, with glycosylation being an important aspect of its modification (Faye et al. 1986; Capková et al. 1997; Lukowitz et al. 2001; Tan et al. 2010, 2013; Velaquez et al. 2011, 2015; Behammer et al. 2021). The cell wall is composed of 30% cellulose and 30% hemicellulose with approximately 35% pectin, and 1–5% structural proteins. Hemicellulose is principally xyloglucan (XyG), composing up to 25% of the cell wall that is hydrogen-bonded to adjacent cellulose microfibrils surfaces. By being so, XyG forms a network that may limit CW extensibility as it tethers adjacent microfibrils. XyG may also regulate cell enlargement, acting as a load bearing structure (Cavaleri and Keegstra 2006). XTH enzymatically modifies XyG, a branched polysaccharide having a (β-1–4)-linked D-glucan backbone (Hayashi et al. 1994). The synthesis and secretion of non-cellulosic polysaccharides such as XyG involves Golgi bodies that ultimately direct materials to the cell wall (Davis et al. 2010). The synthesis of XyG is thought to occur in Golgi cisternae (Cocuron et al. 2007; Chevalier et al. 2010). Additional galactosylation and fucosylation branching occurs during XyG maturation, possibly happening in the medial- and trans- Golgi (Cocuron et al. 2007; Chevalier et al. 2010). The cell wall matrix polysaccharides are transported to the apoplast, ultimately, by the conventional secretory pathway involving syntaxin 61 (SYP61) (Crowell et al. 2009; Drakakaki et al. 2012). Polysaccharide secretion which occurs during exocytosis and endocytosis during cell plate formation is mediated by secretory vesicle clusters (SVCs) which contain the secretory carrier membrane protein (Toyoooka et al. 2009; Toyooka and Matsuoka 2009). Notably, the apoplastic XyG-derived oligosaccharides (XOGs) generated by partial XyG hydrolysis possibly are producing molecules that modulate plant growth, morphogenesis and signal transduction (Cutillas-Iturralde and Lorenzes 1997). It is also possible that these molecules, including XyG, are acting as damage associated molecular patterns (DAMPs) that have a role in defense and if so, function in pathogen associated molecular pattern (PAMP) triggered immunity (PTI) which is described later (Chinchilla et al. 2007; Day et al. 2006; reviewed in Jones and Dangl 2006; Fogorelko et al. 2016; Claverie et al. 2018; Wilkop et al. 2019). The results presented by Niraula et al. (2021) demonstrate that XTH43 functions to increase tightly-bound xyloglucan content and chain number while also decreasing XyG chain length. The observations are consistent with the demonstration of xyloglucan 6...
xylosyltransferase (XXT) (XXT2-5) having a defense role to *H. glycines* in *G. max* (Klink et al. 2017). The importance of glycosylation to defense is demonstrated through the observation that XTH43 is predicted to have a signal peptide, be glycosylated, and with transgenic overexpression in an *H. glycines*-susceptible genotype (G. *max* [Williams 82/PI 518671]) producing a resistant outcome (Gupta and Brunak 2002; Steentoft et al. 2013; Pant et al. 2014; Li et al. 2015; Nielsen 2019). Furthermore, a recent study of over 125 non-randomly-selected genes functioning in defense in the *G. max*-*H. glycines* pathosystem are presented here showing that about 20% of them are predicted to have signal peptides, and be glycosylated (Table 1) (Gupta and Brunak 2002; Steentoft et al. 2013; Li et al. 2015; Nielsen 2019; Klink et al. 2021a). The experiments of Niraula et al. (2021) demonstrate a previously unknown function for XTH, its expression leads to a modification of the cell wall that impairs the susceptible interaction with *H. glycines*. Furthermore, Niraula et al. (2020, 2021) demonstrated XTH43 RNAi greatly increases *H. glycines* parasitism in a *G. max* genotype that is normally resistant to parasitism (G. *max* [Peking/PI 548402]). The results of these experiments which will be placed into context within this review link a major *H. glycines* resistance locus (rhg1) to COG function through a putatively glycosylated protein that produces a specific cell wall modification that leads to a defense response. The review will examine genetic analyses in unicellular and multicellular genetic systems, including plants, that have provided much information on the understudied COG complex.

**Table 1. G. max** genes whose predicted proteins contain signal peptides and are predicted to be either N- and/or O-glycosylated. Genes taken from 126 presented in Klink et al. (2021a).

| Gene                          | Accession            | Signal peptide | Glycosylated |
|-------------------------------|----------------------|----------------|--------------|
| β-glucanase                   | Glyma.08G022300      | yes            | yes          |
| Lipase                        | Glyma.08G137000      | yes            | yes          |
| Unknown, plastocyanin-like    | Glyma.13G158200      | yes            | yes          |
| Unknown                       | Glyma.10G161500      | yes            | yes          |
| Unknown                       | Glyma.13G236100      | yes            | yes          |
| PRI-like                      | Glyma.13G094200      | yes            | yes          |
| Secretory protein             | Glyma.20G130000      | yes            | yes          |
| Cationic peroxidase           | Glyma.02G233800      | yes            | yes          |
| Peroxidase III                | Glyma.04G220600      | yes            | yes          |
| Lipase                        | Glyma.15G264200      | yes            | yes          |
| Pectate lyase                 | Glyma.17G126500      | yes            | yes          |
| Cupin domain                  | Glyma.19G059900      | yes            | yes          |
| Xyloglucan                    | Glyma.17G065100      | yes            | yes          |
| endo-transglycosylase/hydrolase| Glyma.17G065100      | yes            | yes          |
| a-hydroxyaniline glucosidase  | Glyma.11G129600      | yes            | yes          |
| Betv 1 pollen allergen        | Glyma.06G098800      | yes            | yes          |
| Reticuline oxidase            | Glyma.15G132200      | yes            | yes          |
| Pathogenesis related 1        | Glyma.15G062400      | yes            | yes          |
| Galactose mutarotase-like protein, | Glyma.19G020700   | yes            | yes          |
| Pollen Ole e 1 allergen and extensin protein, | Glyma.13G178700 | yes            | yes          |
| Endomembrane protein 70 protein | Glyma.09G096700     | yes            | yes          |
| O-glycosyl hydrolase 17 protein | Glyma.14G020000 | yes            | yes          |
| Glycosyl hydrolase 32 protein | Glyma.13G349300      | yes            | yes          |
| FASCICLIN-like                | Glyma.12G069300      | yes            | yes          |
| arabino-galactan protein 17 precursor | Glyma.15G051600 | yes            | yes          |
| Secreted peroxidase           | Glyma.01G171100      | yes            | yes          |
| Pathogenesis-related thaumatin protein | Glyma.12G064300 | yes            | yes          |
| BRASSINOSTEROID INSENSITIVE 1-ASSOCIATED RECEPTOR KINASE 1 | Glyma.15G051600 | yes            | yes          |

