https://doi.org/10.1038/s41577-022-00812-2

The broad spectrum of pathogenic autoreactivity

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Self-reactive immune responses occur in autoimmune diseases and also in chronic inflammatory and metabolic diseases that are not generally considered as autoimmune diseases. How do the mechanisms of autoreactivity in the different settings overlap and how are they distinguished? Evidence indicates that while autoimmune diseases rely on both a supportive genetic background and a cooperative environment, chronic inflammatory and metabolic diseases strongly hinge on a conducive milieu for the activation of pathogenic autoreactive cells even in the absence of facilitating polygenic factors.

Since Paul Ehrlich coined the term 'horror autotoxicus' in reference to autoimmunity, the field of immunology has come a long way towards dissecting the pathogenesis of autoimmune diseases and mapping the underlying genetic and environmental factors. Analyses of genetic polymorphisms in the HLA loci and in genes for cytokines and their receptors; dysregulation of pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) and Toll-like receptors (TLRs); impaired B cell editing and unbalanced conventional versus regulatory T cells; as well as mutations in *AIRE*, *FAS*, *FASL*G, *CTLA4* and *FOXP3* have greatly contributed to our knowledge of the molecular pathways associated with autoimmune diseases. Similarly, insights from the study of pathogen infection, antigen mimicry, antigen post-translational modifications, epitope spreading, intestinal dysbiosis, immunogenic cell death, defective apoptotic cell clearance and tissue injury have all advanced our knowledge of the microenvironment that supports pathogenic autoreactivity[1–3].

Chronic inflammatory and metabolic conditions, such as type 2 diabetes, interstitial lung disease and cardiovascular diseases, as well as self-reactivity secondary to microbial infections, are not generally classified as autoimmune diseases yet it is increasingly clear that they involve B and T cell autoreactivity. Herein, we wish to clarify how some of the mechanisms currently associated with bona fide autoimmunity can be applied to explain the autoreactivity observed in chronic inflammatory and metabolic conditions and describe important differences that distinguish autoreactivity in these different settings.

Around 80 autoimmune diseases have been described so far. Some of these diseases, such as type 1 diabetes, multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus, have a strong genetic link, including to certain MHC alleles, although they are also affected by a conducive environment. By contrast, other chronic inflammatory and metabolic diseases that have manifestations associated with autoantibodies and autoreactive T cells appear to be more closely correlated with a conducive microenvironment than a defined genetic background.

The autoreactivity occurring in the different settings may be driven by different events. On the one hand, in type 2 diabetes or atherosclerosis, for example, the initial pathogenesis is metabolic in nature due to the longstanding excesses in bioenergetic substrates that generate oxidative and endoplasmic reticulum stress, causing tissue lipotoxicity and glucotoxicity and ultimately immunogenic cell death. These processes establish a microenvironment that is rich in pro-inflammatory cytokines and DAMPs that sustains the immunostimulatory activity of dendritic cells and macrophages via the activation of TLRs and the inflammasome[1–4]. Similarly, in interstitial lung disease, perpetual microinjury to the alveolar epithelium, associated with a dysregulated wound healing response, is the cause of self-reactive immune responses. On the other hand, following infection, genetically driven forms of autoimmunity can be caused by pathogen-derived peptides, which 'mimic' self-peptides and cross-stimulate autoreactive immune cells[5]. Autoreactivity following infection may also be driven by bystander activation of previously quiescent autoreactive cells following pathogen-driven tissue damage, which generates an adjuvant-rich microenvironment. This dichotomy in immune responses was best detailed in a transgenic mouse model in which autoreactive T cells, expressing a T cell receptor (TCR) specific for a herpes simplex virus type 1 (HSV-1)-derived peptide that mimics a corneal self-antigen, induced herpes stromal keratitis following low level viral infection. However, when the viral peptide was mutated to abolish MHC class II binding, keratitis could still be induced by the mutant virus, but it required a much greater infectious dose and did not rely on a mimicry mechanism but rather on a broader pathogen-induced inflammatory response[6].

Together, this suggests that the autoreactivity observed in type 2 diabetes and other chronic inflammatory conditions strongly relies on a conducive environment and less on a defined genetic component. Although more studies are necessary, these diseases have some important differences to bona fide autoimmune diseases. Firstly, in experimental models of autoimmunity, as well as in models of microbial mimicry[6], antigen-specific T or B cells are sufficient to drive pathogenic responses and transfer disease to healthy animals, whereas T and B cells harvested from mouse models of type 2 diabetes, cardiovascular disease and lung disease cannot transfer the disease to healthy mice, only to mice with previously established tissue damage[4]. Secondly, in bona fide autoimmune diseases and microbial antigen mimicry, one or a few dominant antigens drive the pathogenic response, whereas the antigenic response is less selective in type 2 diabetes, cardiovascular diseases, lung fibrosis and pathogen-driven self-reactivity, and is often very broad, without a clear immunodominant antigen. Again, this was simplified in the HSV-1-induced keratitis animal model in which the viral

particles capable of antigen mimicry induced a prolonged inflammatory keratitis, and T cells harvested from these mice could passively transfer the disease to non-primed animals. However, although the mimicry-defective virus also induced inflammatory keratitis, the harvested T cells were not able to transfer disease and the cognate antigens are unknown[6]. Similarly, recent studies report a broad autoreactive immune response in patients with severe SARS-CoV-2 infection who develop self-reactive antibodies similar to those seen in patients with extensive lung inflammation following bacterial pneumonia[7]. Finally, in human autoimmune diseases or animal models of autoimmunity, depletion of T or B cells is clinically beneficial, whereas T or B cell depletion in patients with type 2 diabetes or cardiovascular disease, or in mice genetically engineered to lack αβ TCR expression, results in only a negligible decrease in organ inflammation, compared with the decrease in inflammation, and restoration of insulin sensitivity and glucose tolerance, achieved following weight loss.

