Published in final edited form as:
J Autoimmun. 2008 ; 30(1-2): 5–11.

Cell Damage and Autoimmunity: A Critical Appraisal

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Abstract

In April 2007, an international Colloquium bridging scientific and clinical disciplines was held to discuss the role of cellular and tissue damage in the initiation, development and persistence of autoimmune disease. Five potential etiologic and pathophysiologic processes fundamental to autoimmune disease (i.e. inflammation, infection, apoptosis, environmental exposure and genetics were the focus of the presentations and integrative discussions at the Colloquium. The information presented on these topics is condensed in this review.

Inflammation has close clinico-pathologic associations with autoimmunity, but future analyses will require better definition and metrics of inflammation, particularly for the earliest cellular and molecular components dependent on recruitment of elements of innate immunity. Although infection may be associated with increased levels of autoantibodies, most infections and virtually all vaccinations in humans lack well-established links to autoimmune diseases. Further application of well designed, long-term epidemiologic and population-based studies are urgently needed to relate antecedent exposures with later occurring stigmata of autoimmunity with a goal of discerning potentially susceptible individuals or subpopulations. Suspect infections requiring closer interrogation include EB virus (SLE and other diseases), HCV (autoimmune hepatitis), beta hemolytic streptococci (rheumatic carditis) and H. pylori (autoimmune gastritis) among others. And even if a micro-organism were to be incriminated, mechanisms of initiation/perpetuation of autoimmunity continue to challenge investigators. Plausible mechanisms include potentiation and diversion of innate immunity; exposure or spillage of intracellular autoantigens; or provision of autoantigenic mimics. Integrity of apoptosis as a critical safeguard against autoimmunity was discussed in the contexts of overreactivity causing autoantigens to gain enhanced exposure to the immune system, or under-reactivity producing insufficient elimination of autoreactive clones of lymphocytes. Although environmental agents are widely believed to serve as necessary “triggers” of autoimmune disease in genetically predisposed individuals, only a few such agents (mainly drugs and some nutrients) have been clearly identified and their mechanism of action defined. Finally an essential genetic foundation underlies all these hazards for autoimmunity in the form of risk-associated polymorphisms in immunoregulatory genes. They may be predictive of future or impending disease.

Keywords

autoimmunity; cell damage; inflammation; infection; apoptosis; genetics; environmental exposure

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1. INTRODUCTION

Inflammation, infection, environment and apoptosis all may collectively contribute to the initiation and perpetuation of autoimmunity and the progression from benign autoimmunity to established autoimmune disease with its multiple clinical disease manifestations. The elucidation of multiple genetic factors in various diseases will likely lead to a greater understanding of the diverse manifestations of autoimmune disease. Autoimmune diseases have complex regulatory mechanisms that influence the host response to cell injury. Most autoimmune diseases, while increasing in prevalence and severity, are still relatively uncommon distortions of what are likely common physiologic processes. While the major focus of the Colloquium was on pathophysiologic mechanisms involved in the initiation phase of autoimmune disease, important information emerged on processes responsible for clinical expression of disease.

A robust discussion and dialogue raised a number of important topics for future scientific exploration. The participants identified several key goals and recommendations to facilitate the development of improved disease prevention and treatment strategies for autoimmune disease (Table 1). Whereas the ultimate goal is to develop cures for autoimmune disease, it was acknowledged that the development of safer and more clinically effective/efficacious treatment regimens would be a more realistic and still an extremely challenging endeavor.

Inflammation

Understanding the role of inflammation in the development of autoimmunity is still a subject of active investigation and debate. The main contributors to the solution of this conundrum will include the burgeoning fields of cellular and molecular biology and molecular genetics which already have increased our understanding of what precisely constitutes inflammation. One of the fundamental tenets, often unappreciated, of the discipline dedicated to the study of the development of autoimmunity and autoimmune disease is that autoimmunity, per se, does not usually lead to autoimmune disease. A clear distinction needs to be made between initiating events such as cell injury, “danger” and inflammation on the one hand, and the host response including innate immunity and adaptive autoimmunity on the other. Betty Diamond (Feinstein Institute for Medical Research), Diane Mathis (Harvard University) and Polly Matzinger (National Institutes of Health (NIH)) each called for better recognition that autoimmunity may follow tissue damage, but may not progress to autoimmune disease.

