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Mechanisms and Pathophysiology of Autoimmune Disease

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Abstract The first textbook on autoimmunity was published by Ian Mackay and McFarland Burnett in 1963. It was the first attempt to summarize existing knowledge on human autoimmunity. Since that time, there have been tens of thousands of experimental papers and numerous textbooks that focus on the diagnosis and treatment of human autoimmunity. There have been at least as many, if not more, directed at similar issues in animal models. Enormous strides have been made not only in diagnosis, but also in the pathophysiology and especially in treatment. We have gone from the era of simple HLA typing to deep sequencing and, more recently, epigenetic analysis. We have gone from the era of white blood cell differentials to detailed lymphoid phenotyping. We have gone from the era of simple antinuclear antibodies to detailed and sophisticated immunodiagnosis with recombinant autoantigens and disease-specific epitopes. We have gone from the era of using only corticosteroids to selective biologic agents. Diseases that were previously considered idiopathic are now very much understood as autoimmune. We are in the era of autoinflammatory reactions and the concept of both innate versus adaptive immunity in mediating immunopathology. In this edition of *Clinical Reviews in Allergy and Immunology*, we focus on key and cutting-edge issues in the pathophysiology of autoimmunity. The issues are very much oriented and driven by hypothesis, i.e., a prediction of events expected to occur based on observations. It is not meant to be a complete summary of potential mechanisms of autoimmunity, but rather an attempt to accelerate discussion and better understanding. The primary goal is obviously to help our patients with autoimmune disease.

Keywords Autoantibodies · Epigenetics · X chromosome · Geoepidemiology · Autoimmune disease

This special edition of *Clinical Reviews in Allergy and Immunology* is focused on the topic of "hypotheses of autoimmune diseases." We present reviews of some of the more generally accepted hypotheses and add discussion of one or more newer concepts for each hypothesis. We also present some newer hypotheses that are gaining interest to give them a broader audience in order to accelerate discussion, testing, and further development of these newer hypotheses.

A hypothesis is a prediction of events that are expected to occur based on prior observations. As such, a hypothesis should be stated in a manner that can be tested. That testing yields observations which may or may not support the original hypothesis but can be used to refine the hypothesis. And so the development of a hypothesis is an iterative process that benefits from critical review by the scientific and medical communities. A hypothesis can be disproved by results that differ from the predictions, but it cannot be proven since the number of observations is finite, there may be technical and/or ethical limits to the attainment of detailed observations, and there may be too many variables to control readily. However, as a hypothesis (or group of related hypotheses) shows continual accuracy in predicting events, it becomes more generally accepted and can be termed a theory as others confirm the predictions with their own testing and observations. When a theory is accepted by the general scientific or medical community as being validated repeatedly without fail, it can become a law. A

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scientific law is a universally accepted belief that, under specific defined conditions, a particular result will occur invariably.

Theories and laws can then provide the underpinnings for new hypotheses. For example, Sir Isaac Newton's Universal Law of Gravitation published in 1687, relating mass and gravity, allows us to confidently state that the Sun has gravity. Einstein's Theory of Relativity is a collection of hypotheses relating mass and energy. One prediction from Einstein's work in 1911 is that gravity can affect beams of light energy due to the proposed relation of mass and energy. The test of the hypothesis was to see if light from stars behind the Sun could be bent by the Sun's gravity as that light passed close to the Sun. The prediction was that the positions of the stars would appear to shift as the light was bent around the Sun so that the stars could be observed even though the Sun was directly between the Earth and the stars. A total eclipse of the Sun and very precise photographic instruments were needed to make the measurements. In 1919, a group led by Sir Arthur Eddington was able to collect the data on an island off the west coast of Africa, and those data agreed with Einstein's prediction, i.e., the stars appeared to have shifted their positions during the eclipse. This led to a rise to fame for Einstein, and interest grew for further validation of concepts in his Theory of Relativity.

Another famous hypothesis reached a milestone recently. In July 2011, a conference on X chromosome inactivation was held in Oxford, England, to celebrate the 50th anniversary of the Lyon hypothesis. Most of the pioneers and investigators actively researching X inactivation were present, with Dr. Mary Lyon as guest of honor. The Lyon hypothesis, published in 1961, stated simply that a female cell with two X chromosomes will inactivate one X chromosome, which is formed into a sex chromatin body, and one X chromosome will remain active to provide sufficient X-linked gene expression, similar to XY males and X0 females [1–4]. There have been a few revisions over the years due to differences among species, but the Lyon hypothesis with regard to humans has held up to testing sufficiently that the conference attendees declared that it will now be known as Lyon's Law.

X chromosome inactivation is still under intense investigation, but Lyon's Law has already had an impact on the field of autoimmunity. According to Lyon's Law, it is a random choice early in the development of the embryo as to which X chromosome in the cell is inactivated, either the paternally derived or the maternally derived X chromosome, i.e., a 50:50 chance. All subsequent daughter cells and so on will keep the same parentally derived X inactive so that the adult will be a mosaic of areas where all cells have the paternal X inactive next to areas where all cells have the maternal X inactive. However, in some autoimmune diseases, such as systemic sclerosis and autoimmune thyroiditis, there appears to be skewing or bias in the X inactivation state such that one parentally derived X is more often the inactive X, suggesting a parental-specific X-linked abnormality is involved in these diseases [5–7]. X inactivation in an individual is said to be skewed if ≥80% of cells tested have the paternally derived X inactive or ≥80% have the maternally derived X inactive. Extreme skewing is ≥90%. This suggests as one possibility that, in autoimmune diseases, the peripheral immune system may not have developed sufficient tolerance for some X-linked autoantigens sequestered in the inactive X. Alternatively, it may be that one parentally derived X cannot be properly inactivated, resulting in overexpression of some genes that should only be expressed from the active X chromosome. The details and significance of these findings of skewed X inactivation and diseases are still being determined.

It has been difficult determining all the nuances of X inactivation across species, often starting with mice and attempting to extrapolate these data to other species. Several of the pioneers at the conference stated that mice often appeared to be outliers among the species, with their overly robust genomes that seemed to absorb experimental insults meant to test methylation patterns and gene associations. They joked that elephant genomes would have been more informative if elephants were practical as lab animals. Researchers in autoimmunity can probably relate to these frustrations with mice.

Speaking of elephants, it brings to mind the old universal parable of the blind men and the elephant. After touching the elephant, each blind man had a different concept of the elephant. One touched the elephant's leg and thought it was a tree, another touched the elephant's trunk and thought it was a snake, and so on. If we consider autoimmune diseases (AID) with all their complexity and the shortcomings of our knowledge, we face a similar dilemma. The immunologist perceives AID to be based on dysfunctions of the immune system, the geneticist sees AID as resulting from genetic mutations, the epigeneticist considers AID to result from abnormal methylation patterns, virologists…, nutritionists…, and so on. During the more than 50 years of AID research, there has been a continual need to meld these perspectives.

There are obviously a large number of issues that are not addressed herein, and the reader is directed to recent symposia on the geoepidemiology of autoimmunity [8–53]. The so-called galaxy and kaleidoscope of autoimmunity has been extensively reviewed and is also cited herein for completeness [54–95]. One of the more important points we hope the reader realizes is that these hypotheses are not mutually exclusive. By appreciating the merits and potential limits of each hypothesis and the potential synergies among hypotheses, we hope the readers will be stimulated into imaginative thought exercises and discussions, challenged to question their own long-held perspectives, enticed into exploring the synergies, and emboldened to present their

own ideas. We greatly appreciate the work of the authors who have contributed to this edition and thank them for their efforts.

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