Novel Self-Organized Criticality Theory of Autoimmunity Explaining the Cause of Systemic Lupus Erythematosus (SLE)

Shunichi Shiozawa, MD, PhD
Department of Medicine,
Kyushu University Beppu Hospital
Beppu 874-0838, Japan
e-mail: shiozawa@beppu.kyushu-u.ac.jp

ABSTRACT

The self-organized criticality theory explains that systemic autoimmunity, or systemic lupus erythematosus (SLE), necessarily takes place when host's immune system is overstimulated by repeated exposure to antigen, i.e., external disturbance, to levels that surpass the immune system's stability-limit, i.e., self-organized criticality. The autoreactive lymphocyte clones, which we name autoantibody-inducing CD4 T (*ai*CD4 T) cells, are newly generated *via de novo* T cell receptor (TCR) revision from thymus-passed non-autoreactive clones at peripheral lymphoid organs. They not only stimulate B cells to generate varieties of autoantibodies but also help final differentiation of CD8 T cell into cytotoxic T lymphocyte (CTL) *via* antigen cross-presentation to induce tissue injuries identical to SLE. The causative antigen can be individually different, but such antigen must first be correctly presented to T cells and subsequently overdrive the person's CD4 T cells in relation to his/her HLA to generate *ai*CD4 T cells. The ability of a certain antigen to cause autoimmunity depends on its propensity to be presented and/or cross-presented effectively, resulting in the overstimulation of CD4 and/or CD8 T cells of certain host beyond critical limit, i.e., self-organized criticality.

Keywords: SLE, self-organized criticality, *ai*CD4 T cell, pathogenesis, antigen cross-presentation, antigen presentation

1. INTRODUCTION: IS AUTOREACTIVITY A PRIORI?

The cause of autoimmune diseases, including SLE, systemic sclerosis (SSc), polymyositis/ dermatomyositis (PM/ DM), rheumatoid arthritis (RA) and others, remains unclear. Traditionally, the research in this field was heralded by the discovery of lupus erythematosus (LE) cell in SLE, a classical autoimmune disease. The LE cell engulfing nuclei suggested its attack against self, which subsequently led to the discovery of anti-nuclear and anti-ds DNA autoantibodies and the proposal by Mackey of autoimmune disease theory based on the famous Burnet's clonal selection theory. Because

autoreactivity was a so fascinating concept, subsequent researchers focused on the search of causative autoantigen or the elucidation of the mechanism of autoreactivity. However, is the autoreactivity a priori? Could it be a phenomenon or a cause? This important question must be answered.

We instead, propose here a novel 'self-organized criticality theory' explaining the cause of SLE [1-3] and show that the cause of SLE, or autoimmunity, is not complicated but rather clear when viewed from a different angle, systems engineering. Systemic autoimmunity is caused not by autoimmune reaction but by normal immune reaction, provided that the immune system is overdriven beyond its stability limit.

2. SLE IS UNIQUE

SLE is a multisystem disease characterized by erythematous skin rash, fever, arthralgia, organ involvement including kidney, liver, central nervous system and others, and the presence of anti-ds DNA and/ or anti-Sm autoantibodies and immune complex. SLE is particularly unique in that numerous autoantibodies exceeding 100 are generated [4-6]. In contrast, only a few autoantibodies were produced in the rheumatic diseases other than SLE. Studies show that the anti-Ro autoantibody specifically reactive against an epitope from the latent viral protein Epstein-Barr virus nuclear antigen-1 (EBNA-1) can be raised before the onset of SLE [7,8]. Sjogren's syndrome or SLE develops later in the asymptomatic anti-Ro antibody-positive women who gave birth to babies with neonatal SLE with complete heart block [9]. Thus, while anti-Ro antibody is not uncommon in healthy individuals [7,8] and the typical pathologic features of SLE are not reproducible in the mice immunized with Ro antigen and adjuvant [7], the anti-Ro antibody in SLE seems to be raised against the infectious microbe structurally identical or similar to Ro antigen. This would mean that antigen-driven mechanism is also operating in SLE. Nevertheless, SLE is unique in that it is antigen-driven, but obviously antigen non-specific: the B cells of SLE are broadly, or polyclonally, activated and affinity maturated [4]. In contrast, the rheumatic diseases other than SLE seem to be antigen-driven and antigen-specific [6,10]. Thus, although the clinical signs and symptoms are partially identical, scientific rational seems to be weak for conceptualizing SLE as a whole as an autoimmune disease in conjunction with RA, DM/PM, SSc and others.