Accordingly the need is to develop a more relevant definition of inflammation at the molecular and cellular rather than the clinico-pathologic level. This definition should be one that (i) distinguishes the inflammatory process from tissue injury/damage, tissue repair/remodeling and infection-related immunity; (ii) considers the full range of severity and frequency of inflammation; yet (iii) is not so broad that it includes everything that can generate an immune response. Available parameters to describe inflammation are highly variable and include expression of specific cytokines and chemokines, identification of particular cell populations within peripheral blood or accumulating within tissue, and expression of cell surface markers. Polly Matzinger noted that the NIH has an outstanding Request for Applications to define inflammation. At present, a first step for the occurrence of an immune—and potentially an autoimmune—response is the activation of innate immune processes via pattern recognition receptors comprising Toll-like Receptors (TLRs) on antigen-presenting cells (APCs), although activation does not necessarily require TLR stimulation [1]. Such activation is sometimes referred to as the adjuvant effect [2]. This activation of innate immunity stimulates but may not be seen as “inflammation” in the clinico-pathological sense.

Regardless of how inflammation is defined, examples do exist both of autoimmune disease in the absence of overt inflammation and, of course, inflammation can exist in the absence of relevant autoimmunity. In human disease, it is often difficult to exclude entirely a role of inflammation. Even “non-inflammatory” diseases mediated by autoantibodies like autoimmune hemolytic anemia and autoimmune thrombocytopenia may be a consequence of some prior infection. Additional examples cited at the meeting were autoimmune expressions in inbred mice that regularly and spontaneously develop diabetes (NOD mice) or rheumatoid arthritis-like disease (K/BxN mice) but without any apparent evidence of preceding infection. Yet, inflammation (itself sometimes the result of autoimmunity) is known to worsen autoimmune disease and/or perpetuate the process. Also recognized are certain diseases, referred to as autoinflammatory at least until their pathogenesis can be better defined [3], are characterized by persisting inflammation even though a relevant adaptive autoimmune response is not clearly evident.

Clinically, autoimmune disease may be thought of as either spontaneously occurring or induced by inflammation. In inflammation-induced autoimmune diseases, inflammation may act by switching the cellular or tissue response between proliferative and fibrotic responses. In such a model, distinguishing inductor and effector stages of autoimmune disease, inflammation may be of lasting benefit. Reducing inflammation in certain autoimmune diseases can restore immunologic balance and induce a remission that allows at least temporary withdrawal of immunomodulators. For example, current (and highly effective) treatments for rheumatoid arthritis target leukocyte-mediated or cytokine-mediated inflammation. Combination immunotherapy, targeting more than one biologic/molecular target is being used increasingly. Dianne Mathis remarked that a combination of these treatments may be synergistic, although such treatment entails a risk of too much immunosuppression and consequent infection. Although such treatment combinations may be synergistic in therapeutic efficacy, such regimens may increase the risk of infection or development of malignancies.

Alternative and complementary views on the mechanisms by which inflammation may induce autoimmunity include lowering the baseline for immune activation or by triggering apoptosis, necrosis or spillage of extracellular antigens. Underlying these mechanisms is the knowledge that genetic predisposition is a potent underlying determinant in defining the threshold to generate an immune response.

Colloquium participants agreed that there is a compelling need to improve the understanding of the baseline tissue contribution to autoimmune disease activation, not just the role of the tissue response. Two common examples were cited wherein an organ insult occurs, induces injury, and varying degrees of inflammation ensue, but rarely is there progression to chronic disease or an autoimmune disease. In myocardial infarction with damage/injury to the myocardium, myocarditis does not necessarily result. In acute infectious hepatitis, where extensive inflammation and damage to the liver occurs, autoimmune hepatitis and fibrosis (cirrhosis) occur most uncommonly. Even though autoantibodies may rise following these inflammatory conditions, ongoing autoimmune disease rarely follows. Here again, the genetics of susceptibility must be considered operative in the underlying host response to tissue damage.

