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Unique and shared features of Golgi complex autoantigens

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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.

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

Contents

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