



Unique and shared features of Golgi complex autoantigens

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Available online 21 July 2004

Abstract

Here we summarize recent advances in the characterization of autoimmune antigens associated with the Golgi complex. All Golgi autoantigens identified to date are high molecular weight proteins rich in coiled-coil domains and localized to the cytoplasmic face of the Golgi cisternae. The characteristic features of these Golgi autoantigens are interestingly similar to selected human autoantigens reported in other intracellular compartments such as endosome, centrosome, and centromere. The implication of this class of autoantigens in autoimmunity is discussed.

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Keywords: Golgi complex; Autoantibodies; Giantin; Golgin; Coiled-coil proteins

Contents

1. Introduction	36
2. Golgi autoantigens (Golgins)	36
3. Prevalence of human AGA	37
4. Implications in the mechanism of AGA production	37
5. Other intracellular compartments associated with large coiled-coil protein autoantigens	38
6. Modification of Golgi autoantigens during cell death	39
Acknowledgements	40
Take-home messages	40
References	40

Abbreviations: AGA, anti-Golgi complex antibodies; ANA, anti-nuclear antibodies; dsDNA, double strand DNA; SLE, systemic lupus erythematosus; SjS, Sjögren's syndrome; SSc, systemic sclerosis.

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1. Introduction

Historically, autoantibodies directed to nuclear antigens (ANA) have been the focus of clinicians and research scientists interested in systemic autoimmune diseases. In the past decade, however, considerably more attention has been given to cytoplasmic autoantigens localized in different cytoplasmic organelles such as Golgi complex, endosomes, lysosomes, and GW bodies [1]. In this review, we focus primarily on autoantibodies directed to Golgi complex and Golgi autoantigens, and discuss the potential mechanisms of autoantibodies production to Golgi autoantigens *in vivo*.

The Golgi complex is a conserved cytoplasmic organelle localized in the perinuclear region of eukaryotic cells and is characterized by membrane stacks spatially and functionally organized as distinct cis-, medial- and trans-Golgi networks. The Golgi complex has prominent functions in the processing, transporting, and sorting of newly synthesized proteins derived from the rough endoplasmic reticulum. Anti-Golgi complex antibodies (AGA) were first identified in the serum of a Sjögren's syndrome (SjS) patient with lymphoma [2]. This was followed by other reports describing AGA in various systemic autoimmune diseases including SjS [3] and systemic lupus erythematosus (SLE) [4]. AGA was also reported in 10% patients with HIV infection [5] and 35.7% of HIV carriers [6]; however, in the more recent report of Massabki et al. [7], AGA were not found in 100 HIV-infected patients.

AGA are considered to be rare when compared to other classical autoantibodies such as anti-chromatin, anti-SS-A/Ro, and anti-SS-B/La. Autoantibody screening for patients with suspected autoimmune diseases such as SLE, systemic sclerosis (SSc), and SjS are often performed in the clinical laboratory using ANA test and indirect immunofluorescence microscopy. The ANA test relies on subjective interpretation of immunofluorescence pattern and there have been concerns that sera containing primarily antibodies to cytoplasmic antigens may be reported as "ANA negative" and the misconception that these patients do not have autoimmune antibody. When other techniques such as immunoblotting are used to examine the presence of autoantibodies, it is apparent that many of the

ANA negative sera contain autoantibodies that react with intracellular autoantigens including Golgi complex. Furthermore, the detection of low titer AGA requires optimal fixation conditions and appropriate positive control antibodies.

Bizzaro et al. [8] reported that the presence of high titer AGA might constitute an early sign of systemic autoimmune diseases even in the absence of clinical manifestations. Recently, several studies have demonstrated the predictive value of autoantibodies in the subsequent development of autoimmune diseases. Arbuckle et al. [9] showed that among >5 million US Armed Forces personnel, 88% of the 120 SLE patients identified had at least one lupus related autoantibody up to 9 years prior to the diagnosis of SLE. Rantapaa-Dahlqvist et al. [10] showed that, among the maternity cohorts of Northern Sweden, anti-citrullinated peptide antibodies and IgA rheumatoid factor were found to be significant predictors of rheumatoid arthritis. Further, it has been suggested that virtually all individuals with detectable autoantibodies to insulin, glutamic acid decarboxylase (GAD), and islet cell antigen (ICA512) are destined to develop Type I diabetes within 10 years [11]. Although there is as yet no clear correlation of AGA to specific disease or clinical manifestations, recent advances in clinical and research studies of these cytoplasmic autoantigens may eventually provide better understanding of these issues in the future.