Finally, participants noted that the emergence of autoimmunity may be a corollary of the ‘hygiene hypothesis’ stating that decreased baseline inflammatory (pathogen) burden explains increasing trends in the prevalence of most autoimmune diseases [4].

Infection

Infection has long been invoked as an underlying etiology or trigger for the induction of autoimmune disease. Infection, irrespective of etiology, usually induces a host inflammatory response, which may be diverse in type. A variety of infectious pathogens induce

autoantibodies, most likely through antigen spillage. Usually infectious diseases are self-limited with full host recovery, with or without therapy. Uncommonly, infections induce autoimmune disease in humans. Documented autoimmune diseases that occur as sequelae to infection include rheumatic fever [5] and Guillain-Barre-type polyneuropathy [6], and possibly late-phase Lyme disease [7]. One well-studied example exists in vaccine-induced autoimmune disease (polyneuropathy) following “swine flu” influenza virus vaccine in 1979 [8], but here vaccine adjuvants might be implicated.

Ethnogeography and epidemiology are useful in ascertaining examples of infection-associated autoimmune disease. As an example, Luis Diaz (University of North Carolina) described fogo selvagem (endemic pemphigus foliaceous) in Brazil, which demonstrates a diminishing prevalence inversely related to the distance from a single hyperendemic site. John Harley (University of Oklahoma) described the close relationship of Epstein -Barr virus infection to systemic lupus erythematosus (SLE), and also discussed how endemic malaria appears to trigger the development of antinuclear antibody (ANA), a propensity which may protect West Africans locally but could make émigrés from Africa more susceptible to SLE. This latter observation raises the research question: is ANA self-driven or driven by extrinsic microbial DNA? Relating infection to genetics and polyclonality of the immune response, Ian Mackay (Monash University, Melbourne, Australia) discussed the potential relevance of Helicobacter pylori infection to the development of autoimmune gastritis, a question that can best be addressed epidemiologically [9]. For certain diseases, the basic research question is whether the “trigger” of the autoimmune disease is the infection itself by providing, say, an autoantigen mimic, or a failure of normal immuno-regulation to limit the immune response to infection.

One of the difficulties in establishing the link between infection and the subsequent development of autoimmunity and autoimmune disease involves delineating the operative mechanisms across time and space. Thus the autoimmune disease may follow infection by many years, and/or the underlying infection may be subclinical or unrecognized. The same agent can cause different diseases, and different agents can cause the same disease manifestations. Infection may also have an effect on a target organ that increases its susceptibility to the autoimmune attack. Thus, there appears to be a potential dual role of infection both as an inducer of autoimmunity and then as a promoter of progression from autoimmunity to autoimmune disease. If indeed infections are critically linked to the development of autoimmunity and autoimmune disease, how can the relapsing, remitting pattern of several autoimmune diseases be explained? For example, Betty Diamond enquired whether ‘lupus flares’ were the result of re-activation of ‘old’ lymphocytes or the activation of ‘new’ lymphocytes by re-infection or antigen-cross-reactivity to another antigen/pathogen? Also, the immuno-regulatory mechanisms involved in autoimmune disease flares and remissions need to be better delineated. In recurring or relapsing/remitting illness, research questions remain about the basic nature of autoimmune disease events, and how flares and remissions can be examined in terms of fluctuations in immune regulatory mechanisms.