### Targeted genetic analysis of retrograde trafficking

A genetic examination of the retrograde process has been performed in the unicellular eukaryotic genetic model *S. cerevisiae*, resulting in the identification of the Sec35 and Sec34 mutants (Wuestehube et al. 1996). These discoveries have been followed by a number of different studies that provided additional clarity (VanRheenen et al. 1998, 1999; Kim et al. 1999; Speilbrink and Nothwehr 1999). Subsequent studies also examined Sec35 and Sec34 while showing the association with Sec36, *Complexed with Dor1 (Cod1)/Sec38, Cod4, Sec37, Cod6*, and *Dependent on Roc1 (Dor1)* (Whyte and Munro 2001; Ram et al. 2002; Suvorova et al. 2002). The studies demonstrate deficient growth originating from impaired Golgi complex trafficking (VanRheenen et al. 1998; Whyte and Munro 2001; Ram et al. 2002; Suvorova et al. 2002). Continued studies in mammalian systems (human) led to the identification of a cis-Golgi vesicle tethering machinery protein-coding gene having homology to the *S. cerevisiae* Sec34 (to be named COG3) (Suvorova et al. 2002). Subsequent studies resulted in the identification of the remaining genes, the CONSERVED OLIGOMERIC GOLGI (COG) protein complex name, and gene designations; COG1 (Sec36), COG2 (Sec35), COG3 (Sec34), COG4 (Cod1)/Sec38), COG5 (Cod4), COG6 (Sec37), COG7 (Cod6), and COG8 (Dor1) (Ungar et al. 2002). Consequently, the COG complex is a ubiquitous component of the endomembrane system in eukaryotes (Ungar et al. 2002).

The structure of the COG complex is composed of 8 proteins organized into 2 lobes, termed lobes A and B (Whyte and Munro 2001; Ungar et al. 2002, 2005; Fotso et al. 2005; reviewed in Blackburn et al. 2019). Lobe A is composed of COG1-4 while lobe B is composed of COG5-8. The means by which the COG complex is attached to the Golgi membrane is unclear. What is known is that Golgi localization of lobe A occurs independently of lobe B (Vasile et al. 2006; Willett et al. 2016). The major connection of the lobe B protein COG8 to lobe A occurs through COG1 (Whyte and Munro 2001; Ungar et al. 2002, 2005; Fotso et al. 2005; reviewed in Blackburn et al. 2019). Additional linkages exist between the COG complex and different membrane trafficking machinery components including Rabs, soluble N-Ethylmaleimide-Sensitive Factor Attachment Protein Receptor (SNARE) proteins, its interacting proteins, various coiled-coil-containing tethers, and molecular motors facilitating subsequent cellular events that lead to the outcome to which it is associated (i.e. glycosylation) (reviewed in Blackburn et al. 2019). Some of these linkages may include COG4 to STX5 and SLY1, and COG2 to P115 (Sohda et al. 2007; Laufman et al. 2013; Willett et al. 2013, 2014).

### Early genetic studies identify COG complex genes in genetic model multicellular animal systems

Experiments subsequent to those performed in *S. cerevisiae* involving the COG complex and those of the ldl mutants then have been performed in multicellular genetic models including *D. melanogaster* (insect), *C. elegans* (unsegmented
pseudocoelomate), and *Danio rerio* (vertebrate) (Farkas et al. 2003; Ho et al. 2006; Kubota et al. 2006). Studies in *D. melanogaster* have identified COG5 and COG7 functioning in cytokinesis, cell elongation, and the assembly of a specialized Golgi architecture during spermatogenesis, while having additional general roles (Farkas et al. 2003; Belloni et al. 2012; Frappalo et al. 2017). The pleiotropic effects indicate a broad function in cell physiology for the COG complex and, by the conserved nature of the COG complex, reveal they spanned evolutionary distance. Experiments presented in *C. elegans* have identified cog1 and cog3 mutants affecting glycosylation, and relating to organ morphogenesis (Kubota et al. 2006; Struve and Reinhold 2012). Clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR associated protein 9 (CRISPR-Cas9) gene editing also has provided crucial information on COG function as shown in *C. elegans*. For example, while *C. elegans* cog4 mutants, surprisingly, exhibit no morphological anomalies, other defects have been revealed through RNA interference (RNAi) targeting its COG1, 2, 3, 5, 6, 7, and 8 genes in the CRISPR-Cas9-generated cog4 genetic background (Zafra et al. 2021). The work of Zafra et al. (2021) is particularly important because it uses CRISPR-Cas9 of COG4 in *C. elegans* to understand the ultra-rare human Saul-Wilson Syndrome (SWS) that is caused by a G515R mutation in the COG4 protein. SWS is a skeletal dysplasia leading to pri-mordial dwarfism and progeroid appearance (Xia et al. 2021). The *D. rerio* fat-free (ff) mutation found in cog8 produces an impairment of lipid transport while a dominant mutation in cog4 results in pleiotropic defects including impaired gastrulation, decrease in body length, and larval stage defects in jaw cartilage chondrocyte intercalation (Ho et al. 2006; Xia et al. 2021). The defects caused by cog4 G516R mutation in *D. rerio* are important to understand as they relate to SWS. Importantly, the experiments demonstrate how generating highly deleterious mutations in genetic model COGs like those of *D. rerio* that are originally identified in humans can provide a way in which to understand the function(s) of genes that are central to metabolism and are otherwise difficult to study in multicellular organisms. This point is important in understanding the COG complex as it relates to plant biological processes and those involving interactions with pathogens.