2. Golgi autoantigens (Golgins)

Immunoblotting and immunoprecipitation analyses have shown that proteins recognized by human AGA were heterogeneous [12]. Within the past 10 years, our laboratories and others have cloned and identified several novel Golgi autoantigens. These have been achieved primarily by cDNA expression cloning using human autoantibody probes. These Golgi autoantigens are referred to as giantin/macrogolgin/GCP372, golgin-245/p230, GMAP-210, golgin-160/GCP170, golgin-95/GM130, and golgin-97 [5,13–16]. These proteins have relatively high molecular weights that range from 100 to 370 kDa. Golgins were originally described as autoantigens identified in the Golgi complex recognized by autoantibodies from patients with systemic

autoimmune diseases [15]. They share common structural features that include long coiled-coil alpha helical rod-like domains throughout the entire protein except for the amino- and carboxyl-termini [17]. Recent evidence suggests that golgins are necessary for tethering events in membrane fusion during vesicular transport and as structural supports for Golgi cisternae [18]. More recently, several other Golgi proteins such as golgin-84, an 84 kDa transmembrane Golgi protein [19], have been categorized as golgins because of the presence of coiled-coil domains despite the fact they have not been identified as autoantigens [17].

The other common feature shared by Golgi autoantigens is that biochemical evidence and immunoelectron microscopy data show that they are peripheral or transmembrane proteins localized to the cytoplasmic face of the Golgi complex. It has been reported that several golgins, such as golgin-245 and golgin-97, are attached to Golgi membranes through a GRIP domain in the carboxyl-termini [20]. In contrast to other Golgi autoantigens, giantin has a single short transmembrane domain in the carboxyl-termini while the bulk of the protein extends into the cytoplasm [5]. These common features of Golgi autoantigens lead us to propose that these Golgi autoantigens may have common biochemical characteristics and functions that make them preferred autoimmune targets among the approximately 100 Golgi complex proteins described to date [21].

3. Prevalence of human AGA

Although human AGA have been reported to recognize a number of Golgi proteins, the individual Golgi autoantigen that is the most common target was not identified until recently when we reported the prevalence of human AGA to five of the most common Golgi autoantigens [22]. A total of 80 AGA human sera were used to investigate the prevalence of these autoantibodies using immunoprecipitation and ELISA with purified recombinant antigens. The prevalence of reactivity of the 80 human AGA sera is summarized in Table 1. The most common Golgi complex autoantigen target was giantin (50%) and the second most common target

was golgin-245 (24%). The lowest frequency reactivity was to golgin-97 (3.8%). There were 25 AGA sera (31.3%) which did not react with any of the five Golgi autoantigens used in this study suggesting that there are other unidentified Golgi autoantigens. Interestingly, the frequency of sera reactive with the five Golgi autoantigens was numerically correlated with molecular masses of the native Golgi autoantigens (Table 1). In addition, we showed that none of the sera had AGA to more than three of these five Golgi autoantigens. There were 6, 15, and 34 sera with antibodies to 3, 2, and 1 of 5 Golgi autoantigens, respectively. Interestingly, the sera containing the autoantibodies to more than one Golgi autoantigen reacted with either giantin or golgin-245. In other words, serum autoantibodies that bound golgin-160, GM130, and golgin-97 did not overlap each other, although the number of sera with these three autoantibodies were small [22]. These results also suggest that the human autoimmune response to Golgi autoantigens appear to be highly specific because many AGA sera react with only one (42.5%) or two (18.8%) of the five autoantigens. Since giantin was the most common Golgi autoantigen, epitope mapping was performed using six overlapping partial length giantin constructs confirming that epitopes of giantin are located throughout the length of the protein with the major epitope localized to the carboxyl-terminal domains [22].

4. Implications in the mechanism of AGA production

The Golgi autoantigens identified to date are related in that they have similar overall secondary

Table 1
Frequency of autoantibodies to specific Golgi autoantigens in 80 human anti-Golgi autoimmune sera

Golgi autoantigen (kDa)	Positive sera (%)
Giantin (370)	50.0
Golgin-245 (245)	23.8
Golgin-160 (160)	13.6
Golgin-95/GM130 (130)	7.5
Golgin-97 (97)	3.8
Uncharacterized Golgi antigens	31.3

structures, as evident by their extensive coiled-coil rod domains in the central region of the protein. As stated in the previous section, it is interesting that the significant difference of frequency of autoantibodies was observed to the Golgi autoantigens examined. For example, the frequency of antibody to giantin was 13-fold greater than that to golgin-97. To understand the mechanism of AGA production, it is important to consider why giantin has a higher frequency of reactivity than other golgins. Differences between giantin and other golgins include the fact that giantin is the largest Golgi protein and contains a greater number of coiled-coil subunits than other golgins and only giantin possesses a transmembrane domain, which may ensure its tighter association with Golgi complex membranes even when it is released during cell lysis.

