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Innate immunity in systemic lupus erythematosus: Sensing endogenous nucleic acids

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Historically, the involvement of complement – an integral part of the innate immune response- in the pathogenesis of lupus was recognized early. Emphasis shifted quickly however to the specific immunity with scientists concentrating on the adaptive immune response (autoantigens, autoreactive T cells and autoantibodies). Similarly, the detection of interferon alpha (IFNα), another key mediator of innate immunity, in the sera of active lupus patients by Hooks and Moutsopoulos in 1979 was poorly understood and thus ignored for many years. More recently however, the realization that a) endogenous ligands ("stressors") derived from a "stressed" host can be potent inducers of inflammatory mediators, and b) a cross-talk exists between the innate and the specific immune response, has motivated investigators to take a closer look at innate immunity. To this end, studies have revealed novel inducers, sensors, mediators and effectors in the innate arm of immunity of key relevance to the pathogenesis of lupus. According to the current paradigm, nucleosomes containing nucleic acids (RNA and/or DNA) and other endogenous danger ligands that can bind to pathogen associated molecular pattern receptors are incorporated in apoptotic blebs, which in turn promote the activation of dendritic and B cells and the production of IFNα and autoantibodies, respectively. These molecules find their way to specific receptors (toll-like receptors, TLRs; the nucleotide binding and oligomerization domain receptors, NLRs; and the retinoid acid inducible gene-I-like receptors, RLRs) some of which are located intracellularly. Thus in lupus, apoptotic material is not only a source of autoantigens and molecules with adjuvant activity, but also a source of endogenous molecules that can be potent inducers of inflammatory cytokines.

1. Introduction

Autoimmunity is the reflection of the basic problem confronting living organisms, which is how to defend against foreign invasion, while maintaining control of the defending forces and preserving homeostasis [1]. These mechanisms though are not fail-proof. Dysfunctional innate and/or adaptive immune responses to external pathogens or endogenous molecules derived from a "stressed host" account for an increasingly number of human diseases, both acute and chronic. These molecules collectively called "stress associated molecular patterns" (SAMPs) include, among others, products of apoptotic or necrotic cells, metabolic products, and more recently, even nutrients [2].

In 1979, J J Hooks and H M Moutsopoulos published their seminal paper on the detection of immune interferon (IFN) in human SLE [3]. In this paper they reported that type II or immune interferon were present in the serum of lupus patients and showed a good correlation with disease activity. Further characterization of IFN showed that it consisted of IFN-alpha subtypes or a mixture of alpha and gamma IFN. Following a series of publications confirming the study, the finding was largely abandoned and forgotten until Ronnblom and associates showed that apoptotic U937 cells combined with lupus IgG produced IFN-alpha, following FcγRIIa-mediated uptake by plasmacytoid DCs (pDCs) [4]. During the same year, J Banchereau and his colleagues reported that IFN-alpha from lupus patients sera induced normal monocytes to differentiate into DCs. These DCs could capture antigens from dying cells and present them to CD4-positive T cells, raising the possibility that unabated induction of DCs by IFN-alpha may drive the autoimmune response in SLE [5].

Over the ensuing years, demonstration in candidate gene and genome wide association (GWA) studies that several genes encode components of the pathways upstream and downstream of type I IFN-alpha production, further secured the key position of IFN-alpha in the pathogenesis of SLE [6,7]. Importantly, the presence of

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IFN-alpha had also been linked to severity of the disease in microarray studies further supporting the central role of this cytokine in this disease [8–10].

This brief review will highlight selected innate immunity pathways in lupus and the lessons learned.

2. How does lupus start?

Lupus starts with a general autoimmune/preclinical phase characterized by autoantibodies common to other systemic autoimmune diseases, such as anti-Ro and anti-La and proceeds with a more disease-specific autoimmune phase with anti-Sm and anti-RNP antibodies as the disease is becoming clinically apparent [11]. Antibodies against nuclear proteins containing nucleic RNA and/or DNA dominate the immune response in lupus. These observations pose several important questions: What is the source of these autoantigens? How are they recognized? What could account for the dominance of the immune response against nuclear antigens so characteristic of the disease?

During the last years, it has become apparent that increased production of autoantigens during apoptosis, decreased disposal and deregulated handling and presentation, are all important for the initiation of the autoimmune response in lupus (Fig. 1). Nucleosomes containing nucleic acids (RNA and/or DNA) and other endogenous danger ligands that can bind to pathogen associated molecular pattern receptors are incorporated in apoptotic blebs, which in turn promote the activation of dendritic cells (DCs) and B cells and the production of IFN-alpha and autoantibodies, respectively [12–14]. These molecules find their way to specific receptors some of which are located intracellularly (see below). Apoptotic material is not only a source of autoantigens and molecules with adjuvant activity that increases their immunogenicity, but also a source of endogenous molecules that can be potent inducers of inflammatory cytokines following binding to distinct types of innate immunity sensors (see below) [14].

