Chapter 31

Role of Calreticulin Autoimmunity in the Pathogenesis of Photosensitive Cutaneous Lupus Erythematosus

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1. Introduction

Skin disease in lupus erythematosus (LE) patients can be divided into two categories: lesions that have a histopathology that is specific for LE (LE-specific skin disease), and lesions that have a histopathology that can be seen in disorders other than LE (LE nonspecific skin disease). Examples of LE-specific skin disease include acute cutaneous LE (e.g., butterfly rash), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous LE (e.g., discoid LE). Cutaneous small-vessel leukocytoclastic vasculitis manifested clinically as dependent palpable purpura or urticarial vasculitis would be an example of LE-nonspecific skin disease. The etiology and pathogenesis of LE-specific skin disease is thought to be a direct manifestation of the underlying systemic autoimmune process that is responsible for systemic LE (SLE). Comprehensive overviews of the etiopathogenesis of LE-specific skin disease have recently been presented elsewhere (1–3).

Certain forms of photosensitive LE-specific skin disease, such as SCLE and neonatal LE, are strongly associated with the production of autoantibodies to the Ro/SS-A (Ro) ribonucleoprotein (RNP) autoantigen complex (data reviewed in refs. 4 and 5). Considerable evidence, albeit still circumstantial, has suggested that Ro autoantibodies participate directly in the pathogenesis of both SCLE and neonatal LE skin lesions as well as congenital heart block (data reviewed in refs. 2 and 3). This chapter discusses the evidence that supports this hypothesis and reviews a series of studies suggesting that other related autoantigens, such as calreticulin (CR), might be relevant to the pathogenesis of photosensitive cutaneous LE.
Fig. 1. Autoantigen modulation in epidermal keratinocytes during UVB-induced apoptosis. PCD is triggered in a subpopulation of human epidermal keratinocytes following irradiation with physiologically significant fluences of UVB. During apoptosis cytoplasmic blebs derived in part from the ER appear in the plasma membrane. These cytoplasmic blebs have been found to contain autoantigens such as Ro, CR, ribosomal autoantigens, and the signal recognition particle. C1q has been observed to bind to these cytoplasmic blebs through a mechanism that remains to be elucidated. One possibility is that C1q binds to CR present in these cytoplasmic blebs (C1q is known to have an affinity for binding to CR).

2. Ro Autoimmune Response and the Pathogenesis of Photosensitive Cutaneous LE

It has been observed that ultraviolet B (UVB) radiation can perturb the normal intracellular distribution of Ro antigens in human epidermal keratinocytes with resultant expression on the surface of viable cells, a location where these autoantigens could interact with Ro autoantibodies from the circulation (6–11). Preliminary evidence indicates that the 52-kDa component of Ro might be preferentially upregulated at the surface of cells by UVB (12) and UVB-induced epidermal cytokines (13). These observations have led to the hypothesis that cell surface–bound Ro autoantibodies could target epidermal keratinocytes for cytotoxic injury through effector mechanisms, such as antibody-dependent cell-mediated cytotoxicity thereby contributing to the pathogenesis of LE-specific skin disease (2,6). Such a mechanism could meld the Ro autoantibody association of SCLE and neonatal LE with the mononuclear cell infiltrate that characterizes the histopathology of these lesions.