Molecular mimicry, antigen expression/spillage and modification of self components can provide the antigen-specific signal necessary for the induction of autoimmune disease rather than tolerance. Infections can also produce the adjuvant effect which is exerted via Pathogen-associated Molecular Pattern (PAMP) recognition and Toll-like and related receptors needed to progress an autoimmune response to autoimmune disease. One prominent inquiry raised in general discussion was whether the progression to autoimmune disease is direct, or indirect by occurring as a bystander effect from a hyper-response to a pathogen. Finally, another theory raised in discussion was that infection may switch the class of a protective immune response and divert the immune system to a pathogenic mode, leading to autoimmune disease.

Apoptosis

Despite considerable interest and research in this area, the role of apoptosis in the pathogenesis of autoimmunity and the generation of autoimmune disease has yet to be established and remains elusive and controversial.

Apoptosis, detected by DNA laddering, has been identified as a unique form of cell death, different from necrosis and autophagic cell death. Effective apoptosis rids the host of damaged cells usually without causing inflammation. Despite the identification of apoptosis as a distinct type of cell death, there may be overlap with other forms of cell death such as 'excitoxicity' perhaps exemplified by activation-induced cell death. The distinction is of importance as necrotic cells are more pro-inflammatory than apoptotic cells. Philip Cohen (University of Pennsylvania) discussed problems that may arise from apoptic cells mainly when the burden of removing them rises to the extent that the monocyte-macrophage system is unable to cope. Apoptic inclusion bodies have also been described in dendritic cells. Infection or environmental exposures may raise the apoptotic burden to initiate autoimmune disease or even explain exacerbation and remissions. If apoptotic cells cannot be cleared by the monocyte-macrophage system, they remain as potential sources of antigen to induce autoimmunity.

In another context, apoptosis is a common event in the effector phase for target cell killing. It is strongly implicated in autoimmunity because, while a normal process, it can lead to abnormal antigen presentation, especially of previously sequestered antigens. Additionally, the presence of antibodies may move cells into different antigen degradation pathways.

Defective apoptosis is the basis of autoimmune lymphoproliferative syndromes of childhood associated with loss –of-function mutations of CD95(fas)-fas ligand. Another clinical example of the role in autoimmunity of defective apoptosis is an autoimmune disease called neonatal lupus syndrome, of which congenital heart block is one clinical manifestation. In this disorder, a mother usually with SLE or Sjogren's syndrome carries a fetus that develops in utero varying degrees of heart block, and may deliver an infant with congenital complete heart block. The phenomenon is associated with the transplacental passive transfer of high titer antibodies directed to the Ro(SS-A)/La(SS-B) antibody system. According to Jill Buyon, New York University, these pathogenic autoantibodies divert the normal clearance pathways of apoptotic cardiocytes to clearance by macrophages, with ensuing activation of TLRs, thereby initiating an inflammatory response, fibrogenesis and damage to the cardiac conduction system [10].

Participants thus agreed that while apoptosis is important in certain diseases, more evidence is needed to establish its role in the development of autoimmune disease, particularly in organ-specific autoimmune diseases. Insights into the role of apoptosis, including normally-occurring apoptosis in the course of tissue remodeling, may lead strategies to prevent or modulate autoimmune Type 1 diabetes [11], for example, including the development of agents to limit apoptosis. However it was considered doubtful whether apoptosis itself would be sufficient to explain entirely the occurrence of autoimmune Type 1 diabetes, or other expressions of autoimmunity..

Environmental Exposure

It is highly likely, though unproved in most instances, that environmental agents contribute to the immunopathogenesis of autoimmune disease. Celiac disease stands out as an autoimmune disorder where the environmental precipitant, gluten, is known [12]. In addition, there are a relatively limited number of fully validated examples of medically induced autoimmune diseases; most of these are attributable to drugs like L tryptophan and two demethylating agents (procainamide, and hydrolyzine). In most instances, the autoimmune disorders induced by

these agents are self limited and resolve with discontinuation of the offending agent. In other instances, nonspecific or crossreactive mechanisms may result in chronic disease.

