

Autoimmunity under the umbrella of *Danger Model* : new insights into tolerance, rejection and autoimmune therapeutics

Muhammad Asif Qureshi

Dow University of Health Sciences, Karachi, Pakistan

Autoimmune disorders are characterized by loss of tolerance (no immunological reaction against self antigens) and destruction of self by a self-reactive immune system. What incites this abnormal (and persistent activation) of immune response in autoimmune disorders is poorly understood. Only a few autoimmune disorders have known etiology, such as expression of autoantigens. This can be exemplified by an array of autoantigens that have been identified in the systemic lupus erythematosus (SLE), including histones, DNA, ribosomal proteins amongst others.¹ Moreover, in rheumatoid arthritis, a member of chitinase like proteins called CHI3L1 (also called YKL40) has been identified as an autoantigen.^{2,3} In a murine model of skin carcinogenesis, we have shown that murine homologues of human CHI3L1, annotated as Chi3L1, act as an autoantigen.⁴ However, our understanding of inciting autoantigens in pathogenesis of autoimmune disorders remains scarce.

For an effective immune tolerance and surveillance, it is important to present self and non-self antigens to the naive T-cells in a continuous and appropriate manner. In immunological diction, presentation of self and non-self antigens to the T-cells is defined in terms of signals. **Signal 1** is provided by most cells of the body (including immune and non-immune cells) where the self and non-self antigens are presented to naive T-cells in associated with major histocompatibility complex (MHC). However, **signal 2** (also called co-stimulatory signal) is provided only by professional antigen presenting cells (APCs) such as dendritic cells (DCs).⁵ Appropriate provision of signal 1 and signal 2 is imperative to maintain tolerance and combating against the endogenous as well as exogenous threats. Abnormalities of the former can lead to autoimmune disorders, while disorders in the latter

can lead to inappropriate immune response against invading pathogens.

There is plenty of evidence to believe that several genetic and environmental factors play a key role in the pathogenesis of autoimmune disorders.⁵ However, and despite extensive research, the underlying mechanisms are largely unknown, conceivably because autoimmunity has routinely been addressed from the perspectives of self non self (SNS) model of immune response activation⁶ and only recently, the concepts of autoimmunity have begun to spur under the umbrella of the "**danger model**".⁷ SNS model is probably not equipped well to construe the mechanisms underlying tolerance and then its loss during autoimmunity.⁸ SNS model has no astute explanation for several pertinent questions. For example, autoantigens have been identified in only a few of the several autoimmune disorders as identified above. What about the underlying factors in other autoimmune disorders? Even for the known autoantigens, we do not know how these autoantigens break tolerance and induce autoimmune reaction. Moreover, the factors involved in the transformation of a "homeostatic autoimmune reaction" (see below) to a "pathologic autoimmune disorder" are largely obscure.

The Matzinger's "danger model" answers these questions and provides several insights into the pathogenesis of autoimmune disorders by making some basic assumptions:⁹ (1) General response of immune system is to remain OFF unless there is damage. This means that the tissue resident APCs are activated only if they receive danger signals and that the circulating T-cells are not activated in response to signal 1 alone; (2) T-cells can receive signal 2 only from professional APCs such as DCs; (3) Thus, presence of signal 1 in the absence of signal 2 leads to tolerance while presence of both signal 1 and signal 2 leads to activation of immune

response; (4) Activated effector class of cells, such as NKT-cells and CTLs do not require any signal 2 for their action. Therefore, once the initiating danger has been overcome, these destructive cells must be turned off. Otherwise, their persistent action can lead to tissue damage.

Moreover, according to Matzinger's model, the pathogenesis of autoimmune disorder lies in the deregulated tissue homeostasis (such as persistent necrosis/injury) rather than a faulty immune system, as previously thought.⁹ The injured cells can release their contents, which are recognized by the APCs, leading to the activation of T-cells (signal 1) and provide co-stimulatory signal (signal2), thus exposing self antigens to the T-cells. As a result, a transient state of autoreactivity develops which lasts until the injurious cause is over. Transient appearance of autoimmune reaction follows several injurious conditions such as during viral infection infections.¹⁰ However, if the initiating insult persists, the cellular contents will continue to activate APCs, resulting in an ongoing autoimmune reaction, now called an autoimmune disorder. It is important to note here that the immune system is not at a fault here, as it is doing its normal job. However, it is the persistence of the inciting cause that leads to destructive phenomena associated with autoimmune disorders. There could be several reasons as to why an autoimmune reaction will persist on continuous basis. For example, defects in antigen presentation, such as mutations in MHC loci, can lead to altered MHC associated antigen profile (MAP) displayed at the cell surface.⁷ In other words, signal 1 is no more normal and is recognized as a danger signal by the APCs. It is, therefore, not surprising that a vast majority of genetic mutations associated with autoimmune disorders are present within MHC loci.^{11,12}

To conclude, the Matzinger's model has not only

improved our understanding for tolerance and autoimmunity, it has also highlighted the importance of contriving new therapeutic strategies. I believe that it's now time to aggressively delve into identifying disease specific danger signals to try and inhibit them rather than regressing an otherwise normal but chronically activated immune response.

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Corresponding author email: a.queshi@duhs.edu.pk
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