### The function of the human COG complex

A large body of work exists on human COG complex genes, particularly in relation to the identification of severe genetic defects, and even mortality caused by their mutations (reviewed in D’Souza et al. 2020). The COG-CDG defects resulting from naturally occurring mutations in COG complex are currently identified for 7 of the 8 COG complex genes (Wu et al. 2004; Foulquier et al. 2006; Kranz et al. 2007; Paesold-Burda et al. 2009; Reynolds et al. 2009; Lübbershusen et al. 2010; Kodera et al. 2015). More than 100 individuals having mutations spanning 7 of the 8 COG complex genes (COG1, 2, 4, 5, 6, 7, and 8), and consisting of 31 different mutations, exist (reviewed in D’Souza et al. 2020). It is unclear why mutations do not occur for COG3, but perhaps cog3 mutants in humans result in lethality. COG3 (Sec34p) binds to COG1 (Sec36p) and COPI (Sec21p-γ-COP1) in *S. cerevisiae* and human cell lines, important linkages to the central hub of the COG complex and vesicle, respectively (Suvarova et al. 2002; Zolov and Lupashin 2005). COG3 CRISPR-Cas9 knock-outs (KOs) in human cell lines lead to deficiencies in cis/medial-Golgi glycosylation, nearly abolishing Cholera toxin binding, but these deficiencies are also found in other examined COG complex genes (Blackburn et al. 2016; Blackburn and Lupashin 2016). COG3 CRISPR-Cas9 KOs have morphological defects in Golgi structure, impaired retrograde trafficking and sorting along with aberrant sialylation and fucosylation (Blackburn and Lupashin 2016). The sialylation of N-glycans play essential roles relating to pathogen recognition, the immune system, and cancer while fucosylation functions in cell–cell interactions, inter-cellular and intracellular recognition, inflammatory processes, and fertilization, indicative of central roles in cell physiology (Vajaria et al. 2016; Hüllen et al. 2021). However, defect severity varies according to the affected subunit (Blackburn and Lupashin 2016; Adusumalli et al. 2021). Mutant cog5 produces Leber congenital amaurosis, an unfolded protein response (UPR) leading to the upregulation of protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), a UPR modulator which could activate a number of different signaling processes (Tabbarah et al. 2020). Lobe A KOs (including COG3) exhibit a more defective Golgi appearance and have the most hypo-glycosylated lysosome-associated membrane protein 2 (LAMP2) (Blackburn et al. 2016). LAMP2 is a heavily glycosylated protein functioning with LAM1 to regulate autophagy which otherwise leads to embryonic lethality (Terasawa et al. 2016). This result may explain why naturally occurring cog3 mutants are not identified in humans. The numbers of human cog mutants in existence in relation to the 31 different mutations in more than 100 individuals include cog1 (2 mutations), cog2 (2 mutations), cog3 (0 mutations), cog4 (4 mutations), cog5 (10 mutations), cog6 (6 mutations), cog7 (2 mutations), and cog8 (5 mutations) (reviewed in D’Souza et al. 2020). Great phenotypic diversity is seen between individuals, making the development of a homogeneous platform to study COG complex functionality of paramount importance. The COG complex components physically and functionally interact while also binding with other vesicle trafficking components. These mutations likely alter the effectiveness of the various complex components to establish and bind with other proteins, changing the ability of Golgi vesicles to traffic and transport cargo. Consistent with this idea, the acute knock-down (KD) of COG3 produced COG complex-dependent (CCD) vesicle accumulation and notably, these vesicles carried Golgi v-SNARE molecules (Zolov and Lupashin 2005). The recycling intermediates are mistargeted and ultimately undergo degradation. Therefore, while COG proteins do not bind Golgi-resident enzymes, disruption of the receptor alters their ability to function. The development of single cell models is providing a crucial platform to better understand the COG complex-related diseases (Sumya et al. 2021). The information presented here is important to understand their role in plant interactions involving the COG complex.

### The COG complex in a model plant genetic system identifies its basic functions

While a previous study identified a COG gene sequence (ldlb-like, COG1) in *A. thaliana*, the initial identification of a role of a COG gene in plants occurred in *A. thaliana* (JOURNAL OF PLANT INTERACTIONS 347)}
with the discovery of the EMBRYO YELLOW (EYE) gene (Chatterton et al. 1999; Ishikawa et al. 2008). EYE was shown to be homologous to the human and Drosophila COG7 (Ishikawa et al. 2008). The eye mutant exhibited abnormal embryo coloration and morphology, produced bushy plants having an aberrantly organized shoot apical meristem (SAM) producing irregular phyllotaxy and unexpanded leaves (Ishikawa et al. 2008). The epidermis is characterized by the presence of much smaller cells as compared to the wild-type, indicating a role in cell and organ expansion, organization, and extracellular matrix production (Ishikawa et al. 2008).

Subsequent experiments performed in A. thaliana have identified cog2, cog3, cog6, cog7, and cog8 mutations impairing cell expansion and meristem organization (Oda et al. 2015; Tan et al. 2016; Vukašinović et al. 2017; Rui et al. 2020, 2021). The results imply functions for the plant COG complex in cell wall organization and structure. These observations are significant due to the importance of correct cell wall structure during other aspects of the plant life cycle, including defense during plant-pathogen interactions (Darvill et al. 1985). A role for the COG complex in cell wall biology is not limited to plants as mutations in Aspergillus nidulans COG2 and COG4 result in abnormal staining of the cell wall; indicating defects in cell wall structure, composition, or both (Gremillion et al. 2014). These observations are consistent with the defects found in the plant cell walls, indicating a conserved role in the processes by which they are generated. The secretion of other materials, delivering them into the cell wall, further demonstrates the importance of vesicle transport in the generation of it, and positioning of materials and proteins for its subsequent enzymatic modification and defense processes (Hart et al. 1993). Studies reveal numerous plant and fungal cell wall components are synthesized in the Golgi as glycoproteins and proteoglycans with proper functionality of the Golgi glycosylation machinery being essential for the correct assembly and organization of their cell walls, including fungal virulence (Moore et al. 1991; Burget et al. 2003; López-Fernández et al. 2013; Poulsen et al. 2015; Ford et al. 2016; Wang et al. 2017; Okekeogbu et al. 2019). Oda et al. (2015) have identified 2 novel coiled-coil proteins including vesicle tethering 1 (VETH1) and VETH2 that recruit the exocyst protein EXO70A1. The exocyst performs many roles in defense interactions occurring between plants and pathogens, including bacteria, fungi, parasitic nematodes, and insects (Pecenková et al. 2011; Guo et al. 2018; Sharma et al. 2020). The exocyst, like the COG complex, is a multi-protein complex also composed of 8 proteins encoded by the Sec3 (EXOC1), Sec5 (EXOC2), Sec6 (EXOC3), Sec8 (EXOC4), Sec10 (EXOC5), Sec15 (EXOC6) Exo70 (EXOC7), and Exo84 (EXOC8) genes and is important for vesicle transport (TerBush and Novick 1995; TerBush et al. 1996; Guo et al. 1999; He and Guo 2009). Furthermore, structural similarities have been identified between COG and exocyst proteins (Cavanaugh et al. 2007; Richardson et al. 2009; Lees et al. 2010; Ha et al. 2016). EXO70A1 has a number of roles in plant cell biology and various interactions including polar growth, PINOID (PIN) auxin efflux carrier recycling and polar auxin transport, localized deposition of seed coat pectin, cytokinesis and cell plate maturation, pollen self-incompatibility, tracheary element development, regulation of root cell elongation and meristem size, exocytosis, xylem development, Casparian strip development, plasma membrane phosphatidylinositol 4,5-bisphosphate (PIP2)-binding, and vegetative growth (Synek et al. 2006, 2021; Samuel et al. 2009; Fendrych et al. 2010; Kulich et al. 2010; Drdová et al. 2013; Li et al. 2013; Cole et al. 2014, 2018; Zhang et al. 2016; Kalmbach et al. 2017; Vukašinović et al. 2017; Kubátová et al. 2019; Larson et al. 2020; De Caroli et al. 2021; Pang et al. 2021; Wu et al. 2021; Zhang et al. 2021; Ortmannová et al. 2022). VEHT1 and VEHT2 are shown to be essential for correct patterning of secondary cell wall deposition, leading to their binding to the cortical microtubules through an interaction with COG2 (Oda et al. 2015). Plant secondary cell walls are composed largely of XyG, metabolized by XTH, which has a signal peptide and is glycosylated as it is transported to the apoplast to modify the cell wall structure (Fry et al. 1992; Méndez-Yañez et al. 2017). Notably, the glycosylated XTH has a more stable interaction with its ligand which may increase its efficiency (Méndez-Yañez et al. 2017). XTH is described in a later section when it is expanded on in the review of the G. max COG complex function in the defense interaction with the parasitic nematode H. glycines ( ). Similar results are obtained by Vukašinović et al. (2017) for COG2 and EXO84b. Like EXO70A1, EXO84b functions in cytokinesis and cell plate maturation; plasma membrane dynamics; rapid root cell elongation and determination of meristem size, PEN3 ATP-binding cassette (ABC) transporter lateral membrane trafficking and polar tethering, and xylem development (Fendrych et al. 2010, 2013; Cole et al. 2014; Mao et al. 2016; Vukašinović et al. 2017). The G. max exocyst functions in generating its defense interaction to H. glycines, further strengthening the results obtained for its COG complex (Lawaju et al. 2020; Sharma et al. 2020). The A. thaliana COG3 and COG8 proteins are essential for the growth of pollen tubes, functioning in maintaining Golgi morphology and homeostasis during vesicle trafficking (Tan et al. 2016). The results of Rui et al. (2020) for COG6 are similar to Tan et al. (2016) in that they identify roles for COG6. Importantly, Rui et al. (2021) identify the A. thaliana Syn- taxin of plants 31 (SYF31) and SYF32 maintain the morphology of the Golgi apparatus and are essential for pollen development, happening through their interactions occurring directly with COG3. These results are important because they corroborate much earlier observations of a defense interaction function for the G. max SYF31 (Gm-SYP38) against H. glycines which is described in a later section (Pant et al. 2014).