Critical factors in determining the potential effect of environmental influences on the development of autoimmunity are the temporal relationship and cumulative dose effect. As an example, participants considered that substantial lymphocyte infiltration of the thyroid can occur without any change in thyroid function. This “iceberg” phenomena or concept of “subclinical disease” is ubiquitous in clinical medicine and is not limited to autoimmune disorders. The development of sensitive and specific surrogate biomarkers is required to assess onset of subclinical processes that herald overt disease. Comparably, for other autoimmune diseases e.g., type 1 diabetes or primary biliary cirrhosis, latencies of up to several years can exist between the onset of autoantibody production and appearance of overt clinical disease. Thus, as with the need for better definitions and a metric for inflammation, a global need exists for better early signals of autoimmune disease than just reliance on the presentation of symptoms [13]. Surrogate markers are called for here. Also, the meeting was informed by Michael Amos of progress being made at the National Institute of Standards and Technology on new standards for autoantibody measurement: “bringing metrology to serology”. 14]. The mechanisms of the environmental effect on the induction of autoimmunity and the development of autoimmune disease could be as varied as the environmental antigens themselves. Several of those were discussed: oxidative damage, changes in cell signaling, targeting of class II MHC molecules (Kirsten Falk, Max Delbrueck Center for Molecular Medicine, Berlin, Germany), and induction of autoimmune disease by chemically altered self antigen as a result of xenobiotic exposure (M. Eric Gershwin, University of California Davis). Evidence was presented by Kirsten Falk that an organic chemical could occupy an “antigen-pocket” of class II MHC as an “MHC-loading enhancer.” Eric Gershwin provided evidence in the context of primary biliary cirrhosis (PBC) that ambient xenobiotics (foods, cosmetics) could associate with critical autoantigenic epitopes to generate potent antigenic mimics [15]. Noel Rose (Johns Hopkins University) pointed to the role of dietary iodine in enhancing autoimmune thyroid disease [16].

Genetics

The burgeoning field of the human molecular genetics of autoimmune diseases indicates that autoimmune diseases are multigenic, heterogeneous in genetic basis, complex and elusive. Genetic susceptibility is strongly implicated in every model of the etiology of autoimmune disease. The transformation from susceptibility (which includes polyclonality and cellular vulnerability) to autoimmunity (and a larger immune repertoire) to autoimmune disease, is defined as a stochastic experience.

Individuals with identical genomes may not necessarily develop a particular autoimmune disorder (i.e. incomplete penetrance). For example, concordance rates of disease among monozygotic twin pairs range from 0.15 in rheumatoid arthritis to 0.63 in primary biliary cirrhosis demonstrating that the genetic influence varies greatly in different situations. From a simple probabilistic standpoint, the higher prevalence of autoimmune diseases among women might be explained by the presence of two X chromosomes, presuming the existence of an immune response gene on the X chromosome, but currently hormonal influences are seen as the more important. Moreover, the relative contribution of each of these different genetic contributors varies over time, such that the occurrence of autoimmune disease is in part related to age and its impact on the immune system.

Ward Wakeland (University of Texas Southwestern Medical Center) emphasized the need for, and potential utility of, genomic screening, well illustrated by the number of disease susceptibility loci identified in murine lupus. Based on increasingly reported data from genome wide scans, genetic influences will contribute significantly to human autoimmune disorders,

prompting a call in autoimmune diseases for genome-wide association studies in a cost-effective manner [17]. While genetic predisposition was not an organized focus of the meeting, the recent plethora of reports has appeared on functional polymorphisms of what may be considered immunoregulatory genes, disclosed mostly by genome wide association scanning. The results are revealed as single nucleotide polymorphisms (SNPs) conferring gain or loss of function of relevant molecules. A contemporary but not exhaustive listing (and excluding MHC-encoded molecules) specifies gene loci that (usually weakly) influence predisposition to prominent and often multiple autoimmune disordes such as SLE, rheumatoid arthritis, Type 1 diabetes, autoimmune thyroid disease, autoimmune myocardis, vitiligo and multiple sclerosis (MS). Included are: *CTLA-4* encoding a down-regulatory molecule [18–19]; *PTPN22* encoding a protein tyrosine phosphatase signaling molecule [20]; *NALP1* encoding a molecule involved in innate inflammation [21]; *STAT4* encoding a signaling molecule required for activity of Th17 cells [22]; genes encoding receptors for interleukins 2 and 7 implicated in MS [23] ; *FCRL3* encoding an Fc receptor-like molecule that serves as a B-cell activator [24]; and *Bim* (demonstrated in mice but likely with a human ortholog) that potentiates apoptosis [25].

