AUTOIMMUNE DISEASES

patients with RA after the year 2025. In patients diagnosed prior to this time and requiring reconstructive approaches for joint damage, techniques will be developed for resurfacing joints with autologously generated cartilage.

REFERENCES


Research Advances in Systemic Lupus Erythematosus

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Systemic lupus erythematosus is an autoimmune disease with a significant genetic component to susceptibility. Some environmental risks are known, and identification of specific genetic factors promises to define new molecular targets for therapy. Broad immunosuppression will be replaced by early, selective, and individualized intervention. Mortality rates will decline, and insights into therapy may apply to other autoimmune conditions.

Current Scientific Foundation

Lupus involves abnormal activity of the immune system in response to environmental stimuli encountered by the genetically susceptible host. Family studies emphasize the heritability of the SLE diagnosis, but susceptibility is polygenic, involving multiple genes with a threshold effect. Deficiencies of complement and other opsonins, genetic variants of IgG and C-reactive protein receptors, and inflammatory cytokine promoter variants have been implicated as components of genetic susceptibility factors. Breaks in tolerance and immune hyperactivity lead to tissue injury by both myeloid and lymphoid effector cells. The presence of autoantibodies and autoreactive T cells indicates broad involvement of the immune system, and noninflammatory mechanisms also contribute to vascular and organ injury.

Animal models and clinical observations suggest that different sets of genes can produce similar clinical phenotypes. Consequently, identification of both environmental events and genetic factors may provide important insights into therapy.

Major Clinical and Research Advances

Clinical management of SLE is based on use of nonsteroidal anti-inflammatory drugs (NSAIDs), the addition of hydroxychloroquine and other agents originally developed as antimalarials, targeted and judicious use of glucocorticoids, including large intravenous doses, and aggressive use of other immunosuppressive agents, such as cyclophosphamide. Vigorous management of comorbid conditions, including hypertension and infection, has decreased mortality in persons with SLE.2,3

The immune system plays a crucial role in the pathogenesis of both active inflammatory and noninflammatory mechanisms of organ damage in SLE. Autoreactivity encompasses a broad range of specificities that can include inciting antigens and other antigens through spreading of the immune response. Nucleosomes, apoptotic material, and efficient pathways for routine, nonimmunogenic clearance appear pivotal in pathogenesis of SLE. Equally, effector pathways for inflammation are critical for the development of end-organ damage.

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netic susceptibility factors is critical for understanding SLE.

Cutting-Edge Research

Substantial investigative efforts are focused on studying SLE multiplex families and affected sibling pairs to establish regions of linkage in the genome with the SLE phenotype. Identification of candidate genes associated with disease susceptibility, severity, and response to therapy is progressing in parallel, and elucidation of gene expression profiles in immune cells may identify targets for intervention and guide the discovery of new candidate genes.

Although apoptosis per se does not appear to be grossly defective in SLE, the processing of apoptotic cells and debris contribute to immune dysregulation. Apoptotic material may alter the local tissue environment and the presentation of self as antigenic. Therefore, the determinants of tolerance and the pathways that circumvent tolerance are central to the lupus diathesis.

Critical Efforts, Discoveries, and Tools

The Human Genome Project will provide the framework for understanding the basis of individual genetic susceptibility to and severity of SLE. The strong heritability, measured by the risk of disease among siblings, and the convergence of several investigative groups on specific genetic regions of interest underscore the promise of this approach. Nonetheless, the task of unraveling this complex, and perhaps heterogeneous, disease is daunting. Effective collaborations with large cohorts of both simplex and multiplex families will be essential. Appropriate understanding of “phenotype” and access to state-of-the-art informatics tools are essential for this undertaking.

The ability to take the discoveries from genetics, functional genomics, and pathophysiology to the bedside will require appropriate clinical tools to evaluate efficacy and outcomes. Many of these tools are at hand, and they must be woven into an overall effort addressing new therapies.

Forecast for Research Advances

The next 25 years will contain remarkable progress in the understanding and management of SLE. Identification of susceptibility genes and their contribution to disease pathways will provide insight into the understanding of environmental triggers. Assessment of individual genetic “portfolios” with gene array technology, combined with advances in knowledge about exogenous stimuli, will facilitate prevention of SLE. New markers of immune activation and deviation will enable early therapeutic intervention. Biotechnology will provide more effective means of immunomodulation, perhaps through antigen-specific tolerance induction, selective deletion of activated immune cells, or interruption of inflammatory cascades. Glucocorticoid use will decline and alkylating agents will no longer be part of the therapeutic armamentarium. Early, effective interventions will reduce comorbidities, which will be attenuated further by aggressive management of the causes of morbidity.

Gene therapy for such a complex genetic disease will be used first for drug delivery, not germ line modification. Discoveries in one autoimmune disease will have lessons and applications for other diseases. More targeted therapies will replace broad, nonspecific immunosuppression for most treatment.

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