The COG complex and defense during interactions with pathogens-Hordeum vulgare (barley)

The earliest indication that the COG complex plays important defense functions in plants in their interactions with pathogens came from a study made by Ostertag et al. (2013). In the study, Ostertag et al. (2013) used a non-comprehensive keyword-based query approach to identify proteins involved in membrane trafficking in S. cerevisiae, plants, and metazoans. The use of transient-induced gene silencing (TIGS) in Hordeum vulgare (barley) epidermal cells mediated by microprojectile-mediated transformation of B. graminis f. sp. hordei spores, by increasing susceptibility, led to the identification that HvCOG3 (AK249208), HvEXO70F-like (AK362856), and HvARFA1b/c
(TA29770_4513) perform defense functions as compared to an empty vector control. Furthermore, as expected TIGS of the susceptibility gene MILDEW LOCUS O (MLO) led to an increase in resistance. In their studies, Ostertag et al. (2013) acknowledged that very little was understood regarding the COG complex and plant interactions with pathogens that lead to defense. Consequently, they ran the opposite experiment whereby HvCOG3, driven by the CaMV promoter was transiently overexpressed in H. vulgare epidermal cells. The overexpression led to a significant, 71% decrease in penetration rate of B. graminis f. sp. hordei in experiments that enumerated the percentage of penetrated cells relative to all attacked cells (Ostertag et al. 2013). The results clearly demonstrated a defense role for HvCOG3 and very likely, were indicative of what would be found for the remaining components of the COG complex although they were not examined up to that point. However, the suppressed infection could also be explained that by a disbalance had been produced between COG subunits by overexpression of COG3, leading to a partial dysfunction of lobe A and, thus, the entire COG complex and in doing so, altering the Golgi glycosylation pattern which could change the cell wall composition and thus, indirectly affect B. graminis penetration rate. Ostertag et al. (2013) employed two different constructs to understand whether HvCOG3 was involved in secretion. The first construct contained an enhanced green fluorescent protein (GFP) fused with a signal peptide (s) that they hypothesized would lead to the engineered GFP having the signal peptide (sGFP) (Ostertag et al. 2013). This signal peptide would facilitate its movement into the secretion system and, ultimately, the sGFP would be secreted in comparison to a GFP lacking the secretion signal (Ostertag et al. 2013). The hypothesis was that the sGFP* cells would exhibit less GFP fluorescence due to sGFP being secreted in comparison to the GFP* cells whose GFP lacked the secretion signal. This hypothesis turned out to be proven true whereby sGFP* cells had less measurable GFP signal than the GFP* control lacking the secretion signal (Ostertag et al. 2013). In contrast, co-transfection with the HvCOG3 TIGS construct led to an increase in GFP fluorescence generated by the sGFP construct within the sGFP* cell as compared to the control (Ostertag et al. 2013). This result was taken as evidence that the HvCOG3 TIGS impaired secretion and microscopic analyses demonstrated strong sGFP fluorescence at the nucleus and tubular structures that may represent ER localization or leakage into the cytoplasm under conditions hampering Golgi transport (HvCOG3 TIGS) (Ostertag et al. 2013). To bring greater clarity to this observation, Ostertag et al. (2013) co-expressed the HvCOG3 RNAi construct along with a green fluorescing Golgi marker protein containing the HDEL target peptide, sGFPHDEL, produced by an in-frame substitution of part of H. vulgare CALRETICULIN 3 gene with the GFP gene sequence (reviewed in Hückelhoven and Panstruga 2011). The sGFPHDEL co-localizes with the known G. max endo-β-mannanase 1 (GmMAN1) red fluorescent protein (RFP) -linked Golgi marker (Yang et al. 2005). The experiment quantified the number of detectable Golgi bodies revealing HvCOG3 TIGS reduced the amount of Golgi bodies, consistent with the observations of Zolov and Lupashin (2005) (Pavelka and Ellinger 1983; Ostertag et al. 2013). Later, Ostertag et al. (2013) has performed TIGS of all of the remaining HvCOGs (1, 2, 4, 5, 6, 7, and 8), demonstrating that while each experiment resulted in an increase in susceptibility that only HvCOG1 and HvCOG3 did so to a statistically significant level.