3. GENERATION OF AUTOREACTIVE CLONE: AUTOIMMUNE DISEASE THEORY vs SELF-ORGANIZED CRITICALITY THEORY

One of the biggest obstacles we face in elucidating the pathogenesis of autoimmunity today is the mechanism how autoreactive lymphocyte clones could survive or emerge beyond the firewall called 'forbidden clone of Burnet'[11]. According to Mackey's autoimmune disease theory and its subsequent modification, peripheral autoreactive lymphocytes can derive either (1) from a few autoreactive clones that have slipped through the negative selection in thymus, or (2) from a few thymus-passed non-autoreactive clones that have happened to recovered from anergy. Such clones must expand in order to acquire full ability to generate wide varieties of multi-specific autoantibodies exceeding 100. This was expected to be done through cross-reaction to infectious microbes, i.e., molecular mimicry, or

epitope-spreading [12]. However, the evidence for molecular mimicry is weak: TCR does not cross-react with similar peptides [13]. Instead, molecular mimicry may occur during antigen processing, which means that strong immunization such as thru TLR is required. However, there are no proceeding infectious episodes experienced in SLE. There appear no direct experimental evidence supporting the epitope-spreading theory. Even if present, strong immunization must be required for epitope-spreading and again, there are no proceeding infectious episodes in SLE.

On the other hand, the self-organized criticality theory explains that autoreactive lymphocyte clones are newly generated *via de novo* T cell receptor (TCR) revision from thymus-passed non-autoreactive clones at periphery [1-3]. We name this novel T cell type an autoantibody-inducing CD4 T cell (*ai*CD4 T cell), and this *ai*CD4 T cells straightforwardly guarantee multi-specific autoreactivity. Self-organized criticality is an established technical term in systems engineering. The theory explains that systemic autoimmunity, or SLE, necessarily takes place when host's immune system is overstimulated by repeated exposure to antigen, i.e., external disturbance, to levels that surpass the immune system's stability-limit, i.e., self-organized criticality. The *ai*CD4 T cell not only stimulates B cells to generate varieties of autoantibodies but also helps final differentiation of CD8 T cell into cytotoxic T lymphocyte (CTL) *via* antigen cross-presentation to induce tissue injuries identical to SLE [1]. This scenario is consistent with the current consensus that CD4 T cells normally die *via* activation-induced cell death (AICD) after repeated exposure to a single antigen, whereas naïve CD4 T cells having a 'cross-reactive' TCR with lower affinity can be activated through repeated exposure to the same antigen and survive due to weak TCR signaling, ultimately acquiring autoreactivity [14]. The important difference is, however, that it is not cross-reactive CD4 T cell but the *ai*CD4 T cell with *de novo* TCR revision that causes SLE [1-3].

4. EVOLUTIONAL ASPECT: REPEATED STIMULATION WITH ANTIGEN

In view of evolution, our life is a continuous battle against invasive microbes [2,3]. Our immune system is built up on a balance between pathogen-induced tissue injury and defense-induced tissue injury [15]. Host dies if pathogen is too strong due to the former and the host also dies if immune defense is too strong due to the latter, because the battle field is our body. Our evolutional success would be to survive until the age of reproduction and reproduce or multiply our species. To this end, our defense system became stronger enough to suppress pathogens to undersea levels, the levels with no apparent infectious disease. Our defense, however, must not be too strong to 'eradicate' pathogens at the expense of exhaustive battles taking place in the body, and therefore, the inflammation in today's living organisms tends to be unhealed [15]. We have developed in evolution such a balanced defense system directed to invasive microbes, but not against 'self' [2,3]. The cause of systemic autoimmunity, i.e., SLE, is not an exception. Therefore, there are no space for the reactivity against 'self' in evolution.

5. SLE AS *ai*CD4 T CELL DISEASE

While immature lymphocytes in thymus can proliferate autonomously, proliferation of the mature lymphocytes residing at periphery is not spontaneous and thus antigen-driven, which means that if V(D)J recombination takes place at periphery,

it must necessarily be antigen-driven. Microbial stimuli such as lipopolysaccharide (LPS) will expand this antigen-driven mechanism *via* TLR4 or other ligands for pathogen-associated molecular patterns (PAMPs) [16]. We found that TCRβ chain was not revised [17], probably because T cells expand *via* TCRβ in an antigen-driven fashion [2,3]. An exogenous antigen such as Epstein-Barr virus [7,8] may overdrive the T cells of SLE *via* TCRβ [2,3]. The rearrangement of the TCRβ chain is also inhibited due to histone modification, changes in locus conformation, or subnuclear segregation of the corresponding TCRβ genes in thymus [18]. Instead, as in thymus, TCRα chain may be rearranged rather freely and acquire autoreactivity upon repeated stimulation with antigen [2,3]. Otherwise, the lymphocyte having a certain autoreactive TCRα chain that happened to fit structurally with a particular antigen-selected TCRβ chain might expand. We have some preliminary results at hand that TCR revision also occurs in human SLE.

