Editorial
Autoimmune diseases and fungal infections: immunological mechanisms and therapeutic approaches
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Autoimmune disease represents a breakdown of natural tolerance to autoreactive antigens. Pemphigus and lupus erythematosus are common autoimmune diseases either skin-specific or with predominant skin involvement. During the past decades, much progress has been made in understanding the mechanism of autoimmune diseases and the immunological mechanism in some infectious diseases such as fungal infections. Various novel approaches have been developed in the treatment of these diseases.

Pemphigus
Pemphigus is a life-threatening autoimmune bullous disorder. It has several subtypes with distinct clinical, pathological, immunological and molecular features. Pemphigus vulgaris is the most common type followed by pemphigus erythematosus, pemphigus foliaceus, and pemphigus vegetans. In 1990, a subtype of pemphigus, paraneoplastic pemphigus (PNP), was reported. It was characterized by severe, painful mucosal erosions, blister formation, and lichen planus-like lesions. It is also highly associated with constrictive bronchiolitis. PNP is often associated with lymphoproliferative diseases although it can also be associated with other types of malignancies. The typical histopathological features are acantholysis and deposition of immunological molecules such as IgG, IgM, C3 on the intercellular spaces of epidermal keratinocytes.

It is wildly accepted that the immunological mechanism of pemphigus, regardless of subtypes, is mediated by self-reacting T lymphocytes and autoantibodies directed against antigens (desmoglein 1 and 3) in the desmosomes linking keratinocytes. It was found that sera from PNP patient recognize antigens of the plakin protein family including desmoplakin, desmogleins 1 and 3. In 1999, de Bruin et al found that periplakin and envoplakin were also the target antigens in paraneoplastic pemphigus. Wang et al found that the tumor cells of Castleman's disease were able to produce antibodies against antigens of human epidermis. They also found clonal rearrangement, resulting in similar variable regions of IgV(H), in tumor B cells isolated from patients with Castleman's disease. Successful treatment of Castleman's tumor led to decrease of the antibody level and improvement of the disease. In this issue of Chinese Medical Journal, Li et al confirmed the finding of de Bruin by the ELISA technique. Also they found that purified anti-envoplakin and anti-periplakin autoantibodies from PNP sera were capable of dissociating cultured human epidermal keratinocytes, suggesting that envoplakin and periplakin are among the major target antigens in paraneoplastic pemphigus.

Conventional treatment usually include use of high-dose corticosteroids, sometimes with adjuvant immunosuppressive agents. Significant reduction in corticosteroid requirements can be seen in patients receiving immunosuppressive agents. The side-effect of corticosteroids and/or immunosuppressive agents is often associated with their long-term use of high-dose and often lead to treatment failure. New therapies with biologic agents (in particular rituximab) and calcineurin inhibitors as well as intravenous administration of immunoglobulin are promising but controlled trials are inadequate to establish their role. Allogeneic/autologous hematopoietic stem cell transplantation (HSCT) is a modality for the treatment of drug-resistant pemphigus vulgaris.

Lupus erythematosus (LE)
LE is a heterogenous autoimmune disease with complex pathogenesis. The characteristics of SLE is the production of autoantibodies directed against nuclear antigens and chronic inflammation affecting multiple tissues. Recent studies have suggested that type-I interferons (type-I IFNs) and IFNalpha in particular are prominent cofactors for SLE.

Activation of auto-reactive B-lymphocytes is an immunological feature of SLE, which leads to the production of various autoantibodies. The high level of anti-DNA antibodies can be found in active lupus, suggesting that anti-dsDNA antibodies are involved in the pathogenesis of lupus nephritis through their ability to bind to cell surface antigens or components of the glomerular basement membrane either directly (cross-reactivity) or indirectly (via chromatin material). Anti-SSB antibody is often associated with mild disease in patients with LE. Immunization of rabbits with SSB peptide and DNA could inhibit anti-dsDNA antibody production, suggesting the “protective” role of anti-SSB antibody against anti-dsDNA antibody.

Besides B cells, T lymphocytes also play important roles in SLE. Epigenetic factor has significant effect on T-cell

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functions by modulating its DNA methylation pattern. DNA hypomethylation could be found in patients with active lupus, suggesting it might be involved in the pathogenesis of SLE.  

The treatment strategy for SLE is to suppress immunological and inflammatory process, thereby to diminish or prevent tissue damage. Systemic corticosteroids and immunosuppressive agents are the treatment of choice. In recent years, some promising therapeutic approaches have been used in clinical practice. Intravenous human gamma-globulin is effectively used in the treatment of severe/refractory SLE. Rituximab, a human/murine chimeric monoclonal antibody, is another effective and safe modality for treating SLE. While it is very effective in the depletion of B cells, current research suggests that it may also influence other cells of the immune system by re-establishing immune homeostasis and tolerance.  

HSCT is one of the modalities for the treatment of refractory SLE. Both depletion of the autoreactive immunologic memory and a profound resetting of the immunological function and apply adequate approaches. 

References


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