**G. max as a model to understand the COG complex**

The studies presented in the animal systems have identified their orthologous COG complex genes, discovered highly deleterious naturally occurring mutations, revealed how COG relative protein concentrations influence the amount of other COG gene products, and delineated signaling events that underlie their regulation (Ungar et al. 2002; Sarkas et al. 2003; Wu et al. 2004; Zolov and Lupashin 2005; Foulquier et al. 2006; Ho et al. 2006; Kubota et al. 2006; Kranz et al. 2007; Paesold-Burda et al. 2009; Reinders et al. 2009; Lübbehuesen et al. 2010; Kodera et al. 2015; Xia et al. 2021). The results indicate analogous regulatory features may exist in plants and that the information generated in these systems may help better understand animal biology. The identification of the G. max SYP38 (STX5 [Sed5p homolog]) functioning during the defense response that G. max has to H. glycines provides a probe into plant COG complex biology (Pant et al. 2014; Rui et al. 2021). Recent studies employing single cell systems to distill knowledge out of various processes involving the COG complex down to their basic unit simplify its understanding (Blackburn et al. 2016, 2019; Blackburn and Lupashin 2016; Sumya et al. 2021; reviewed in D’Souza et al. 2020). However, in many cases, an understanding of the process requires its intact cellular environment when studying specific systems. Such a case is G. max, one of the most important crop plants on a global scale that experiences numerous abiotic and biotic challenges in dire need of study (Savary et al. 2019). The Golgi apparatus performs many functions with glycosylation featured prominently in various processes (Okamoto et al. 2015; Yin et al. 2017; Su et al. 2018; Tsuno et al. 2018; Xia et al. 2020). This point is important due to the importance of glycosylation in defense and, in particular, immune receptor biology (Trempel et al. 2016).

**G. max is a crop with a sequenced genome of approximately 978 megabases (Mb), having approximately 56,044 protein-coding loci** (Schmutz et al. 2010; Goodstein et al. 2012). Further analysis predicts approximately 88,647 transcripts, indicating alternative splicing is an important feature of G. max biology (Schmutz et al. 2010; Goodstein et al. 2012; Klink et al. 2021b; Zhou et al. 2021). G. max seed yield is severely impaired by interactions with H. glycines, causing more agronomic loss than any single other pathogen (Allen et al. 2017). A cell biology and developmental genomics approach has been used to study the G. max infection by H. glycines, unraveling the nature of its defense response (Klink et al. 2005, 2007, 2009, 2010a, 2010b, 2011, 2021a, 2021b; Matsye et al. 2011, 2012; Pant et al. 2014; Sharma et al. 2016, 2020; McNeece et al. 2019; Lawaju et al. 2020; Niraula et al. 2020, 2021). In those studies laser microdissection (LM) has been used to isolate pericycle (experimental control) and very likely, epidermal cells) at 0 days post infection (dpi) and parasitized root cells (syncytia) undergoing a defense response at 2 different time points (3, and 6 dpi) in 2 different genotypes capable of interactions that lead to susceptible and resistant reactions (in G. max[Peking/PI 548402] and G. max[PI 88788]) that are dependent on the race of H. glycines used for the infections.
The G. max COG complex is composed of 2 COG paralogs for each of the COG1-8 genes (16 total COG genes), consistent with the allotetraploid nature of its genome (Schmutz et al. 2010; Lawaju et al. 2020). Targeted study of agricultural crops of global importance and in the U.S. provide an understanding of COG gene family structure and the presence of alternate splice variants while, until recently, very little functional information had existed (Klink et al. 2021b). Analysis of G. max COG gene expression occurring in shoot apical meristems, stems, leaves, root hairs, root nodules, flowers, seed pods, and seeds have identified the relative transcript abundances (RTAs) of each COG1-8 paralog, and alternative splice variants (Goodstein et al. 2012; Klink et al. 2021b). The maintenance of each paralog indicates each has important functions since gene duplication can lead to the loss of the extra gene copy if it does not perform a function (Klink et al. 2021b). Analysis of LM data has identified COG gene expression occurring within syncytia undergoing a defense interaction with H. glycines in the G. max [Peking/PI 548402] and G. max [PI 88788] genotypes (Klink et al. 2021b). These paralogs include COG1-2, COG2-2, COG4-2, COG5-1, COG6-1, and COG7-2 (Lawaju et al. 2020; Klink et al. 2021b). Importantly, COG7-2 has an alternate splice variant (COG7-2-b) that is expressed within the syncytium (Lawaju et al. 2020; Klink et al. 2021b). COG3-1 and COG8-1 expression occurring within syncytia undergoing the defense response cannot be ruled out since their RTAs could not be determined because probe sets are not fabricated onto the microarrays (Klink et al. 2021a). The analyses have identified alternate splicing of COG complex components occurring during G. max resistance during its interactions with H. glycines (Lawaju et al. 2020; Klink et al. 2021a). The importance of the alternate splicing and functionality of the COG genes in defense would require functional transgenic analysis to make the determination.

**Functional transgenic analyses of G. max COG genes relating to defense to H. glycines**

Functional transgenic analyses employing COG overexpression and generation of a condition mimicking a hypomorphic null allele (RNAi), using expression vectors designed specifically to examine their effect on the G. max defense response to H. glycines parasitism, reveal COG complex component function (Lawaju et al. 2020; Klink et al. 2021a). The experiments show that only the COG paralogs that are expressed within the syncytium undergoing the defense response (COG1-2, COG2-2, COG4-2, COG5-1, COG6-1, and COG7-2-b), and whose expression could not be determined due to the lack of probe sets (COG3-1, and COG8-1) function in the interaction that leads to a defense response (Lawaju et al. 2020; Klink et al. 2021a). Notably, the overexpression of components of the COG complex are among the most effective ways, among over 125 studied genes, in suppressing H. glycines parasitism (Lawaju et al. 2020; Klink et al. 2021a). COG gene overexpression can lead to as high as an 87.12% decrease in parasitism (i.e. COG1-1–OE) (Lawaju et al. 2020; Klink et al. 2021a). In contrast, RNAi leads to as high as a 22.1-fold increase in H. glycines parasitism (i.e. COG7-2-b–RNAi) which makes them more susceptible than the H. glycines-susceptible G. max [Williams 82/PI 518671] genotype control check used in the experiments (Lawaju et al. 2020). The observation of the G. max COG7-2-b functions in defense may be the first demonstration in plants of the importance of a specific COG splice variant other than its primary transcript in a biological process, providing a window into understanding the diversity of COG gene and/or complex functions. Surprisingly, under the analysis procedures, in few cases does COG overexpression or RNAi generate quantifiable effects on root mass (Lawaju et al. 2020). These outcomes may be due to the specific functions of the G. max COG genes occurring in specific cells at specific times in defense interactions or other processes relating to its allotetraploid nature. In the cases that do exhibit statistically significant effects, COG3-1, COG4-1, COG4-2, and COG5-1 overexpression decreases root mass as compared to the control (Lawaju et al. 2020). In contrast, COG3-1, COG4-1, COG5-1, COG7-1, and COG7-2 RNAi increases root mass as compared to the control (Lawaju et al. 2020). COG3-1, COG4-1, COG5-1 have overlapping but opposite outcomes occurring between the overexpression and RNAi experiments as would be expected for effects that are specifically attributed to gene function.

