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.1 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 al2 found that periplakin and envoplakin were also the target antigens in paraneoplastic pemphigus. Wang et al3 confirmed the finding of de Bruin by 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 inculde 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.5,6

Lupus erythematosus (LE)

LE is a heterogenous autoimmune disease with complex pathogenesis.7 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 IFNa is a prominent cofactor for SLE.8 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).9 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.10

Besides B cells, T lymphocytes also play important roles in SLE. Epigenetic factor has significant effect on T-cell...
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.11

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.12 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.6

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 adaptive immune system are achieved in treated patients. Graft versus host disease can be found in allogeneic HSCT which requires further medical treatment.13,14

Candidosis

Candidosis, either mucocutaneous or systemic, is a common fungal infection. It is predominantly caused by the commensal Candida albicans (C. albicans), and can be seen in healthy individuals but more often affect immunocompromized individuals, e.g. AIDS patients, organ transplant recipients and those receiving administration of two or more broad-spectrum antibiotics.15 Toll-like receptors (TLRs) play roles in recognizing candida infections. TLRs have been identified as a major class of pattern-recognition receptors. Recognition of pathogen-associated molecular patterns (PAMPs) by TLRs, either alone or in heterodimerization with other TLR or non-TLR receptors, induces signals responsible for the activation of innate immune response.16 Li et al17 in this issue of Chinese Medical Journal, reported that C. albicans native insoluble β-glucan is involved in activation of immune responses in human monocytic cell line THP-1 cells and this is mediated through Dectin-1, not TLR2.

Cell-mediated immunity plays an important role in defending and clearing of this pathogen. It has been shown that CD4+ T-cells and the p40 subunit of interleukins 12 and 23 are strict prerequisites for resistance. Resistance to this yeast is found to be associated with Th1 immunity while Th2 immunity is associated with susceptibility to systemic infection.18 Natural killer cells and CD8+ cytotoxic T cells are involved in damaging and clearing this pathogen.19

Candidosis can be treated with several antifungal agents such as nystatin, itraconazole, fluconazole, and amphoterin. B. Fan et al20 reported candida strains isolated from vulvovaginal candidosis were all sensitive to nystatin. The resistant rate of C. albicans toazole agents was 0–4.9%. In some severe/refractory cases, antifungal susceptibility test is required for selection of antifungal agents and monitoring drug resistance during treatment. It is also crucial to monitor host immunological function and apply adequate approaches.

REFERENCES


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