COMMENT

Different domains of β_2 -glycoprotein I play a role in autoimmune pathogenesis

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Systemic lupus erythematosus (SLE) is an autoimmune disease in which autoantibodies to self-antigens appear in a consistent and sequential pattern.¹ Autoantibodies to the plasma protein β_2 -glycoprotein I (β_2 GPI), either alone (anti- β_2 GPI) or bound to an anionic phospholipid (mainly, cardiolipin), are among the earliest to appear. β_2 GPI, a highly conserved plasma protein consisting of 326 amino acids, is the main autoantigen in primary SLE or SLE secondary antiphospholipid syndrome (APS).² β_2 GPI consists of 5 domains and exists in either a circular or linear form (Fig. 1), depending on its binding to anionic phospholipids.

The T-cell response to β_2 GPI observed in mouse models³ has been proposed to potentially be responsible for the spread of a B-cell epitope to multiple SLE-related autoantibodies⁴ since β_2 GPI binds to apoptotic cells,⁵ which express several SLE-associated autoantigens.⁶ Indeed, previous studies have demonstrated that a T-cell response to β_2 GPI is associated with a spread of multiple B-cell epitopes to SLE-related autoantibodies,⁷ although the epitope specificity of the β_2 GPI-specific T-cell response is determined by the MHC class II haplotype of an individual. Of note, one β_2 GPI T-cell epitope (peptide 23, NTGFYLNAGDSAKCT) was shown to also be recognized by T cells from an HLA-DRB1*0403⁺ autoimmune patient, suggesting that the induced β_2 GPI-specific T-cell response mimics that in an autoimmune disease. These data suggested that the generation of a β_2 GPI-reactive T-cell response may be associated with the epitope spread to SLE-related autoantibodies, independently of the epitope specificity or MHC class II restriction. Thus, the generation of a β_2 GPI-reactive T-cell response has been hypothesized to represent a critical initiating event leading to a B-cell epitope spread, with consequent production of a wide range of SLE-related autoantibodies.

Salem and colleagues⁸ have evaluated the proliferative response of splenic T cells from mice with induced and spontaneous SLE to peptides spanning the entire sequence of the human β_2 GPI. They found that mice with induced and spontaneous SLE recognize a common T-cell epitope in domain III of β_2 GPI. β_2 GPI-reactive CD4⁺ T cells from the two models differed primarily in cytokine production: T cells from the mice with induced SLE expressed IFN- γ , whereas those from MRL/lpr mice expressed both IL-17 and IFN- γ . These data indicate that the generation of a β_2 GPI-reactive T-cell response is shared by both induced and spontaneous models of SLE and that this T-cell response may mediate the epitope spread to autoantibodies in both models.

One of the main novelties of this study is the role of domain III of β_2 GPI in the T-cell response in mice with SLE.

The five domains (DI–DV) of β_2 -GPI have been described as short consensus repeats. Amino acid sequence analysis has indicated that β_2 -GPI is a unique protein with high internal homology between these domains, among which domain I represents the main antigenic target for autoantibodies.² Domain V has an extended C-terminal loop region containing several hydrophobic residues; this domain is highly flexible and has been demonstrated to be responsible for the interaction with negatively charged phospholipids. As already mentioned, the circulating β_2 GPI has a circular shape, with domain I interacting with domain V, sterically inhibiting the binding of the molecule to phospholipids and preserving a certain crypticity of potential autoantigenic epitopes.

It has been reported⁹ that the ability of individual phospholipids to induce a response of a specific reactive T-cell line is principally correlated with their β_2 GPI-binding capacity. Indeed, dendritic cells or macrophages, pulsed with a phospholipid-bound β_2 GPI, induced a response of p276–290-specific CD4⁺ T-cell lines in an HLA-DR-restricted and antigen processing-dependent manner, but those pulsed with β_2 GPI alone did not. The binding capacity of β_2 GPI to lipids not only depends on the strength of the negative charge but also depends on the fluidity of the lipid layer. In general, the membrane fluidity is influenced by the length of fatty acid chains, the number of unsaturated double bonds, and/or the phase transition temperature of each lipid. Therefore, these structural differences likely also contribute to the efficiency of revealing the cryptic epitope containing the intact major phospholipid-binding site in APCs. Recently, de Moerloose et al.¹⁰ have demonstrated that the motif polarity of β_2 GPI may be more important than the amino acid sequence, and these motifs are not confined to domain I. Moreover, domain II has been reported to play a role in the antiphospholipid (aPL)-binding site. In particular, while the signal peptide (p1), containing an aPL-interacting motif, was not present in the mature β_2 GPI, CD4⁺ T cells were able to recognize the p1 sequence, suggesting that the signal peptide could trigger autoimmune responses. Furthermore, aPL-interacting motifs present in peptides have the ability to inhibit the aPL activity and might provide a prevention strategy for APS as an alternative to the use of anticoagulants.

In addition to being a circulating protein, able to change its structure and bind a phospholipid, β_2 GPI also has the ability to form dimers and complexes with HLA class II molecules, and it can undergo post-translational modifications, such as oxidation, glycation or biotinylation,² which can even enhance its affinity for anionic phospholipids.

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Fig. 1 Domains of β_2 -glycoprotein I. β_2 GPI consists of 5 domains and exists in either a circular or linear form, depending on its binding to anionic phospholipids

The modulation of antigen processing and some post-translational modifications may be a consequence of high-affinity binding, which may influence the processing of autoantigens. Although additional developments are necessary to find the exact association of residues needed to obtain the highest antigenicity, the work by Salem et al.⁸ may lead to future progress in the development of more sensitive and specific diagnostic tools for evaluating the role of antiphospholipid response and,

furthermore, may contribute to potential peptide-based or β_2 GPI domain-based therapeutic strategies.

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