During the past decade, the antigen specificity of some of the T and B cells observed in chronic inflammatory diseases has been mapped. In a mouse model of high-fat high-fructose-associated type 2 diabetes, nested T and B cell epitopes derived from protein disulfide isomerase family A member 3, a protein involved in immunogenic cell death, have been reported[2], in addition to peptides derived from apolipoprotein B[1]. Both epitopes generated T helper 1 and T helper 17 cell-driven immune responses in the liver, visceral fat and aorta, in addition to generating pathogenic autoantibodies. An increase in autoantibodies, which often infiltrate targeted organs, has also been observed in obesity-associated models and models of cardiovascular disease[4]. For instance, increased circulating levels of antibodies specific for cardiac or vascular proteins, such as troponin I3, cardiac type and oxidized apolipoproteins, as well as stress-related proteins such as heat shock proteins, have been observed in cardiovascular disorders and atherosclerosis. Similarly, antibodies specific for several cytosolic proteins such as glutamate decarboxylase 1, islet cell autoantigen 1, INSM transcriptional repressor 1 and solute carrier family 30 member 8, have been quantified in the plasma of patients with metabolic syndrome and type 2 diabetes. Finally, an increased abundance of autoantibodies specific for glycolytic enzymes and proteins involved in cellular responses to stress were observed in patients with type 2 diabetes and atherosclerosis[4].

Autoreactive T cells are part of the conventional peripheral T cells' repertoire and their cognate recognition of MHC-presented self-antigens is pivotal to generating a tonic signal for the survival of both conventional T cells and regulatory T cells, as clearly shown by apoptotic cell death in the absence of MHC class I and II molecules. Normally, conventional T cells are kept in check by regulatory T cells, which are thymically selected to recognize self-peptides through a relatively high-affinity TCR and thus potentially require for survival a lower antigen concentration than conventional T cells[8–10]. In chronic inflammatory and metabolic conditions, the increased availability of tissue antigens owing to immunogenic cell death increases their MHC epitope copy number presented by activated dendritic cells[1,2]. The increased MHC presentation, together with a conducive immunogenic microenvironment, may be sufficient to prime conventional T cells and override regulatory T cell suppression in favour of pathogenic autoreactivity, which will aggravate tissue damage. The inflammatory microenvironment would favour the generation of neo-epitopes due to protein post-translational modifications, especially carbonyl groups and glycated moieties[1,7].

Thus, if in autoimmunity genetic polymorphism favours dysfunctional immune responses and environmental factors contribute to the activation of self-reactive T cells, in chronic inflammatory and metabolic conditions, the pathogenic environment is a condition that is required for the activation of autoreactive T cells, perhaps even in the absence of conducive polygenic factors.

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Published online: 23 November 2022

References

1. Clement, C. C. et al. Pleiotropic consequences of metabolic stress for the major histocompatibility complex class II molecule antigen processing and presentation machinery. *Immunity* **54**, 721–736 (2021).
2. Clement, C. C. et al. PDIA3 epitope-driven immune autoreactivity contributes to hepatic damage in type 2 diabetes. *Sci. Immunol.* **7**, eabl3795 (2022).
3. DuPage, M. & Bluestone, J. A. Harnessing the plasticity of $CD4^+$ T cells to treat immune-mediated disease. *Nat. Rev. Immunol.* **16**, 149–163 (2016).
4. Winer, S. & Winer, D. A. The adaptive immune system as a fundamental regulator of adipose tissue inflammation and insulin resistance. *Immunol. Cell Biol.* **90**, 755–762 (2012).
5. Oldstone, M. B. Molecular mimicry and autoimmune disease. *Cell* **50**, 819–820 (1987).
6. Panoutsakopoulou, V. et al. Analysis of the relationship between viral infection and autoimmune disease. *Immunity* **15**, 137–147 (2001).
7. Woodruff, M. C. et al. Dysregulated naive B cells and de novo autoreactivity in severe COVID-19. *Nature* **611**, 139–147 (2022).
8. Mercadante, E. R. & Lorenz, U. M. Breaking free of control: how conventional T cells overcome regulatory T cell suppression. *Front. Immunol.* **7**, 193 (2016).
9. Finkel, T. H. et al. The thymus has two functionally distinct populations of immature alpha beta$^+$ T cells: one population is deleted by ligation of alpha beta TCR. *Cell* **58**, 1047–1054 (1989).
10. Josefowicz, S. Z., Lu, L. F. & Rudensky, A. Y. Regulatory T cells: mechanisms of differentiation and function. *Annu. Rev. Immunol.* **30**, 531–564 (2012).

Competing interests

The authors declare no competing interests.