6. CONCLUSIONS: SELF-ORGANIZED CRITICALITY THEORY AND SLE

According to self-organized criticality theory, the causative antigen can be individually different, but such antigen must first be correctly presented to T cells and second, overdrive the person's CD4 T cells in relation to his/her HLA to generate *ai*CD4 T cells [1]. The *ai*CD4 T cells then help full maturation of CD8 T cell to CTL *via* antigen cross-presentation. Accordingly, the propensity to develop SLE depends basically on one's genetically determined, or sometimes functional, ability to present and/or cross-present antigen to T cells. Thus, the ability of a certain antigen to cause autoimmunity is due to its propensity to be presented and/or cross-presented effectively, resulting in the overstimulation of CD4 and/or CD8 T cells of certain host beyond critical limit, i.e., self-organized criticality. Importantly, this means that even subliminal antigenic stimulation can overdrive the immune system of certain host. Such subliminal stimulation with antigen does not evoke apparent infectious episodes and thus, this could be why precedent infectious episodes are unapparent in SLE.

References

[1] Tsumiyama K, Miyazaki Y, Shiozawa S. Self-organized criticality theory of autoimmunity. **PLoS ONE** 2009; 4 : e8382.

[2] Shiozawa S. Cause of systemic lupus erythematosus: a novel self-organized criticality theory of autoimmunity. **Exp Rev Clin Immunol** 2011; 7:715-7.

[3] Shiozawa S. Pathogenesis of SLE and aiCD4 T cell: new insight on autoimmunity. **Joint Bone Spine**, in press.

[4] Sherer Y, Gorstein A, Fritzler MJ, et al. Antibody explosion in systemic lupus erythematosus: more than 100 different antibodies found in SLE patients. **Sem Arthritis Rheum** 2004; 34: 501 -37.

[5] Mahler M, Silverman ED, Schulte-Pelkum J, et al. Anti-Scl-70 antibodies in SLE: Myth or reality? **Autoimmun Rev** 2010; 9:756-60.

[6] Singh U, Singh S, Singh NK, et al. Anticyclic citrullinated peptide autoantibodies in systemi lupus erythematosus. **Rheumatol Int** 2011; 31: 765-7.

[7] McClain MT, Heinlen LD, Dennis GJ,et al . Early events in lupus humoral autoimmunity suggest initiation through molecular mimicry. **Nat Med** 2005; 11:85-9.

[8] Arbuckle MR, McClain MT, Rubertone MV,et al. Development of autoantibodies before the

clinical onset of systemic lupus erythematosus. **N Engl J Med** 2003; 349:1526-33.

[9] Julkunen H, Eronen M. Long-term outcome of mothers of children with isolated heart block in Finland. **Arthritis Rheum** 2001; 44:647-52.

[10] Snir O, Rieck M, Gebe JA, et al. Identification and functional characterization of T cells reactive to citrullinated vimentin in HLA-DRB1*0401-positive humanized mice and rheumatoid arthritis patients. **Arthritis Rheum** 2011; 63:2873-83.

[11] Chervonsky AV. Influence of microbial environment on autoimmunity. **Nat Immunol** 2010; 11:28-35.

[12] Yuki N. Infectious origin of, and molecular mimicry in Guillain-Barre and Fisher syndromes. **Lancet Infect Dis** 2001; 1:29-37.

[13] Garcia KC, Adams JJ, Feng D, Ely LK. The molecular basis of TCR germline bias for MHC is surprisingly simple. **Nat Immunol** 2009; 10:143-147.

[14] Paliard X, West SG, Lafferty JA, et al. Edivence for the effects of a superantigen in rheumatoid arthritis. **Science** 1991; 253, 325-9.

[15] Nathan C, Ding A. Nonresolving inflammation. **Cell** 2010; 140: 871-82.

[16] Richez C, Blanco P, Rifkin I, Moreau J-F, Schaeverbeke T. Role for toll-like receptors in autoimmune disease: The example of systemic lupus erythematosus. **Joint Bone Spine** 2011; 78, 124-130.

[17] Uto K, Tsumiyama K, Shiozawa S. The de novo revision of TCRβ but not TCRβ is responsible for the generation of autoantibody-inducing $CD4^+$ (*ai* $CD4^+$) T cell that causes systemic autoimmunity. **Arthritis Rheum** 2011; 10(Suppl): S752.

[18] Krangel M. T cell development: better living through chromatin. **Nat Immunol** 2007; 8:687-94.