Journal of Autoimmunity 31 (2008) 311–324

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Advances in pemphigus and its endemic pemphigus foliaceus (Fogo Selvagem) phenotype: A paradigm of human autoimmunity

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ARTICLE INFO

Article history:
Received 1 August 2008
Received in revised form 8 August 2008
Accepted 10 August 2008

Keywords:
Pemphigus vulgaris
Pemphigus foliaceus
Fogo Selvagem
Desmoglein
Treatment

ABSTRACT

Pemphigus encompasses a group of organ specific, antibody mediated autoimmune diseases of the skin characterized by keratinocyte detachment that leads to the development of blisters and erosions, which can become life-threatening. The pathogenic autoantibodies recognize desmogleins, which are members of the desmosomal cadherin family of cell adhesion molecules. Desmoglein 3 is targeted in pemphigus vulgaris while desmoglein 1 is targeted in pemphigus foliaceus and its endemic form, Fogo Selvagem. This review will briefly define the salient features of pemphigus and the proposed steps in pathogenesis. We will then summarize the most recent advances in three important areas of investigation: (i) epidemiologic, genetic, and immunologic features of Fogo Selvagem, (ii) molecular mechanisms of injury to the epidermis, and (iii) novel therapeutic strategies targeting specific steps in disease pathogenesis. The advances in each of these three seemingly separate areas contribute to the overall understanding of the pemphigus disease model. These recent advancements also underscore the dynamic interplay between the treatment of patients in a clinical setting and basic science research and have led to an integrative understanding of disease pathogenesis and treatment, allowing pemphigus to serve as a paradigm of human autoimmunity.

1. Introduction

The development of autoimmune disease is one of the fundamental enigmas of immunology. The triggers that direct the immune response against self-antigens are believed to be multifactorial, involving both genetic susceptibility and environmental factors. Current research is aimed at understanding the molecular details of both genetic and environmental contributions. These studies are often limited by the complex nature of such interactions and the seemingly sporadic development of disease in the general population. An ideal research model would focus on an organ specific autoimmune response directed against a well-defined autoantigen in a population of patients in which the prevalence of disease is fairly high and environmental and genetic factors could be studied over a long period of time. The rarity of such research models in today's geographically mobile society has led many researchers to turn to animal models of disease, which have been quite instructive. The application of these findings to human clinical disease is ongoing.

Our area of interest lies in autoimmune diseases of the skin, which include pemphigus vulgaris (PV) and pemphigus foliaceus (PF). The pemphigus spectrum of diseases has many features that fulfill the criteria for an ideal research model of human autoimmune disease described above. These diseases involve autoantibody formation directed against the desmoglein (Dsg) family of cell adhesion molecules in keratinocytes, resulting in keratinocyte detachment (acantholysis) and intraepithelial blister formation. The anti-Dsg autoantibodies are pathogenic by passive transfer into mice and can be followed as markers of disease activity [1,2]. Desmoglein 3 (Dsg3) has been identified as the target of PV autoantibodies, while desmoglein 1 (Dsg1) is the autoantigen recognized by PF autoantibodies [3]. These self-antigens have been fully characterized, allowing researchers to map epitopes throughout disease progression. Furthermore, the skin and sera of patients are easily accessible for collection and use in research settings. While the molecular features of pemphigus are well-defined, the rare and sporadic development of disease in the general population is somewhat limiting to research efforts.

Abbreviations: Dsg, desmoglein; PF, pemphigus foliaceus; FS, Fogo Selvagem; PV, pemphigus vulgaris; MG, myasthenia gravis; AchR, acetylcholine receptor; IVIg, intravenous immunoglobulin; IA, immunoadsorption.

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doi:10.1016/j.jaut.2008.08.003

Although pemphigus is rare in the general population, endemic foci of disease have been identified in certain regions of Brazil. This endemic form of PF, also known as Fogo Selvagem (FS) amongst local inhabitants of rural Brazil, shares similar clinical, histological and immunologic features with the non-endemic form of PF seen in the USA and around the world. As in the non-endemic form of PF, FS is characterized by pathogenic IgG autoantibodies that recognize the Dsg1 ectodomain [4,5] resulting in subcorneal blisters producing localized or generalized skin syndromes (Fig. 1). Novel immunologic features of this disease have been uncovered through studies of a highly endemic focus of FS in the Limao Verde Amerindian reservation in Brazil [6]. Investigations on the evolution of the anti-Dsg1 autoimmune response and the appearance of disease in the inhabitants of Limao Verde and neighboring communities provide a unique opportunity to study the development of autoimmune disease in a well-defined, geographically limited population with a high prevalence of disease.

Collectively, the current body of knowledge in the pemphigus field points to a multistep model of disease pathogenesis in which (i) a genetically susceptible individual is exposed to (ii) a triggering environmental antigen that leads to (iii) autoreactive T and B cell activation with specific autoantibody class and subclass responses and epitope spreading. Subsequent (iv) binding of desmoglein specific autoantibodies then triggers (v) desmoglein signaling and apoptotic events that may be associated with acantholysis and blister formation. This latter step of pathogenesis focusing on downstream events following autoantibody binding has proven to be an exciting and active area of research over the last several years and has led to a better understanding of the molecular mechanisms of injury to the epidermis. Not only does this multistep model of pathogenesis provide a unique example of how an ideal research model can lead to a comprehensive and global view of the development of autoimmunity, but it also serves as a springboard for novel approaches to the treatment of pemphigus aimed at interfering with each step of pathogenesis.