**G. max COG complex-interacting partners and pathogen defense**

The α-SNAP-5 gene found in the rhg1 locus is largely believed to be the rhg1 gene itself (Matsye et al. 2011, 2012; Pant et al. 2014; Sharma et al. 2016; Liu et al. 2017; Lakhssassi et al. 2020a, 2020b). An important aspect of the Lakhssassi et al. (2020a) work is the identification of the Bet VI pathogenesis-related protein Glyma.08G323000, described as promoting a molecular interaction between the Rhg4 protein GmSHMT08 and rhg1 protein GmSNAP18 (α-SNAP-5) during the G. max defense response to H. glycines. The S. cerevisiae α-SNAP (Sec17p) binds the S. cerevisiae SYP31 homolog Sed5p which also binds to COG4 and COG6 (Novick et al. 1980; Hardwick and Pelham 1992; Lupashin et al. 1997; Sheshakova et al. 2007; Bubeck et al. 2008). The G. max SYP31 homolog, SYP38, functions in the defense process to H. glycines (Pant et al. 2014). Furthermore, co-regulated expression occurs between SYP38 and α-SNAP-5 (Pant et al. 2014). Lawaju et al. (2020) took those experiments further, showing an increased SYP38 RTA in each of the transgenic COG gene (i.e. COG1-2, COG2-2, COG3-
COG complex genes are co-regulated in *G. max*

The expression of the *G. max rhg1* gene, α-SNAP-5, occurs with SYP38 in the syncytium undergoing a defense response interaction to *H. glycines* parasitism (Pant et al. 2014). Like the analyses presented for α-SNAP-5, transgenic experiments show SYP38 functions in the defense response to *H. glycines* parasitism (Pant et al. 2014). Furthermore, as stated, α-SNAP-5 and SYP38 are co-regulated in their expression (Matsye et al. 2011, 2012; Pant et al. 2014; Sharma et al. 2016). SYP38, homologous to Sed5p, is a component of the Golgi SNARE complex and interacts with COG4 and COG6 (Shestakova et al. 2007). Furthermore, the *A. thaliana* COG3 interacts with SYP31 (GmSYP38 homolog), strengthening the hypothesis that COG complex subunits and SYP31 act together (Rui et al. 2021). The result supports the hypothesis that the *G. max* COG complex, as an interactor with SYP31 (that also interacts with α-SNAP-5) functions in its defense response interaction to *H. glycines* parasitism (Pant et al. 2014). In an expansion of this co-regulation concept to COG genes, Zolov and Lupashin (2005) showed how a siRNA of *Cog3* in human HeLa cells leads to the expected decrease in Cog3p accumulation. However, Cog3 siRNA also leads to a decrease in Cog1p, Cog2p, and Cog4p abundance (Zolov and Lupashin 2005). Further analysis demonstrates Cog3 siRNA has no effect on Cogs5p-8p protein content (Zolov and Lupashin 2005). Since Cog3 siRNA only affects protein accumulation of the components of COG complex lobe A, there appears to be some level of specificity while also demonstrating that the complex members can sense and surveil interacting...
members. This outcome could occur at the transcriptional level or through targeted protein degradation that results in the maintenance of correct protein component stoichiometry.

Experiments presented in *G. max* examine the RTAs of each COG gene functioning in defense to *H. glycines* as they relate to COG gene overexpression or RNAi (Lawaju et al. 2020; Klink et al. 2021b). The results demonstrate that in many cases the overexpression of a tested COG gene that functions in defense leads to an increase in RTA of the other tested COG genes (Lawaju et al. 2020; Klink et al. 2021b). RNAi of these same COG genes typically has the opposite effect (Lawaju et al. 2020; Klink et al. 2021b). The results are consistent with the siRNA experiments of Zolov and Lupashin (2005). However, Zolov and Lupashin (2005) did not perform reciprocal experiments or examine overexpression as was done in Klink et al. (2021b). The results provide compelling evidence that the COG complex proteins in animals and plants are somehow sensing the relative levels of the other components of the complex and utilizing that information in ways that relates to gene expression and/or protein abundance (Zolov and Lupashin 2005; Klink et al. 2021b). A detailed gene expression analysis of COG complex-interacting proteins had, thus, been warranted.

**Figure 2.** The role COG complex proteins play in the defense response that *G. max* has to *H. glycines* parasitism. The specific *G. max* COG complex proteins are COG1-2, COG2-2, COG3-1, COG4-2, COG5-1, COG6-1, COG7-2-b, and COG8-1. The large, dashed line surrounding the COG complex proteins represents the co-regulated gene expression occurring among their encoding COG genes as demonstrated by Lawaju et al. (2020). Harpin treatment leads to an increase in RTA for COG1-2, COG2-2, COG3-1, COG4-2, COG5-1, COG6-1, COG7-2-b, and COG8-1 (Lawaju et al. 2020). α-SNAP is believed to be rhg1 (Matsye et al. 2011, 2012; Sharma et al. 2016; Liu et al. 2017). Serine hydroxymethyltransferase (SHMT) is believed to be Rhg4 (Liu et al. 2012). Bet (Bet VI) is believed to provide a link between α-SNAP-5 and Rhg4 (Lakshussi et al. 2020a, 2020b). SYP38 overexpression leads to an increase in RTAs at various points for XTH43. NONEXPRESSOR OF PR1 (NPR1-2), ENHANCED DISEASE SUSCEPTIBILITY 1 (EDS1-2), BIK1-6, PATHOGENESIS RELATED 1 (PR1-6), PR3 and SHMT. The association of COG proteins with membranes does not imply direct contacts as direct contacts are likely occurring through other weak and transient proteinaceous or substrate associations (Antoniow and Pierpoint 1978; Legrand et al. 1987; Fry et al. 1992; Cao et al. 1994; Falk et al. 1999; Veronese et al. 2006; Liu et al. 2012; Pant et al. 2014; reviewed in Blackburn et al. 2019).