3. Inducers and sensors of innate immunity

In contrast to adaptive immunity which uses specific immune receptors for each antigen, the innate immune system utilizes unique sets of molecules – collectively called pattern recognition receptors (PRRs) – that have been selected to recognize molecular patterns derived from pathogens and damaged cells [1]. These patterns are thought to represent a threat to host's homeostasis ("danger" signals). As such, PRRs are strategically located on cell membranes, in the cytosolic and in the endosomal compartments of the eukaryotic cells [15].

To date, we recognize at least three distinct types of receptors (Table 1): a) the toll-like receptors (TLRs), which recognize nucleic acids on the cell membranes or on endolysosomal compartments but not in the cytosol; b) the nucleotide binding and oligomerization domain (NOD) receptors (NLRs), which monitor the cytosolic compartment closely interacting with TLR signalling pathways; and c) the retinoid acid inducible gene (RIG)-I-like receptors that recognize RNA or DNA in the cytoplasm (RLRs).

4. Toll-like receptors (TLRs) and autoimmunity in lupus

TLRs are key components of the innate immune system, activating multiple inflammatory pathways and coordinating systemic defence against pathogens. Data from animal models and circumstantial data from humans suggest that inappropriate activation of TLR pathways by endogenous or exogenous ligands may lead to the initiation and/or perpetuation of autoimmune responses and tissue injury [16].

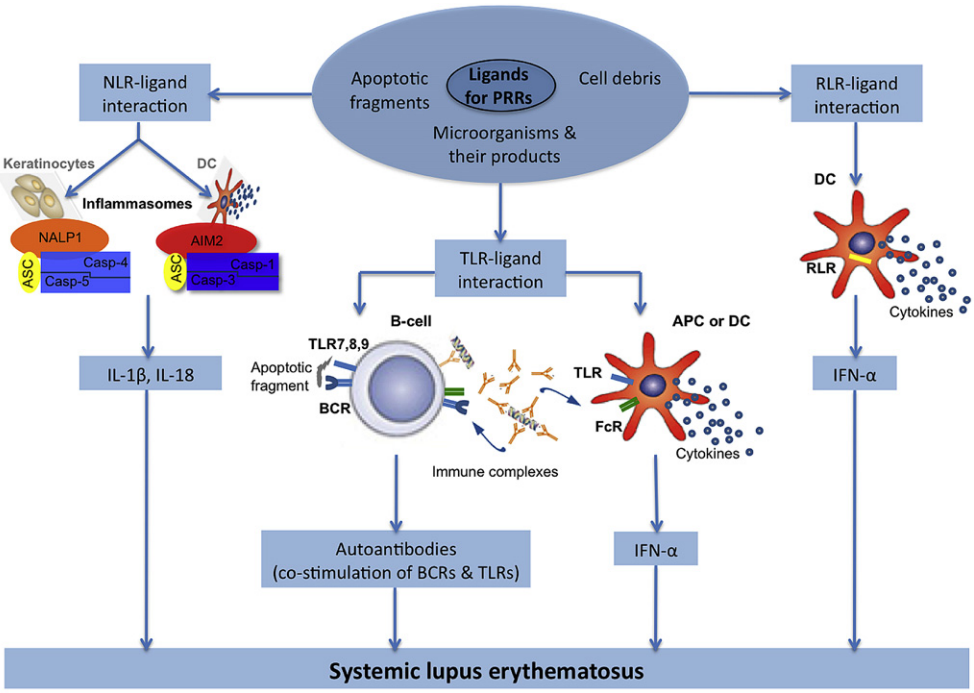

Fig. 1. Sensing of nucleic acids by pattern recognition receptors is a central feature of innate immunity in lupus. This is mediated by Toll-like receptors (TLRs) and cytosolic receptors such as NLRs and RLPs ultimately leading to the production of inflammatory cytokines such as IFNa and IL-1. IFNa promotes the activation/maturation of mDCs that engage quiescent autoreactive T and B cells producing autoantibodies. Once autoantibodies are produced and immune complexes containing ribonucleoproteins and nucleosomes have been formed, their uptake by DCs via the Fc receptors or by B cells via the BCRs facilitates their endosomal delivery to TLRs, resulting in TLR-dependent IFNa production, and promotion of plasma cell differentiation in concert with T cell derived factors, such as IL-21. This amplifies the immune response, which from now on becomes self-sustained.