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Environmental adjuvants, apoptosis and the censorship over autoimmunity

Patrizia Rovere-Querini*, Angelo A. Manfredi, Maria Grazia Sabbadini

H San Raffaele Scientific Institute and Vita-Salute San Raffaele University, DIBIT 3A1, Via Olgettina 58, 20132 Milano, Italy

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Abstract

Alterations during apoptosis lead to the activation of autoreactive T cells and the production of autoantibodies. This article discusses the pathogenic potential of cells dying in vivo, dissecting the role of signals that favor immune responses (adjuvants) and the influence of genetic backgrounds. Diverse factors determine whether apoptosis leads or not to a self-sustaining, clinically apparent autoimmune disease. The in vivo accumulation of uncleared dying cells per se is not sufficient to cause disease. However, dying cells are antigenic and their complementation with immune adjuvants causes lethal diseases in predisposed lupus-prone animals. At least some adjuvant signals directly target the function and the activation state of antigen presenting cells. Several laboratories are aggressively pursuing the molecular identification of endogenous adjuvants. Sodium monourate and the high mobility group B1 protein (HMGB1) are, among those identified so far, well known to rheumatologists. However, even the complementation of apoptotic cells with potent adjuvant signals fail to cause clinical autoimmunity in most strains: autoantibodies generated are transient, do not undergo to epitope/spreading and do not cause disease. Novel tools for drug development will derive from the molecular identification of the constraints that prevent autoimmunity in normal subjects.

Keywords: Apoptosis; Adjuvants; Cross-presentation; Dendritic cells; Phagocytosis; Autoimmunity

Contents

* Corresponding author. Tel.: +39 2 2643 4864; fax: +39 2 2643 4786.
E-mail address: rovere.patrizia@hsr.it (P. Rovere-Querini).

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Several recent reviews outline the links between excessive/deregulated apoptosis and autoimmunity (see for example [1–8]). However, if apoptosis is required for autoimmunity, why apoptosis is so widespread and autoimmunity so uncommon? Here, we will focus on recent findings that may help reconciling the paradox.

Accumulation of apoptotic cells and the development of clinical autoimmunity are dissociated in vivo. To study the outcome of excessive apoptosis in vivo, two approaches at least are feasible. The multifaceted array of phagocyte receptors or of soluble factors bridging dying cells to phagocytes can be targeted, producing animals that lack adequate clearance of cell corpses; on the other hand, animals can be directly challenged with apoptotic cells (see below). Several groups have followed the former approach in the last years, generating animals in which apoptotic cells accumulate. In several systems, apoptotic cells accumulate and autoimmune features develop [9–13]. Genetic factors however play an important role in the expression of autoimmunity: the absence of soluble factor, like the first component of the classical complement activation pathway, C1q or of tethering receptors, like the CD14 molecule, consistently result in defective disposal of cell debris in vivo, but do not cause disease in normal, non-predisposed, backgrounds [14,15].

An alternative approach to evaluate the homeostatic response to dying cells is to use them as vaccines. Vaccination is in general the most effective mean to achieve protection against infectious diseases. In response to the infectious agent, antigen-presenting cells are recruited, which in turn migrate in secondary lymphoid organs. They activate T lymphocytes that specifically recognize epitopes derived from the invading pathogen. Upon activation, T cells proliferate and differentiate: the interaction with helper T cells license antigen-specific B cells to proliferate, form germinal centers, or differentiate into plasma cells and secrete antibodies. Antibodies are crucial to clear extracellular pathogens and to limit the spreading of viruses or intracellular bacteria.

T cells that recognize specific epitopes characteristic of a given microbe are rare in subjects who have not met it previously. The aim of a vaccination procedure is on one hand to increase many-fold the numbers of those T cells and on the other to clonally expand a population of long-lived, antigen-specific memory T cells. As a result, a future infection with the same pathogen elicits a faster and more effective response: for example, the secondary antibody response is earlier, larger and comprises larger amounts of IgG antibodies, endowed with a progressively higher affinity for the antigen. Moreover, the response against the original single antigenic epitope spreads to other epitopes and often to different antigens that belong to supra-molecular structures (epitope spreading), an event that further adds to the protection achieved.

We exploited the vaccination procedure in an experimental model of systemic autoimmunity to verify whether the processing of apoptotic cells, alone or in combination with additional factors, were per se sufficient to elicit a bona-fide autoimmune disease, characterized by the production of a wide array of autoantibodies and by the ensuing damage of target organs, like the kidney. We vaccinated pre-immune NZB × NZW F_1 mice with syngeneic thymocytes, committed to apoptosis by irradiation, or with dendritic cells (DCs) that phagocytosed them [16,17]. We also compared the outcome of this vaccination in other genetic backgrounds, which do not develop spontaneously autoimmune features. The vaccination with apoptotic cells per se had no effect. Dying cells however had all the antigens required to initiate and maintain the autoimmune response: they become both immunogenic (i.e. they efficiently induced autoantibodies) and pathogenic (i.e. they induced an accelerated and lethal renal disease) when injected together with proper adjuvant signals (Fig. 1).

Adjuvants for dying cells. Adjuvants work through different mechanisms: they increase trafficking of inflammatory leukocytes at the site of antigen injection; they promote the activation state of antigen presenting cells, facilitating their further migration to the lymph nodes and enhancing their ability to productively stimulate resting antigen-specific T cells; they induce the release of cytokines for indirect effects on immune cells.

The most potent antigen presenting cells, the DCs, process murine dying cells and cause autoimmune responses when injected in vivo [16,18]. Their state of activation/differentiation, or “maturation”, is possibly important in vivo, representing a requirement for