On another tack, the relevance of extrinsic modification of DNA—epigenetics—was exemplified by Bruce Richardson (University of Michigan) in his discussion on the capacity of chemicals (e.g. 5-azacytidine) to cause hypomethylation of DNA, considered to enhance gene expression and contribute to the pathogenesis of human SLE [26].

Effector Processes

The Colloquium also explored the determinants of localized tissue damage in the face of a generalized autoimmune response. All of the effector mechanisms of immunity could be expected to participate, with T cells being given a major role. However antibody-mediated damage was emphasized by several discussants who provided several examples. Among these was the spontaneous arthritis in K/BxN (T-cell receptor transgenic on NOD background) mice studied by Dianne Mathis, wherein pathogenic autoantibodies are produced against the ubiquitously expressed enzyme glucose phosphate isomerase (GPI). Disease expression, however, is present mainly in the joints. Antigen-antibody complexes on articular surfaces initiate inflammation via the alternative complement pathway for which there is a lack at articular surfaces of the usual cellular complement inhibitors [27].

In PBC, as described by Eric Gershwin, the primary antigenic epitope is located in the E2 components of the 2-oxoacid dehydrogenase enzyme complex. This mitochondrial enzyme component can be aberrantly expressed on the surface of the biliary epithelial cell (BEC) of the small intrahepatic bile ducts during the course of apoptosis, such that the bile duct epithelial cells become uniquely vulnerable to both self-reactive antibodies and T cells [28]. Further, as reported by Betty Diamond, in damage to the central nervous system in SLE (neuropsychiatric lupus), a subset of autoantibodies to dsDNA are capable of reacting with peptides and in particular with receptors for N-methyl-D-aspartate (NMDA) expressed by cerebral neurons, and this may be associated with cognitive impairment [29]. Among ’effector processes’ Joost Oppenheim (National Cancer Institute) described an interesting cross-desensitization between receptors for chemokines (mobilized in inflammatory responses) and opiates, so possibly explaining distressing but poorly understood “myalgic syndromes” often encountered in multisystem autoimmune diseases. Finally we note that this report is part of a special issue on the Mosaic of Autoimmunity and we note both other papers in this volume as well as related papers that focus on the themes discussed in the workshop in the Journal of Autoimmunity and Autoimmunity Reviews [30–89].

Conclusions

The Colloquium emphasized the two-way relationship between cell injury and autoimmune disease. A number of mechanisms were recognized by which injury to cells induced by infectious, chemical or physical agents can initiate the autoimmune process. The induction may involve expression or overexpression of cell constituents that are usually not well presented to the immune system or to which tolerance has not been induced. Inflammation, the normal response to cell damage, attracts the cells and mediators that promote, augment and direct the immune response. In fact, the borders between inflammation and autoimmunity are often obscure. Cell injury may also be the consequence of the autoimmune response. The quantity and quality of the autoimmune response, the milieu of its induction and the genetics of the host determine a possible pathologic outcome. The intrinsic and external factors leading to the degree and localization of cell damage need to be considered in relationship to the differing vulnerabilities of tissues.

Acknowledgements

The Colloquium was organized by the American Autoimmune Related Diseases Association and co-sponsored by the Johns Hopkins Center for Autoimmune Disease Research and the Sjogren's Syndrome Foundation, with financial support from the National Institutes of Health, Genentech and Abbott.

The authors thank Drs. Elaine Alexander and Eric Gershwin for their suggestions, corrections and additions to this report.

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