5. Other intracellular compartments associated with large coiled-coil protein autoantigens

It is important to note that autoimmune responses to Golgi autoantigens appear to be highly specific and not merely directed to cross-reactive epitopes of the coiled-coil domains, which is the most obvious common feature of Golgi autoantigens [22]. It is interesting that large coiled-coil rich proteins (≥ 100 kDa) have been reported as autoantigens in other cytoplasmic compartments (Fig. 1). For example, in the endosomal compartment, the two known autoantigens are early endosomal protein EEA1 (180 kDa) [23] and CLIP-170 (170 kDa) [24]. There is also a series of centrosomal autoantigens identified as coiled-coil-rich proteins including pericentrin, a 220 kDa protein [25], ninein, a protein with alternatively

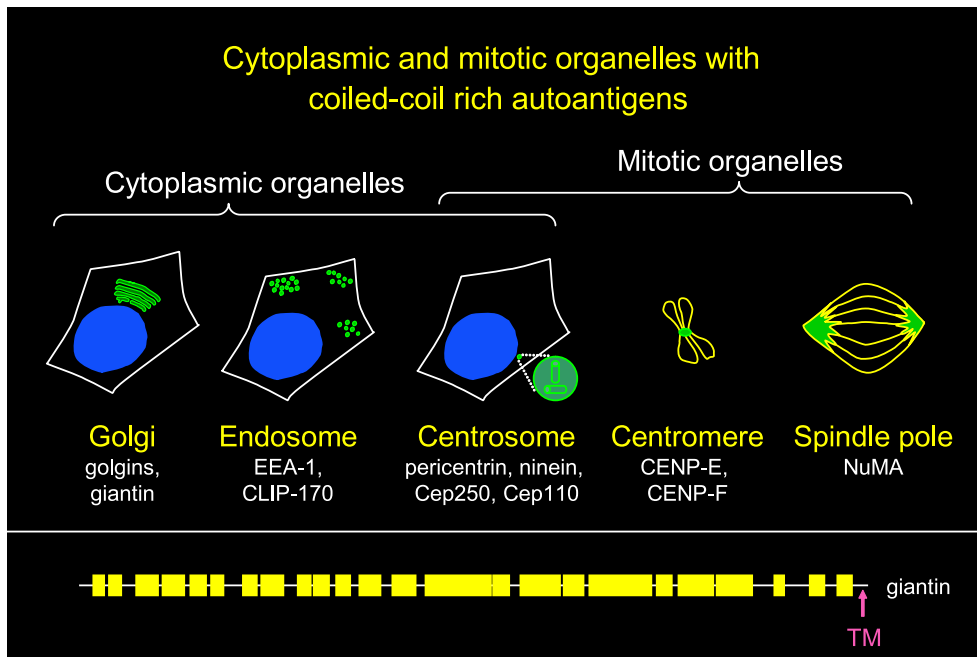


Fig. 1. Cytoplasmic compartments with coiled-coil rich autoantigens. Golgi autoantigens, such as giantin illustrated here with a transmembrane domain (TM), are typically rich in coiled-coil domains (depicted as yellow boxes). A number of human autoantigens that are rich in coiled-coils have overall similarity to the Golgi autoantigens described to date. These antigens are primarily localized to cytoplasmic and mitotic organelles. It is interesting to note that many other cytoplasmic compartments known to be targets in autoimmune diseases, such as ribosomes, mitochondria, lysosomes and GW bodies do not contain coiled-coil rich high molecular weight autoantigens. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

spliced products of 245 and 249 kDa [26], Cep250 (250 kDa), and Cep110 (110 kDa) [27]. Centromere autoantigens have been described but the two interesting ones related to this discussion are CENP-E [28] and CENP-F [29]; both are high molecular weight proteins (312 to 400 kDa) and have the same type of overall structure as discussed above. NuMA is another large coiled-coil protein located at the mitotic spindle pole and is the most common target autoantigen in sera with mitotic spindle apparatus staining [30]. Non-muscle myosin (~200 kDa) is a cytoskeletal autoantigen [31] qualified in the same group of high molecular weight and coiled-coil-rich autoantigens. It is noteworthy that coexisting autoantibodies to these other coiled-coil rich organelles was not observed in our analysis of AGA sera [22]. These endosomal, centrosomal, mitotic apparatus and intracellular autoantigens are, like the golgins, proteins with high molecular weights and an overall high content of coiled-coil domains. The combination of these two physical features in autoantigens may contribute to the induction and production of autoimmune antibodies in certain disease states. One exception to the rule are the lower molecular weight nuclear envelope associated lamins, which are also autoantigens that are rich in coiled-coiled domains [32].