In this review we will summarize recent findings in three exciting areas of investigation, including (i) epidemiologic and immunologic features of FS, (ii) mechanisms of immunologic injury to the epidermis, and (iii) novel therapeutic strategies targeting specific steps in disease pathogenesis. Advances in each of these areas contribute to the overall understanding of pemphigus at different steps of the multistep model.

2. Advances in the epidemiologic and immunologic features of FS

2.1. The endemic regions of FS in Brazil and the Limao Verde reservation

FS occurs in Brazilian states located between 45°–60° west longitude and 5°–25° south latitude in regions with an altitude between 500 and 800 m (1600–2600 feet) [7–9]. The weather in endemic regions of FS is subtropical and supports coffee, sugarcane and cacao in the northern regions, while corn, soybeans and cotton are the predominant crops in southern regions.

Young adults and children are typically affected and there is no reported sex or racial predisposition [7–12]. FS patients are outdoor workers, usually farmers or family members of a farmer. The daily activities of a family include agriculture, care of livestock and home chores (i.e. cooking, caring for small animals, or washing laundry in nearby rivers or streams). Many wives take part in farming activities as well. The family shares a common bedroom and personal hygiene is poor. The diet primarily consists of high carbohydrates and low protein intake.

The houses are usually built of reed walls and thatched roofs with open doors and windows. They commonly harbor rodents and other small wild animals and are usually infested with blood-feeding arthropods such as bedbugs and Reduviid bugs. A variety of other insects are found in nearby rivers and streams, including Simuliids (black fly, also known as "borrachudo" in Portuguese) and sandflies. Epidemiological studies have shown that the number of new cases of FS is greatest at the end of the rainy season (September–March) and least during the dry summer (April–August), suggesting that insect multiplication and increase in the number of FS patients are related phenomena [7–9]. Interestingly, the same ecological systems found in the "pemphigus country"

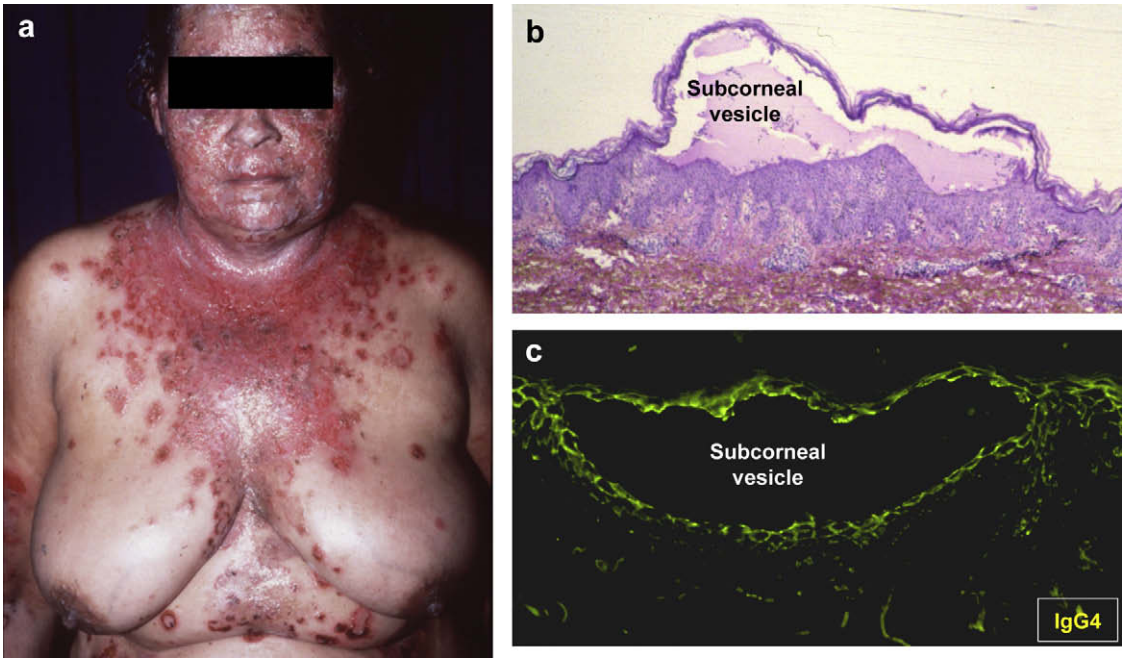

Fig. 1. Clinical presentation of Fogo Selvagem with (a) spontaneous generalized blisters and erosions. (b) Biopsies of these lesions demonstrate intraepidermal subcorneal vesicles due to cell detachment (acantholysis). (c) Direct immunofluorescence locates the total IgG or IgG4 to the surface of detached epidermal cells.