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Novel self-organized criticality theory of autoimmunity explaining the cause of SLE

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Since the discovery of LE (lupus erythematosus) cell by Haargraves, reactivity against self has been considered the cause of autoimmune diseases. However, recent immunology tells that autoreactive clones are not forbidden and autoantibodies are seen ubiquitously in various diseases. Thus, Mackey's autoimmune disease theory must be amended or re-considered. We have, instead, investigated the cause of SLE from a different angle, i.e., a view of systems biology, and found that systemic autoimmunity necessarily takes place when host's immune system is over-stimulated by repeated exposure to antigen to levels that surpass system's self-organized criticality. While Mackey's theory requests autoreactivity as a pre-requisite, this novel 'self-organized criticality theory' needs no pre-requisites.

Methodology/Principal: Findings The method we have chosen was to overstimulate immune system maximally with antigen to the levels far beyond its steady-state, i.e., high-zone tolerance. The results show that systemic autoimmunity necessarily takes place when host's immune system is overstimulated by repeated exposure to antigen to levels that surpass system's self-organized criticality. We have repeatedly immunized mice normally not prone to autoimmune disease with the same antigen including OVA, KLH or SEB, and discovered that such repeated immunization by any antigen reproducibly led to the development of systemic autoimmunity, i.e., SLE. Further, autoantibodies are induced not by cross-reaction to antigen but by de novo T cell receptor (TCR) revision, i.e., V(D)J recombination, at periphery in spleen, which gives rise to a novel T cell type we term an autoantibody-inducing CD4 T cell (aiCD4 T cell). The aiCD4 T cell not only stimulated B cells to generate varieties of autoantibodies but also helped final differentiation of CD8 T cell into cytotoxic T lymphocyte (CTL) via antigen cross-presentation to induce lupus tissue injury, with 100% efficiency. While the TCRβ chain of aiCD4 T cell was never revised, the TCRα chain was rearranged, which means that exogenous antigen drives CD4 T cell proliferation via by TCRβ at periphery in spleen whereas auto-reactivity could be acquired via TCRα revision.

Conclusions/Significance: As to whether or not repeated immunization with antigen makes sense in a real world, the answer would be yes, since our immune system is built up on a delicate balance between pathogen-induced tissue injury and defense-induced tissue injury: host dies if pathogen is too strong due to the former and host also dies if immune defense is too strong due to the latter because the battle field is our body. To avoid both types of injury, we suppress, but not eradicate, pathogens to avoid exhaustive battle in the body, and thus, pathogens invade into body repeatedly below sea-level. Thus, the ability of a certain antigen to cause SLE depends on its propensity to be presented and/or cross-presented to overstimulate CD4 and/or CD8 T cells of the host beyond his/her critical limit, i.e., self-organized criticality.

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Epidemiology and treatment for osteoarthritis

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Osteoarthritis (OA) is one of major causes of significant morbidity and an extensive use of health-care resources due to its being the most common degenerative joint disorder. Prevalence of OA increases with age. It's estimated that 27 million people over the age of 25 in the United States have OA. Data on X-Ray surveys have demonstrated that more than 80% of people over the age of 55 have OA X-ray changes in some joint. Although many treatment approaches are widely used in the treatment of knee OA, none of these can completely cure the knee OA. According to guidelines by the ACR, EULAR and OARSI, current therapies for OA are effective in reduction of pain and secondary functional disability. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen have been widely used in the management of pain in OA. In the guidelines, acetaminophen was stated as initial therapy for the patients with mild-to-moderate pain. The other drugs for OA including chondroitin sulfate and glucosamine are regulated as nutritional supplement in the United States, although a number of studies support their efficacy. Non-pharmacologic methods including patient education, weight loss, exercise, and physical therapy agents such as short-waves, acupuncture, low level laser and electrotherapeutic approaches are used in the treatment of acute and chronic pain of OA for the purpose of pain relief and reduction of secondary functional disability. Surgical options for OA include osteochondral transplants, autologous chondrocyte implantation, osteotomy and joint replacement treatment.

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