6. Modification of Golgi autoantigens during cell death

It has been observed that many autoantigens are parts of multi-protein–nucleic acid complexes [33] although it remains unclear why and how the immune system is able to recognize or target these intracellular autoantigens. It has been proposed that many intracellular autoantigens such as SS-A/Ro and SS-B/La are translocated to apoptotic blebs during apoptosis and these apoptotic blebs may trigger autoantibody production [34]. Interestingly, Golgi autoantigens were not localized to apoptotic blebs as shown in our previous study [35]. Immunofluorescence analysis in our studies showed that Golgi complex was altered and developed distinctive characteristics during apoptosis and necrosis [35]. Our data suggest that, unlike SS-A/Ro and certain other autoantigens, the expression

of autoantigens on surface blebs of apoptotic cells is not a universal requirement for autoantibody production. One possible explanation is that they may be recognized as surface structures on cytoplasmic organelles that are released to the immune system in aberrant disease states associated with unregulated apoptosis, or necrosis, resulting from injury or infection. An emerging view is that modified forms of autoantigens generated during cell death might stimulate autoantibodies responses if they are presented to the immune system in a proinflammatory context [36]. Casciola-Rosen et al. [36] have also proposed that modification of autoantigens during cell death, particularly proteolytic cleavage, may be crucial for the generation of autoantibodies in autoimmune diseases. Indeed Casiano et al. [37] have shown that a variety of intracellular autoantigens are cleaved into fragments during apoptosis and necrosis. Recently, our laboratory and others have shown that some Golgi autoantigens gave distinct cleavage fragments during apoptosis and necrosis [35,38]. It has been speculated that these modified forms of autoantigens may have enhanced immunogenicity because of exposed cryptic epitopes that are not generated during antigen processing [39,40]. These epitopes may be recognized as surface structures on cytoplasmic organelles such as Golgi complex released to, or processed by, the immune system in aberrant disease states. This may explain why giantin has the highest frequency because during cell death it may be more stably associated with the remaining Golgi surface membrane than other golgins by virtue of its transmembrane domain. Autoantibodies responses may be amplified and sustained upon repeated stimulation if the exposure of intracellular antigens to the immune system is associated with defective clearance of apoptotic cells, prolonged primary or secondary necrosis, T-cell cytotoxicity associated with chronic infection, or even antigen mutation or overexpression. It would be important not only to assess the immunogenic potential of subcellular particles and proteolytic fragments released during cell death, but also to continue investigating possible defects leading to aberrant apoptosis or phagocyte function and/or aberrant antigen expression in systemic autoimmune diseases.

Acknowledgements

This work was supported in part by National Institutes of Health Grants AI39645 and AI47859 (EKLC), and Canadian Institutes for Health Research Grant MOP-38034 (MJF).

Take-home messages

- Golgi autoantigens are generally high molecular weight proteins between 100 and >350 kDa and rich in coiled-coil domains in the central region with non-coiled-coil or globular domains at both amino- and carboxyl-termini.
- Golgi autoantigens are displayed on the cytoplasmic face of Golgi complex and are not localized to apoptotic blebs during apoptosis.
- Giantin, the highest molecular weight Golgi autoantigen reported, is the predominant target of human anti-Golgi complex antibodies (AGA) and multiple non-cross-reactive epitopes have been mapped spanning the 345 kDa protein.
- Other high molecular weight proteins with similar features have been reported in cytoplasmic and mitotic organelles suggesting that these selected proteins become autoimmunogenic based on their subcellular association and molecular features.

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The World of Autoimmunity; Literature Synopsis

A recombinant *Yersinia enterocolitica* lipoprotein in autoimmunity to thyrotropin receptor

Graves' disease is mediated by autoantibodies to the thyrotropin receptor. *Yersinia enterocolitica* produces a lipoprotein that can cross-react with the thyrotropin receptor and thus can act as a potential trigger of thyroid autoimmunity. Gangi et al. (*Autoimmunity* 2004;37:515) cloned the lipoprotein gene from *Yersinia enterocolitica* and expressed a recombinant lipoprotein. This recombinant lipoprotein was found to be mitogenic for B cells of C3H/HeJ mice, which are lipoprotein hypo-responsive, and induced production and secretion of significant levels of interleukin-6 from splenocytes. Moreover, the mice generated autoantibodies against the recombinant lipoprotein, and this antibody cross-reacted with thyrotropin receptor. In addition, the lipoprotein also induced increased expression of B7.1 and B7.2. The authors concluded that lipoprotein can cause breakdown of self-tolerance to thyrotropin and thus contribute to the pathogenesis of Graves' disease.