### G. max COG complex gene expression influences the syntaxin 31 homolog SYP38

The co-regulated expression occurring between α-SNAP-5 and SYP38, and interactions of their protein products with COG complex proteins at some level, indicates the possibility of regulated expression happening between SYP38 and COG genes (Rui et al. 2021). The overexpression of *G. max* COG1-2, COG2-2, COG3-1, COG4-2, COG5-1, COG6-1, COG7-2-b, and COG8-1 increase SYP38 RTA (Lawaju et al. 2020). In contrast, COG4-2 and COG5-1 RNAi decrease SYP38 RTA while the others have no statistically significant effect (Lawaju et al. 2020). The results provide clear evidence that the RTAs of COG genes and SYP38 are intertwined much like that of α-SNAP-5 and SYP38 (Pant et al. 2014; Lawaju et al. 2020). Rui et al. (2021) show the *A. thaliana* SYP31 and SYP32 maintain the morphology of the Golgi apparatus and are essential for pollen development through direct interactions with COG3. The *S. cerevisiae* SYP31 homolog, Sed5p binds Sec17p, a homolog of the mammalian α-SNAP (Hardwick and Pelham 1992; Lupashin et al. 1997; Bubeck et al. 2008; Matsye et al. 2012; Pant et al. 2014; Sharma et al. 2016). Sec17p is sufficient for or can work in concert with Sec18p (N-ethylmaleimide Sensitive Fusion Protein [NSF]) at the fusion step of vesicle and target membranes, consistent with defense roles in plants for SNARE and defense roles for *G. max* α-SNAP-5, NSF-1 and SYP38 (Collins et al. 2003; Matsye et al. 2012; Pant et al. 2014; Zick et al. 2015; Sharma et al. 2016; Song and Wickner 2021). Evolutionary studies have determined that the conserved nature of the COG complex results from constraints required for maintaining the interactions occurring between the individual COG complex components, as well with other vesicular trafficking partners which preserve its functional integrity (Koumandou et al. 2007; Smith and Lupashin 2008; Quental et al. 2010).

### Plant defense gene expression relating to COG complex function during pathogen interactions

The animal COG complex functions to a certain extent in defense processes involving sialylation, among other processes (Vajjaria et al. 2016; Hüllen et al. 2021). Plant defense processes function through a two stage platform including PTI and effector triggered immunity (ETI) (Chinchilla et al. 2007; Day et al. 2006; reviewed in Jones and Dangl 2006). PTI is engaged when a cell surface pattern recognition receptor (PRR) recognizes a PAMP, leading to the activation of a co-receptor that induces phosphorylation of a cytoplasmic receptor-like kinase, ultimately leading to activation of mitogen activated protein kinase (MAPK) signaling and generation of a downstream output defense response (Chinchilla et al. 2007; Day et al. 2006; reviewed in Jones and Dangl 2006). MAPK is a conserved protein, functioning along with mitogen activated protein kinase (MAPKK) and mitogen activated protein kinase kinase kinase (MAPKKK) as a cooperative enzyme switching cells from one discrete state to another (Sturgill and Ray 1986; Rossomando et al. 1987, 1989; Boulton et al. 1991; Boulton and Cobb 1991; Dérijard et al. 1994; Freshney et al. 1994; Han et al. 1994; Kyriakis et al. 1994; Lee et al. 1994; Rouse et al. 1994; Lee et al. 1995; Zervos et al. 1995; Zhou et al. 1995; Huang and Ferrell 1996). MAPKs are shown in *G. max* to regulate
COG gene expression which will be discussed later (Chang et al. 2007; McNeece et al. 2019; Klink et al. 2021a). This observation may relate, analogously, to the relationship between COGs, Wnts, and MAPKs in animal systems (Chang et al. 2007; Xia et al. 2021). Plant PRRs and associated co-receptor proteins processed through the endomembrane system are important to defense (Mbengue et al. 2016; Collins et al. 2020). A stronger defense platform, ETI, can become receptor kinase-activated, leading to further engagement of its interacting cytoplasmic receptor like kinases driving the phosphorylation of MAPKs and generating an output defense response. However, if activation reaches a certain threshold, a hypersensitive response (HR) ensues, sacrificing the cell and tissue. G. max has 32 MAPKs, 11 MAPKKs, and 150 MAPKKKs, indicating their interactions are intricate, exhibit a level of specificity, and do relate to COG RTAs (Neupane et al. 2013; McNeece et al. 2019; Klink et al. 2021b). The analysis of G. max synctia undergoing a defense response identifies 12 MAPKs undergoing expression in those cells during the defense response, indicating some may have a specific localized defense function. A functional transgenic analysis of the 32 MAPKs, producing roots undergoing overexpression or RNAi, demonstrate 9 that function in defense and are referred to as defense MAPKs (McNeece et al. 2019). Analyses show 7 (i.e. MAPK2, MAPK3-1, MAPK4-1, MAPK6-2, MAPK16-4, and MAPK20-2) undergo expression in syncytia undergoing the defense response (McNeece et al. 2019). MAPK5-3 and MAPK13-1 could not be determined to exhibit expression within the syncytium due to the lack of microarray probe sets (McNeece et al. 2019). None of the MAPKs lacking expression within the syncytium function in defense (McNeece et al. 2019). RNA-seq experiments of the defense MAPK-OE root RNA, confirmed by RT-qPCR, show in specific cases that MAPKs increase the RTA of COG genes (Lawaju et al. 2020) (Figure 2). Furthermore, COG RTAs are increased by treatment with the Erwinia amylovora (fire blight) bacterial signaling effector harpin (Wei et al. 1992; Lawaju et al. 2020). The result relates, analogously, to the effect that Wnt has with p38 MAPK in animal systems in signaling (Chang et al. 2007). Other nematode associated molecular pattern (NAMP) effectors (i.e. ascR18) activate MAPK3 and MAPK6 but have not been demonstrated to involve the COG complex (Manosalva et al. 2015). However, RT-qPCR in G. max has identified several proven defense genes experience an increase in RTAs by MAPK overexpression (McNeece et al. 2019). Harpin treatment also leads to an increase in RTA of the plasma membrane anchored coiled-coil nucleotide binding leucine rich repeat (CC-NB-LRR) PTI gene NONRACE-SPECIFIC DISEASE RESISTANCE 1 (NDR1), that interacts with the nitrate-induced (NOI) domain-containing, intrinsically disordered, molecular recognition feature (MoRF)-containing RPM1-INTERACTING PROTEIN 4 (RIN4), the CC-NB-LRR protein RESISTANCE TO PSEUDOMONAS SYRINGAE PV MACULICOLA1 (RPM1) and the CC-NB-LRR RESISTANCE TO PSEUDOMONAS SYRINGAE2 (RPS2), ultimately functioning through MAPKs to effect a defense response (Tamkun et al. 1986; Wei et al. 1992; Kunkel et al. 1993; Century et al. 1995, 1997; Grant et al. 1995; Shapiro and Zhang 2001; Mackey et al. 2002, 2003; Copppinger et al. 2004; Day et al. 2006; Knepper et al. 2011; Sun et al. 2014; Aljaafri et al. 2017; McNeece et al. 2017, 2019).

