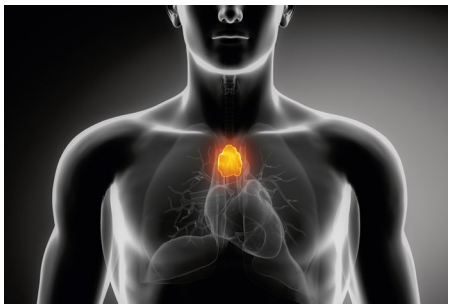
Living with the enemy

Autoimmune disease has proven to be a unique conceptual and medical challenge, but hope for effective targeted therapies is tantalizingly close.

1901 was arguably 'year zero' for the understanding of autoimmune disease; it was in this year that the physician Paul Ehrlich first speculated that the immune system might target host tissues and coined his now-famous term 'horror autotoxicus'. Ever since those first visionary speculations, autoimmune disease has proven to be a unique conceptual and medical challenge. Although much progress has been made in understanding the mechanisms of autoimmune disease and the nature of self-tolerance, effective and highly targeted treatments have proven elusive. Indeed, autoimmune disease remains a major burden on health systems around the world, with type 1 diabetes in the USA alone accounting annually for ~$14 billion in medical costs and lost income. In this Focus, *Nature Immunology* presents a collection of five Reviews covering multiple aspects of autoimmune disease, from its underlying causes to therapeutic interventions. All of the Reviews are freely available for 6 months after going live online (www.nature.com/collections/autoimmune-disease).

Implicit in Ehrlich's original description of 'horror autotoxicus' was the understanding that host mechanisms to prevent the development of a damaging autoreactive response must be in operation. The first of these mechanisms is central tolerance carried out within the thymus. In their Review, Mickie Cheng and Mark S. Anderson provide an update on the understanding of thymic tolerance and, in particular, the key roles of the transcription factors Aire and Fezf2 and the distinct repertoires of self proteins that they regulate. A second and no-less-important layer of tolerance is mediated outside of the thymus, and chief among these peripheral tolerance mechanisms are regulatory T cells (T_{reg} cells). Margarita Dominguez-Villar and David A. Hafler describe the critical function of T_{reg} cells in preventing autoimmune disease. More specifically, they consider the emerging concept of T_{reg} cell instability, a phenomenon now thought to be relevant for impairment of the suppressive function of T_{reg} cells, particularly in the inflammatory conditions seen during autoimmune responses. On the flip side, T_{reg} cells also need to demonstrate a surprising degree of physiological plasticity that seems to be essential for their ability to tailor suppressive functions to specific forms of immune responses.



The thymus is central to maintaining T cell tolerance. Credit: Getty Images/iStockphoto/Thinkstock

While much conjecture surrounds the underlying causes of autoimmune disease, the effect of host genetics is indisputable. Indeed, genome-wide association studies have yielded a bounty of information about the polygenetic basis of autoimmune disease, although parsing this vast corpus of knowledge comes with its own challenges. John A. Todd and colleagues review advances in the tools and approaches in the genetic analysis of autoimmune disease and describe how data can be effectively mined to identify relevant causal genes and pathways. It will almost certainly be insights from such studies as these that will lead to effective therapies in the future.

The past few decades have witnessed a sharp rise in the incidence of autoimmune diseases in the developed world that far outstrips any possible changes that could be accounted for by genetics. All evidence points to important alterations in the environment, and in particular dietary and microbial exposure, whether pathogen or otherwise. In their Review, Elena Verdu and Jayne S. Danska discuss the dietary and microbial influences on type 1 diabetes and draw parallels with celiac disease, which is triggered by the recognition of ingested gluten proteins by immune cells. Understanding these influences offers hope for dietary intervention strategies in the modulation of type 1 diabetes and potentially other autoimmune diseases.

With few exceptions, autoimmune diseases have proven very challenging to treat, much less to 'cure'. Multiple sclerosis, one of the more debilitating autoimmune diseases, is thought to be caused in large part by the action of autoreactive $CD4^+$ T cells. In recent years, however, an unexpected and important pathophysiological role for B cells in multiple sclerosis has been demonstrated. Amit Bar-Or and colleagues lay out the evidence for antibody-independent B cell–mediated pathology in multiple sclerosis and how such insights have led to unexpectedly effective biologic therapies, such as treatment with antibody to the B cell–specific surface antigen CD20.

More than 100 years ago, Ehrlich reflected on the nightmare scenario of the immune system attacking its host, a nightmare that was soon demonstrated to be all too real. Thankfully, substantial advances in fundamental immunology have shed light on the basis of autoimmune disease and are finally offering the possibility of effective treatment, and perhaps even a cure. *Nature Immunology* hopes that this collection of Reviews will inform readers interested in this important topic. We thank Janssen Research & Development for their financial support in producing this special Focus on Autoimmune Disease. *Nature Immunology* is solely responsible for the content of these pages. ❐

Published online: 20 June 2018
https://doi.org/10.1038/s41590-018-0153-8