**Downstream functionality of Golgi-processed defense proteins**

LM of syncytia, accompanied by RNA-seq of the isolated cells undergoing a defense response to H. glycines parasitism, identify a number of expressed putatively-Golgi-localized protein encoding genes having signal peptides that are predicted to be glycosylated and function in defense (Figure 2, Table 1) (Matsye et al. 2011). Among them is XTH43 (Pant et al. 2014). XTH43 exists in a complex locus of duplicated XTH genes on chromosome 17 including XTH41 (Glyma.17G064900), XTH42 (Glyma.17G065000), XTH43 (Glyma.17G065100), XTH44 (Glyma.17G065200), XTH45 (Glyma.17G065300), and XTH46 (Glyma.17G065400), each having 2 introns. Within this locus, only XTH43 is expressed during the defense response within the syncytium undergoing a defense response with RNA-seq data showing it to be among the most highly expressed genes (Matsye et al. 2011). The first intron of XTH43 contains a very large thymine–adenine (TA) microsatellite, TA240, that the other XTHs lack. Functional transgenic experiments of XTH43 in relation to G. max defense to H. glycines parasitism demonstrate it functions very effectively, with XTH43-OE producing as high as an 88.9% reduction in parasitism (Pant et al. 2014). However, from a cytological standpoint, XTH43 appears to function differently than other XTH proteins that act in cell wall loosening (Fry et al. 1992; Hayashi et al. 1994; Pant et al. 2014). Subsequent to the functional transgenic studies revealing XTH43 acts to suppress H. glycines parasitism, biochemical cell wall analyses have determined how XTH43 modifies the cell wall (Pant et al. 2014; Niraula et al. 2021).

**Conclusion**

The COG complex, as its name implies, is evolutionarily conserved among eukaryotes. It performs roles in retrograde vesicle transport that happen concomitantly with glycosylation. Impaired COG function in animals and plants leads to drastic outcomes and in some cases lethality. In plants, the COG complex has basic functions in plant biology and also defense interactions with fungal pathogens in the shoot and plant parasitic nematodes in the root. Future experiments will likely increase the list of plant-pathogen and plant-organism interactions it has roles with. COG complex components facilitate the co-regulated expression of other component members as well as with the SNARE protein SYP31. This latter role is important from the standpoint that SYP31 co-regulates a-SNAP-5 expression, a gene widely believed to be the major defense gene rhg1. Therefore, it is likely that the COG complex has broad yet to be identified roles in plant-organism interactions.

**Acknowledgements**

The authors are thankful to Dr. Gary Lawrence (retired), Department of Biochemistry, Molecular Biology, Entomology and Plant Pathology at Mississippi State University for all of his support over the years. Dr. Robert Nichols and Dr. Kater Hake are thanked for their support. Yixiu (Jan) Pinnix is thanked for excellent technical work. Dr. Jeff Dean, Chair, Department of Biochemistry, Molecular Biology, Entomology and Plant Pathology at Mississippi State University is thanked for his generosity of providing greenhouse, headhouse, and field space for the experiments and maintenance of plant and pathogen stocks. The authors thank Drs. George Hopper, Wes Burger, Scott Willard, and
Reuben Moore, Mississippi Agricultural and Forestry Experiment Station (MAFES), for support. A number of undergraduate student researchers contributed to the effort. The students include Christina Jones, Dollie Welch, Brant McNeceee, Katherine Thrash, Adrienne McMorris, Chase Robinson, Danielle Francis, Brittany Ginn, Kara Jackson, Olivia Long, Hannah Burson, Meghan Calhoun, John Clune, Taylor Henry, Madison Milhoan, Kayla Moore, Neil Shannon, Ashley Dowdy, Katherine McCracken, Erin Curran, Annedre McCMillan, Austin Martindale, Alison Antee, Hannah Miller, Tineka Burkhead, Henry Pittman, Erin Ball, Jamelle Vance, Leslie Canale, Courtney Gagliano, Shelby Janeski, Lauren Langston, Ellen Modeleski, Natalie Rentrop, Hannah Whitlock, Carolyn Chacon, Emily Carter, Erica Sowell, Jody Clark, Chelsea Tittle, Chrissy Miller, Hannah Stimson, Kathryn Stigel, Ashlee Vargason, Robyn Beattie, Anna Bailey Britt, Rand Henderson, Dejahnii Dilworth, Samantha Rushing, Kyle Winston, Megan Young, Morgan Urieh, Chase Nash, Malenke Miller, Rebecca Waters, Anna-Marie Autrey, Kelvin Blade, Jesse Aheal, Aishe Smith, Caroline Kneal, Maggie Kuhn, Landon Heineck, Caleb Stallings, Santana Holloway, Candace Wyatt, Hallie Troell, Caroline Hoggard, Cassidy Knudsen, Katie Anthony, Mathilda Lail, Ellen Condoure, Morgan Castaneda, Rebecca Billingsley, Seth Lenoi, Jared Quave, Iilana Simmons, Lukas Wicht, Emily Sosnowski, Courtney Borgognoni, Hannah Cox, Rashada Boler, Madison Baima, Gill Goodloe, Murry Faulkner, Cameron Roach, Holhe Heydari, Drake Pace, Sarah Heifner, Ryan Bolton, Nadia Nelson, Ngoc Pham, Adam Crighten, Ashwarya Diksht, Harshini Sampathkumar, Ana Simal, Suchit Salian, Nishi Sunthwheel, Priyanka Gadr, Anna Gaudin, Cheyenne Golden and Abagail Grant. Brant McNeceee and Hallie Troell later became graduate students in the lab and co-authors of this work.

Disclosure statement
No potential conflict of interest was reported by the author(s).

Funding
KSL: Hatch number: ALA015-2-14003. VPK: Cotton Incorporated, grants 17-603, 19-603; Mississippi Agricultural and Forestry Experiment Station/Forest and Wildlife Research Center (MAFES/FWRC) Directors’ Doctoral Fellowship Award; MAFES-Special Research Initiative (SRI); SRI, College of Arts and Sciences, Mississippi State University.

Statements and declarations
Ethics Declarations. The authors understand the ethics disclosure statement.

Competing Interests. The authors declare no competing interests.

Data Availability. All data is available in this work.

Ethics Approval. An ethics approval is not required for the work.

Contributions

| Author | Contribution |
|--------|--------------|
| VK     | Conceived, wrote, edited the manuscript |
| BL     | Assembled glycosylation information and contributed to writing the COG complex aspect of the manuscript, editing |
| PN     | Contributed to writing the xyloglucan endotransglycosylase aspect of the manuscript, editing |
| KS     | Contributed to writing the exocyst aspect of the manuscript, editing |
| BM     | Contributed to writing the MAPK aspect of the manuscript, editing |
| SP     | Contributed to writing the SNARE aspect of the manuscript, editing |
| HT     | Contributed to writing the human COG biology aspect of the manuscript, editing |
| SA     | Contributed to writing the human early genetics aspect of COG biology |
| RK     | Contributed to writing the human α-SNAP aspect and aspects as it relates to the COG complex, editing |

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